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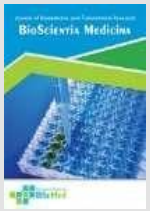

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Hyperthyroidism-Induced Myocardial Ischemia: Quantification and Correlation with fT4 via ^{99m}Tc-Sestamibi Scintigraphy

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A B S T R A C T

Background: Hyperthyroidism exerts significant detrimental effects on the cardiovascular system, increasing the risk of major adverse cardiac events (MACE). While associations with atrial fibrillation and cardiomyopathy are well-documented, the incidence and characteristics of myocardial ischemia, particularly assessed by functional imaging, remain less explored. This study aimed to investigate the incidence of myocardial ischemia in hyperthyroid patients using Technetium-99m Sestamibi (^{99m}Tc-Sestamibi) myocardial perfusion scintigraphy (MPS) and correlate findings with thyroid hormone levels. **Methods:** This prospective preliminary study enrolled fifteen consecutive patients with confirmed hyperthyroidism and no prior history of ischemic heart disease between January and April 2024. All subjects underwent thyroid function tests (TSH, fT4, T3) and a one-day rest/adenosine-stress ^{99m}Tc-Sestamibi MPS protocol. Myocardial ischemia presence, reversibility, severity (Summed Stress Score, SSS), and extent (total ischemic segments) were assessed using the AHA 17-segment model. Spearman correlation was used to analyze the relationship between hormone levels and MPS parameters. **Results:** Fifteen subjects (93.3% female, mean age 34 ± 11 years) were included. Myocardial ischemia was detected in 14/15 subjects (93.3%). Among those with ischemia, 12 (80% of total subjects, 85.7% of ischemic subjects) exhibited reversible defects. Free thyroxine (fT4) levels showed a strong positive correlation with SSS (rs = 0.64, p = 0.01) and the total number of ischemic segments (rs = 0.65, p = 0.01). **Conclusion:** This preliminary study revealed a high incidence of myocardial ischemia, predominantly reversible, in patients with hyperthyroidism detected by ^{99m}Tc-Sestamibi MPS. The severity and extent of ischemia demonstrated a significant positive correlation with fT4 levels. These findings underscore the potential utility of MPS in cardiovascular risk assessment and suggest the need for comprehensive cardiac evaluation in hyperthyroid patients, particularly those with higher fT4 levels.

1. Introduction

Ischemic heart disease (IHD) stands as a critical global health issue and the leading cause of mortality on a global scale. The World Health Organization's Global Health Estimates indicate that IHD was responsible for approximately 9.1 million deaths in 2021, accounting for 13% of all deaths worldwide. While traditional cardiovascular risk factors are well-established, the role of endocrine disorders, notably thyroid dysfunction, is being increasingly recognized in the development of IHD. Hyperthyroidism, a condition marked by the excessive production and secretion of thyroid hormones, primarily thyroxine (T4) and triiodothyronine (T3), has significant and detrimental effects on the cardiovascular system. The increased levels of thyroid hormones lead to a hypermetabolic state, influencing heart rate, rhythm, myocardial contractility, and overall cardiac output.

These physiological changes contribute to an elevated lifetime risk of major adverse cardiac events (MACE). Epidemiological studies have revealed that both overt and subclinical hyperthyroidism are associated with increased all-cause mortality and cardiovascular events, with one large study reporting a 16% higher risk of MACE in individuals with thyroid dysfunction. Cardiovascular complications frequently linked to hyperthyroidism include atrial fibrillation (AF), occurring in 5-15% of patients, thyrotoxic cardiomyopathy, and an increased risk of heart failure and sudden cardiac death. Hyperthyroidism-related AF is particularly notable because it can often be reversed with the restoration of normal thyroid function (euthyroidism).[1-4]

However, the association between hyperthyroidism and myocardial ischemia has not received as much attention as arrhythmias and cardiomyopathy. Nevertheless, emerging evidence indicates a significant link between hyperthyroidism and myocardial ischemia. Several case reports and smaller studies have described myocardial infarction (MI) or severe coronary artery spasm in patients with both overt and subclinical hyperthyroidism, sometimes even when coronary arteries appear normal on angiography. Furthermore, meta-analyses have suggested that hyperthyroidism increases the risk of IHD, even in populations considered to be at low risk. Additionally, a computed tomography angiography study has indicated that hyperthyroidism can affect coronary artery disease. The mechanisms by which hyperthyroidism induces myocardial ischemia are complex and multifactorial. Thyroid hormones increase myocardial oxygen consumption by increasing heart rate, contractility, preload, and afterload. Simultaneously, oxygen supply may be compromised through several mechanisms, including endothelial dysfunction, increased susceptibility to coronary artery spasm, microvascular dysfunction, and a prothrombotic state characterized by hypercoagulability and impaired fibrinolysis. This imbalance between increased oxygen demand and potentially reduced supply can lead to myocardial ischemia. If these conditions persist, they can result in adverse cardiac remodeling, thyrotoxic cardiomyopathy, and eventually heart failure.[5-7]

Despite the existence of these plausible mechanisms and suggestive clinical reports, there is a scarcity of studies that have systematically evaluated the incidence and characteristics of myocardial ischemia in unselected hyperthyroid populations using sensitive functional imaging techniques. Myocardial Perfusion Scintigraphy (MPS) using Single Photon Emission Computed Tomography (SPECT) with tracers like Technetium-99m Sestamibi (^{99m}Tc-Sestamibi) is a well-established non-invasive method for assessing regional myocardial blood flow and detecting ischemia. MPS offers the advantage of identifying perfusion abnormalities indicative of ischemia, often before anatomical changes are apparent or clinical symptoms manifest. Quantitative analysis of MPS, such as the Summed Stress Score (SSS), provides objective measures of the extent and severity of perfusion defects, which are valuable for predicting future cardiac events. Given the potential for significant, yet possibly subclinical, myocardial involvement in hyperthyroidism and the limited data on ischemia prevalence assessed by functional imaging, this study was conducted to address the gap in functional cardiovascular assessment in this endocrine disorder.[8-10] This investigation aimed to comprehensively characterize the myocardial ischemic burden in hyperthyroid individuals using quantitative ^{99m}Tc-Sestamibi MPS, focusing on incidence, reversibility, severity, and extent. Additionally, the study sought to establish the relationship between the degree of thyroid hormone excess, specifically serum free thyroxine (fT4) levels, and these objective measures of myocardial perfusion compromise.

2. Methods

Patients were enrolled consecutively from the outpatient and inpatient services of Dr. Hasan Sadikin General Hospital, Bandung, Indonesia, between January 2024 and April 2024. The study population comprised individuals with clinically and

biochemically confirmed hyperthyroidism. For the purpose of this study, hyperthyroidism was defined based on both clinical assessment and laboratory evidence of thyroid hormone excess, specifically low levels of thyroid-stimulating hormone (TSH) in conjunction with elevated levels of free thyroxine (fT4) or triiodothyronine (T3). To ensure the study focused on the impact of hyperthyroidism on myocardial function without the confounding influence of pre-existing cardiac conditions, patients with a documented history of ischemic heart disease were excluded. This exclusion criterion encompassed individuals with a history of myocardial infarction, prior coronary revascularization procedures (such as percutaneous coronary intervention or coronary artery bypass grafting), or known significant coronary artery stenosis as determined by previous angiographic studies. Detailed baseline demographic characteristics were recorded for all participants upon enrollment. These included age, gender, height, and weight. Anthropometric measurements of height and weight were obtained using standardized techniques. Height was measured using a stadiometer with the patient standing upright without shoes, and weight was measured using a calibrated scale with the patient wearing light clothing and no shoes. These measurements were essential for characterizing the study population and for potential correlation with myocardial perfusion parameters.

The study protocol was meticulously designed and conducted in adherence to the ethical principles outlined in the 1964 Declaration of Helsinki and its subsequent amendments. The Declaration of Helsinki provides a comprehensive set of ethical principles for medical research involving human subjects, emphasizing the importance of informed consent, confidentiality, and the well-being of participants. Prior to the commencement of any study-related procedures, ethical approval was formally obtained from the Research Ethics Committee of Dr. Hasan Sadikin General Hospital, Bandung, West Java, Indonesia. The approval number assigned to this study by the ethics committee is DP.04.03/D.XIV.6.5/37/2024. This ethical clearance ensured that the study protocol met the required standards for the protection of human subjects in research. Informed consent was a fundamental aspect of this study. All participants were provided with detailed information about the study's objectives, procedures, potential risks and benefits, and their right to withdraw from the study at any time without consequence. This information was conveyed in a clear and understandable manner, and participants were given ample opportunity to ask questions and seek clarification. Written informed consent was obtained from each participant before their enrollment and prior to the initiation of any study-related procedures. The informed consent process ensured that participation was voluntary and that participants were fully aware of what their involvement entailed.

To accurately assess the thyroid status of each participant, venous blood samples were collected for the measurement of thyroid function parameters. Blood samples were obtained using standard venipuncture techniques, ensuring minimal discomfort and risk to the participants. Serum levels of thyroid-stimulating hormone (TSH), free thyroxine (fT4), and total triiodothyronine (T3) were measured using a radio-immunoassay (RIA) method. The RIA method is a highly sensitive and specific technique for quantifying hormone levels in serum. The assays were performed using commercially available RIA kits, and the procedures were carried out according to the manufacturers' instructions. A gamma counter (Shinjin Medics, Dream Gamma-5) was used to measure the radioactivity in the samples, which is directly proportional to the hormone concentration. Quality control procedures were strictly followed to ensure the accuracy and reliability of the hormone measurements. This included the use of standard reference materials, repeated measurements of control samples, and regular calibration of the gamma counter. The laboratory reference ranges used to interpret the thyroid function test results were as follows: TSH 0.3–5.0 μIU/mL, fT4 0.7–1.8 ng/dL, and T3 0.8-2.0 ng/mL. These reference ranges are the

standard values used at Dr. Hasan Sadikin General Hospital and are consistent with international guidelines.

All enrolled subjects underwent Myocardial Perfusion Scintigraphy (MPS) within one week following their thyroid function tests. This timeframe was chosen to minimize potential changes in thyroid function that could occur between the blood test and the MPS procedure. To avoid any potential confounding effects of anti-thyroid medications on cardiac hemodynamics or tracer uptake during the MPS study, patients were instructed to abstain from taking these medications until after the completion of the MPS. The decision to withhold anti-thyroid medications was carefully considered in the context of patient safety and the study's objectives. The potential risks of temporarily discontinuing medication were weighed against the need for accurate and reliable MPS results. Patients were closely monitored, and the duration of medication withholding was kept to a minimum. A standard one-day, stress-rest ^{99m}Tc-Sestamibi protocol was employed for the MPS procedure. This protocol is widely used and considered the standard of care for assessing myocardial perfusion. The one-day protocol offers the advantage of convenience and reduced patient burden compared to a two-day protocol. Pharmacological stress testing was performed using intravenous adenosine infusion. Stress testing is a critical component of MPS as it helps to elicit differences in blood flow between normal and ischemic myocardial tissue. In patients with hyperthyroidism, resting tachycardia (an elevated heart rate at rest) is a common manifestation. Exercise stress testing, which is often used in individuals without hyperthyroidism, relies on achieving a target heart rate to adequately stress the cardiovascular system. However, the presence of resting tachycardia in hyperthyroid patients can make it difficult to achieve the additional increase in heart rate required for an effective exercise stress test. Therefore, pharmacological stress testing with adenosine was chosen as the preferred method in this study population. Adenosine is a potent vasodilator that increases blood flow in normal coronary arteries. Diseased arteries, however, may have a limited capacity to dilate, leading to a relative reduction in blood flow to the corresponding myocardial region, which can be detected by the ^{99m}Tc-Sestamibi tracer. Adenosine was infused intravenously at a standard rate of 140 µg/kg/minute for a total duration of 6 minutes. This infusion rate and duration are consistent with established protocols for adenosine stress testing. Continuous electrocardiogram (ECG) monitoring was performed throughout the adenosine infusion to assess the patient's heart rhythm and detect any potential adverse effects. Blood pressure and heart rate were also closely monitored at regular intervals. At the 3-minute mark of the adenosine infusion, the radiopharmaceutical ^{99m}Tc-Sestamibi was administered intravenously at a dose of 5 MBq/Kg body weight. ^{99m}Tc-Sestamibi is a lipophilic cation that is taken up by viable myocardial cells in proportion to regional blood flow. This allows for the assessment of myocardial perfusion. The dose of 5 MBq/Kg was chosen based on standard imaging protocols to ensure adequate image quality while minimizing radiation exposure to the patient. SPECT imaging acquisition commenced approximately 60 minutes after the tracer injection during the stress phase. This delay allows for sufficient uptake of the tracer into the myocardium and clearance from the background. For the rest study, performed later on the same day, a higher dose of ^{99m}Tc-Sestamibi was administered intravenously at rest. The rest study provides a baseline assessment of myocardial perfusion in the absence of stress. The dose used for the rest study was higher than the stress dose to improve image quality and signal-to-noise ratio. Imaging for the rest study was also acquired 60 minutes post-injection. Imaging was performed using a dual-head SPECT gamma camera system (Infinia Hawkeye GP 3, GE Healthcare), equipped with low-energy, high-resolution collimators. This gamma camera system is widely used in nuclear cardiology and provides high-quality images of myocardial perfusion. Low-energy, high-resolution collimators were used to optimize the spatial resolution of the

images. Standard acquisition parameters for cardiac SPECT were utilized, including electrocardiogram (ECG)-gating for functional assessment. ECG-gating synchronizes the image acquisition with the patient's cardiac cycle, allowing for the assessment of left ventricular function, including ejection fraction and wall motion. This provides additional information beyond just myocardial perfusion. Acquired SPECT data were reconstructed using standard filtered back-projection or iterative reconstruction algorithms. Reconstruction algorithms are used to create tomographic images from the raw projection data acquired by the gamma camera. Filtered back-projection and iterative reconstruction are two common methods used in SPECT imaging. Attenuation correction was likely performed using the integrated CT component of the SPECT/CT system, although this was not explicitly stated for the primary analysis. Attenuation correction is an important step in SPECT image processing that corrects for the attenuation of gamma rays by tissues in the body, which can affect the accuracy of the perfusion assessment. The use of an integrated CT system allows for accurate attenuation correction based on the CT images. Processed images were analyzed using dedicated nuclear cardiology software (Xeleris 4.0, GE Healthcare). This software provides tools for image display, processing, and quantitative analysis of myocardial perfusion.

Myocardial perfusion was assessed based on the standardized American Heart Association (AHA) 17-segment model of the left ventricle. The AHA 17-segment model is a widely accepted and standardized method for dividing the left ventricle into distinct segments, allowing for consistent and reproducible assessment of regional myocardial perfusion. Each segment is assigned to a specific coronary artery territory (left anterior descending artery (LAD), left circumflex artery (LCx), or right coronary artery (RCA)). All MPS studies were independently reviewed by two experienced nuclear medicine physicians who were blinded to the patients' detailed clinical information and thyroid function results. Blinding is a critical step to minimize bias in the interpretation of the images. The physicians were not aware of the patients' clinical history, symptoms, or thyroid hormone levels, ensuring that their assessment was based solely on the MPS images. Any discrepancies in interpretation between the two physicians were resolved by consensus. In cases where the physicians initially disagreed on the interpretation of the images, they reviewed the images together and discussed their findings until they reached a consensus agreement. This process ensures the accuracy and reliability of the image interpretation. Perfusion in each of the 17 segments was visually assessed on both the stress and rest images. The assessment involved evaluating the uptake of the ^{99m}Tc-Sestamibi tracer in each segment and comparing the uptake between the stress and rest images. Myocardial ischemia was defined as the presence of a perfusion defect (reduced ^{99m}Tc-Sestamibi uptake) in one or more segments on the stress images that showed improvement or normalization of uptake on the rest images (reversible defect). This definition is consistent with the standard criteria for identifying ischemia on MPS. A reversible defect indicates that the myocardium is receiving inadequate blood flow under stress conditions but has normal blood flow at rest. A fixed defect was defined as reduced uptake present on both stress and rest images, suggestive of prior infarction or scar. A fixed defect indicates that the myocardium has been damaged and is no longer viable. Non-reversible, non-infarct ischemia was likely defined as a stress defect with no corresponding rest defect but also no clear scar pattern. This category represents perfusion abnormalities that do not fit the criteria for either reversible ischemia or fixed defects. The total number of segments exhibiting ischemia and the affected coronary artery territories (LAD, LCx, RCA) were recorded. This provides information on the extent and location of the ischemia. The severity of perfusion defects in each segment was scored using a standard 5-point scale: 0 = normal uptake (>80% of maximum); 1 = mildly reduced uptake (70-80%); 2 = moderately reduced uptake (60-70%); 3 = severely reduced uptake

(50-60%); and 4 = absent uptake (<50%). This scoring system allows for a semi-quantitative assessment of the severity of the perfusion defect in each segment. The Summed Stress Score (SSS) was calculated by summing the scores of all 17 segments from the stress images. The SSS provides an overall measure of the extent and severity of perfusion abnormalities (ischemia and scar) during stress. Similarly, a Summed Rest Score (SRS) was calculated from the rest images. The SRS reflects the extent and severity of perfusion abnormalities at rest. The Summed Difference Score (SDS), representing the extent and severity of reversible ischemia, was calculated as SSS minus SRS. The SDS specifically quantifies the amount of ischemia that is reversible. The SSS was used as the primary semi-quantitative marker for the overall burden (severity and extent) of perfusion abnormalities (ischemia + scar) in correlation analyses.

Data analysis was performed using IBM SPSS Statistics for Windows, Version 25.0 (IBM Corp., Armonk, NY). SPSS is a widely used statistical software package for data management and analysis. The distribution of numerical data was assessed using the Shapiro-Wilk test. The Shapiro-Wilk test is a statistical test used to determine if a dataset is normally distributed. This is important because the choice of statistical tests depends on the distribution of the data. Normally distributed continuous variables were presented as mean ± standard deviation (SD), while non-normally distributed variables were presented as median and interquartile range (IQR). Mean and standard deviation are used to describe the central tendency and variability of normally distributed data, while median and interquartile range are used for non-normally distributed data. Categorical data were presented as frequencies and percentages. This is the standard way to summarize categorical data. The correlation between thyroid hormone levels (fT4, T3, TSH) and MPS parameters reflecting ischemia severity and extent (SSS, total number of ischemic segments) was evaluated using Spearman's rank correlation coefficient (rs). Spearman's rank correlation coefficient is a non-parametric statistical measure of the association between two variables. It was chosen due to the anticipated non-normal distribution of some variables and the ordinal nature of the SSS. A two-tailed p-value less than 0.05 was considered statistically significant for all analyses. The p-value is the probability of obtaining the observed results (or more extreme results) if there is no true effect. A p-value of less than 0.05 is the conventional threshold for statistical significance, indicating that the results are unlikely to have occurred by chance.

3. Results

Table 1 presents a comprehensive summary of the baseline demographic and clinical characteristics of the 15 patients enrolled in the study, as well as the key findings from the myocardial perfusion scintigraphy (MPS); Demographics: The study population had a mean age of 34 years, with a standard deviation of 11 years, indicating a moderate spread of ages within the group. The youngest participant was 20 years old, and the oldest was 57 years old. The gender distribution was heavily skewed towards females, with 14 out of the 15 participants being female (93.3%) and only 1 male participant (6.7%). This marked female predominance is a notable characteristic of the study cohort; Anthropometry: The mean height of the participants was 153.73 cm with a standard deviation of 6.32 cm, ranging from 144 cm to 165 cm. The mean weight was 58.06 kg with a standard deviation of 10.87 kg, ranging from 45 kg to 79 kg; Thyroid Function: Thyroid function tests confirmed that all participants had biochemical hyperthyroidism. The median TSH level was 0.02 µIU/mL, with an interquartile range (IQR) of 0.02 µIU/mL, and the levels ranged from 0.01 to 1.00 µIU/mL. This very low median TSH is a hallmark of hyperthyroidism. The median free thyroxine (fT4) level was 1.70 ng/dL, with an IQR of 2.10 ng/dL, ranging from 1.40 to 3.90 ng/dL. The elevated fT4 levels are consistent with hyperthyroidism. The median total triiodothyronine (T3) level was 1.90 ng/mL, with an

IQR of 1.40 ng/mL, ranging from 1.10 to 3.90 ng/mL. These levels also indicate thyroid hormone excess; MPS Findings: Myocardial ischemia was detected in 14 out of the 15 subjects, indicating a high overall incidence of 93.3% in this hyperthyroid cohort. Of the 14 subjects with ischemia, 12 (80.0% of the total cohort, 85.7% of those with ischemia) exhibited reversible ischemia. This suggests stress-induced ischemia with potential for recovery. The remaining 2 subjects (13.3% of the total cohort, 14.3% of those with ischemia) showed non-reversible ischemia. None of the subjects showed a definite myocardial infarct pattern. Quantitative measures of ischemia in the 14 subjects with myocardial ischemia revealed a mean Summed Stress Score (SSS) of 6.0 ± 4.73 and a mean of 5.0 ± 3.63 total ischemic segments per patient. The Left Anterior Descending (LAD) artery territory was involved in 100% of the ischemic subjects. Multi-vessel involvement was observed in 6 subjects (40.0% of the total cohort, 42.9% of those with ischemia).

Table 1. Comprehensive summary of patient characteristics and study findings (N=15).

Feature category	Parameter	Value
Demographics	Age (years)	
	Mean ± SD	34 ± 11
	Range	20 – 57
	Gender	
	Female	14 (93.3%)
	Male	1 (6.7%)
Anthropometry	Height (cm)	
	Mean ± SD	153.73 ± 6.32
	Range	144 – 165
	Weight (kg)	
	Mean ± SD	58.06 ± 10.87
	Range	45 – 79
Thyroid function	TSH (μIU/mL)	
	Median ± IQR	0.02 ± 0.02
	Range	0.01 – 1.00
	Free Thyroxine (fT4) (ng/dL)	
	Median ± IQR	1.70 ± 2.10
	Range	1.40 – 3.90
	Total Triiodothyronine (T3) (ng/mL)	
	Median ± IQR	1.90 ± 1.40
	Range	1.10 – 3.90
MPS findings		
Overall incidence	Myocardial Ischemia Detected	14 (93.3%)
Ischemia details (N=14)	Reversible Ischemia	12 (80.0% of total; 85.7% of ischemic)
	Non-Reversible Ischemia	2 (13.3% of total; 14.3% of ischemic)
	Definite Myocardial Infarct Pattern	0 (0%)
	Quantitative Measures (N=14)	
	Summed Stress Score (SSS), Mean ± SD	6.0 ± 4.73
	Total Ischemic Segments (n), Mean ± SD	5.0 ± 3.63
	Vessel Involvement (N=14)	
	LAD Territory Involvement	14 (100% of ischemic)
	Multi-vessel Involvement	6 (40.0% of total; 42.9% of ischemic)

Notes: SD = Standard Deviation; IQR = Interquartile Range; TSH = Thyroid-Stimulating Hormone; fT4 = Free Thyroxine; T3 = Total Triiodothyronine; MPS = Myocardial Perfusion Scintigraphy; SSS = Summed Stress Score; LAD = Left Anterior Descending artery.

Table 2 presents the results of the correlation analyses between thyroid hormone levels and myocardial perfusion scintigraphy (MPS) parameters of ischemia severity and extent in the study population (N=15). The table shows the Spearman's rank correlation coefficient (rs), p-value, and correlation strength and significance for each comparison; Free Thyroxine (fT4): There is a strong positive correlation between fT4 levels and the Summed Stress Score (SSS), with rs = 0.64 and p = 0.01. This indicates that higher levels of fT4 are significantly associated with a higher SSS, reflecting greater severity and extent of myocardial perfusion abnormalities. fT4 levels also show a strong positive correlation with the total number of ischemic segments (rs = 0.65, p = 0.01). This suggests that higher fT4 levels are significantly related to a greater number of segments showing ischemia; Total Triiodothyronine (T3): T3 levels exhibit a moderate positive correlation with SSS (rs = 0.47) and the total number of ischemic segments (rs = 0.49). However, these correlations did not reach statistical significance, with p-values of 0.08 and 0.06, respectively. This indicates a trend towards a relationship, but it's not statistically conclusive in this study; Thyroid-Stimulating Hormone (TSH): TSH levels show a weak negative correlation with SSS (rs = -0.19, p = 0.95) and a negligible correlation with the total number of ischemic segments (rs = -0.03, p = 0.99). These findings suggest that TSH levels do not have a significant relationship with myocardial ischemia severity or extent in this hyperthyroid population.

Table 2. Correlation between thyroid hormone levels and myocardial perfusion scintigraphy (MPS) parameters of ischemia severity and extent (N=15).

Thyroid hormone	MPS parameter	Spearman's Rank Correlation Coefficient (rs)	p-value	Correlation strength & significance
Free thyroxine (fT4)	Summed Stress Score (SSS)	0.64	**0.01**	Strong Positive, Significant
	Total Ischemic Segments (n)	0.65	**0.01**	Strong Positive, Significant
Total triiodothyronine (T3)	Summed Stress Score (SSS)	0.47	0.08	Moderate Positive, Not Significant
	Total Ischemic Segments (n)	0.49	0.06	Moderate Positive, Not Significant
Thyroid-stimulating hormone (TSH)	Summed Stress Score (SSS)	-0.19	0.95	Weak Negative, Not Significant
	Total Ischemic Segments (n)	-0.03	0.99	Negligible, Not Significant

4. Discussion

One of the most striking observations in this study is the remarkably high incidence of myocardial ischemia, reaching 93.3%, as detected by ^{99m}Tc-Sestamibi MPS in this cohort of hyperthyroid patients. This finding is particularly significant because it challenges the traditional clinical perspective that often emphasizes other cardiovascular manifestations of hyperthyroidism, such as arrhythmias and cardiomyopathy, over myocardial ischemia. While it is well-established that hyperthyroidism exerts significant effects on the cardiovascular system, leading to increased heart rate, contractility, and oxygen demand, the prevalence of actual myocardial ischemia, as a functional manifestation of these changes, has not been as extensively quantified, especially using sensitive imaging techniques like MPS. The high incidence of ischemia observed in this study suggests that myocardial perfusion abnormalities might be a more common complication of hyperthyroidism than previously recognized. This has important clinical implications. It implies that a

substantial proportion of hyperthyroid patients, even those without typical anginal symptoms or a known history of heart disease, may be experiencing some degree of myocardial ischemia. This subclinical ischemia could contribute to the increased risk of major adverse cardiac events (MACE) that has been observed in hyperthyroid populations. The ability of MPS to detect these perfusion abnormalities before the development of irreversible damage or overt symptoms highlights its potential clinical utility in this context. However, it is crucial to acknowledge the limitations of this finding, primarily the small sample size of the study. With only 15 patients included, the generalizability of this result to the broader population of hyperthyroid individuals is limited. Larger studies with more diverse patient populations are needed to confirm this high incidence and to determine whether it varies across different etiologies or severities of hyperthyroidism. Furthermore, the single-center nature of the study might introduce selection bias, as the patient population at a single institution may not fully represent the spectrum of hyperthyroidism seen in the general population.[11,12]

Another key finding of the study is that the majority of the detected ischemia was reversible. Specifically, 12 out of the 14 subjects with myocardial ischemia demonstrated reversible perfusion defects on MPS. Reversible ischemia, as identified by MPS, indicates a situation where the myocardium is experiencing reduced blood flow under stress conditions, but this flow improves or normalizes at rest. This is in contrast to fixed defects, which represent areas of scar tissue or prior infarction where blood flow is persistently reduced at both stress and rest. The predominance of reversible ischemia in this hyperthyroid cohort has several important clinical and pathophysiological implications. From a clinical standpoint, it suggests that the myocardial dysfunction induced by hyperthyroidism is, to a significant extent, potentially reversible, at least in the early stages. This implies that with timely and effective treatment of the hyperthyroidism, leading to the restoration of a euthyroid state, there is a possibility for improvement or even complete resolution of the myocardial ischemia. This is consistent with clinical observations that some cardiac manifestations of hyperthyroidism, such as atrial fibrillation, can be reversed with successful thyroid management. However, the presence of reversible ischemia also underscores the potential risk associated with untreated or inadequately treated hyperthyroidism. While the ischemia may be reversible initially, chronic or recurrent episodes of ischemia can lead to a cascade of adverse effects on the myocardium. These can include myocardial stunning (temporary dysfunction following ischemia), hibernation (chronic downregulation of myocardial function to survive under reduced blood flow), and ultimately, irreversible damage, such as fibrosis and adverse remodeling. Such processes can contribute to the development of thyrotoxic cardiomyopathy and heart failure, which are serious complications of prolonged hyperthyroidism. The fact that MPS can detect this reversible ischemic process early is of significant value. It provides a window of opportunity for intervention and potentially prevents the progression to irreversible myocardial damage. This highlights the importance of considering functional cardiac imaging in the evaluation of hyperthyroid patients, even in the absence of overt symptoms of heart disease.[13,14]

The pathophysiology of myocardial ischemia in the context of hyperthyroidism is complex and multifactorial, involving a delicate interplay between increased myocardial oxygen demand and potentially compromised oxygen supply. Hyperthyroid states are characterized by elevated levels of thyroid hormones, which have profound effects on the cardiovascular system. Thyroid hormones exert direct and indirect stimulatory effects on the heart, leading to increased heart rate (chronotropy) and enhanced contractility (inotropy). These effects are mediated through various mechanisms, including increased expression of beta-adrenergic receptors in the myocardium and alterations in intracellular calcium handling. The resulting increase in cardiac work translates directly to increased myocardial oxygen demand. In addition

to their direct effects on the heart, thyroid hormones also influence the peripheral vasculature. They can alter vascular tone and may increase afterload, further contributing to the oxygen demands of the heart. Furthermore, hyperthyroidism is often associated with increased blood volume and venous return, which elevates preload and adds to the workload of the myocardium. While the demand for oxygen is significantly increased in hyperthyroidism, the supply of oxygen to the myocardium may be compromised through several mechanisms. One important factor is endothelial dysfunction, which refers to an impairment in the normal function of the cells lining the coronary arteries. The endothelium plays a crucial role in regulating vascular tone and blood flow, primarily through the production of nitric oxide, a potent vasodilator. In hyperthyroidism, endothelial dysfunction can lead to reduced nitric oxide bioavailability, impairing the ability of the coronary arteries to dilate appropriately in response to increased demand, thus limiting coronary blood flow reserve. Another potential mechanism is an increased susceptibility to coronary artery vasospasm. Vasospasm involves a sudden and transient narrowing of a coronary artery, which can severely reduce or even completely block blood flow to the affected area of the myocardium. While the exact mechanisms underlying vasospasm in hyperthyroidism are not fully understood, it is hypothesized that thyroid hormones may alter the reactivity of vascular smooth muscle or influence the balance of vasoconstrictor and vasodilator substances. Microvascular dysfunction, involving abnormalities in the small blood vessels of the heart, may also contribute to ischemia in hyperthyroidism. These small vessels play a critical role in delivering oxygen and nutrients to the myocardial cells. Impaired microvascular function can disrupt this delivery, leading to ischemia, particularly in the subendocardial region, which is most vulnerable to reduced blood flow. Finally, hyperthyroidism can be associated with a prothrombotic state, characterized by alterations in coagulation and fibrinolytic pathways. This can increase the risk of thrombus formation in the coronary arteries, potentially leading to acute coronary syndromes. It is important to note that while accelerated atherosclerosis can occur in some individuals with hyperthyroidism, the ischemia observed in younger patients, such as those in the present study (mean age 34 years), often occurs in the absence of significant obstructive epicardial coronary artery disease. This suggests that functional abnormalities, such as endothelial dysfunction, vasospasm, and microvascular dysfunction, play a more prominent role in the pathogenesis of ischemia in this population.[15,16]

The study also provided insights into the distribution of ischemia across different coronary artery territories. The Left Anterior Descending (LAD) artery territory was the most commonly affected, with perfusion defects observed in all 14 subjects (100%) who exhibited ischemia. The LAD supplies a large portion of the left ventricle, including the apex and the anterior wall, making it a critical vessel for myocardial perfusion. The frequent involvement of the LAD territory might reflect its extensive distribution and potentially higher susceptibility to the demand-supply imbalances or vasospastic influences that characterize hyperthyroidism. Furthermore, a significant proportion of patients (40% of the total cohort, 42.9% of those with ischemia) demonstrated multi-vessel involvement, with perfusion abnormalities affecting more than one coronary artery territory. This finding underscores the potentially diffuse nature of the cardiac impact of hyperthyroidism, suggesting that the mechanisms responsible for ischemia, such as endothelial dysfunction or vasospasm, can affect the coronary circulation more broadly rather than being limited to a single vessel. Multi-vessel ischemia is generally associated with a worse prognosis compared to single-vessel disease, highlighting the clinical significance of this observation in hyperthyroid patients.[17,18]

A cornerstone finding of this study is the strong, statistically significant positive correlation observed between serum free thyroxine (fT4) levels and both the

severity (Summed Stress Score, SSS) and the extent (total number of ischemic segments) of myocardial ischemia detected by MPS. This finding suggests a direct relationship between the degree of thyroid hormone excess and the magnitude of myocardial perfusion abnormality. Free thyroxine (fT4) is a crucial thyroid hormone and is considered a primary marker for assessing the biochemical severity of hyperthyroidism. It represents the unbound and biologically active fraction of thyroxine in the circulation, directly influencing cellular metabolism and function. The strong correlation between fT4 levels and the SSS and the number of ischemic segments implies that higher circulating levels of fT4 are associated with more severe and extensive myocardial ischemia. This dose-response relationship has significant clinical relevance. It suggests that patients with more pronounced elevations in fT4 levels are likely to have a greater burden of myocardial ischemia and, consequently, may be at higher risk for adverse cardiovascular events. This highlights the importance of carefully monitoring fT4 levels in hyperthyroid patients and considering the potential need for more aggressive management of both the thyroid dysfunction and cardiovascular risk factors in those with higher fT4 values. Furthermore, this finding aligns with a broader body of evidence that has established thyroid function parameters, including fT4 levels, as independent predictors of adverse cardiovascular outcomes. Even within the high-normal range, fT4 levels have been shown to be associated with an increased risk of MACE, cardiovascular mortality, atrial fibrillation, and potentially all-cause mortality in various populations, including those with pre-existing cardiovascular conditions. Concurrently, quantitative MPS parameters, such as the SSS, are well-validated prognostic indicators in their own right. An elevated SSS and a greater extent of ischemia, including multi-vessel involvement, have been consistently associated with an increased risk of subsequent MACE and overall mortality across diverse patient populations. These parameters provide objective measures of the severity and extent of myocardial perfusion abnormalities, allowing for risk stratification and prognostication. The strong correlation observed in this study between fT4 (a marker of disease severity) and SSS/ischemic extent (markers of myocardial injury and prognosis) provides a critical link between the endocrine abnormality and its functional cardiovascular consequence. This connection reinforces the rationale for a vigilant and comprehensive approach to cardiac assessment and management in hyperthyroid patients, tailored to the severity of the hyperthyroid state.[19,20]

5. Conclusion

In conclusion, this preliminary study provides compelling evidence for a high incidence of myocardial ischemia in patients with hyperthyroidism, detected through ^{99m}Tc-Sestamibi myocardial perfusion scintigraphy (MPS). The study highlights that a significant proportion of hyperthyroid individuals, even those without typical symptoms of heart disease, may exhibit myocardial ischemia. The predominantly reversible nature of the detected ischemia suggests a potential for myocardial recovery with effective thyroid management, yet also underscores the risk of untreated hyperthyroidism progressing to irreversible damage. Furthermore, the significant positive correlation between free thyroxine (fT4) levels and both the severity and extent of myocardial ischemia, quantified by the Summed Stress Score and the number of ischemic segments, respectively, indicates that the severity of thyroid hormone excess is directly associated with the magnitude of myocardial perfusion abnormalities. This finding emphasizes the importance of careful fT4 monitoring and tailored management strategies to mitigate cardiovascular risk in hyperthyroid patients. While the study's small sample size and single-center design necessitate cautious interpretation and further validation in larger, more diverse populations, the results strongly advocate for the integration of functional cardiac imaging, such as MPS, into the comprehensive cardiovascular assessment of individuals with

hyperthyroidism. This approach could facilitate earlier detection of subclinical myocardial ischemia and guide timely interventions to improve cardiac outcomes in this patient population.

6. References

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