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CARDIOVASCULAR IMPLICATIONS OF CUMULATIVE RADIOIODINE DOSES IN PATIENTS WITH DIFFERENTIATED THYROID CANCER AND TYPE 2 DIABETES MELLITUS, BIHAR, INDIA: A RETROSPECTIVE STUDY.

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ABSTRACT.

Background:
The study aims to investigate the cardiovascular effects associated with cumulative doses of radioiodine therapy in people diagnosed with differentiated thyroid cancer (DTC) and comorbid Type 2 diabetes mellitus, with a focus on elucidating potential risks and outcomes for this patient population.

Methods:
A retrospective cohort study was conducted, enrolling 75 female participants categorized into DTC/−T2DM (Category I) and DTC/+T2DM (Category II). Data on demographic characteristics, radioiodine therapy, cardiovascular outcomes, and clinical parameters were collected from medical records. Statistical analyses were accomplished using SPSS software ver. 18.

Results:
Patients with DTC and without T2DM (DTC/−T2DM) exhibited higher average age (60 ± 6.3 years) and BMI (28.5 kg/m²) compared to patients with both DTC and T2DM (55 ± 5.2 years, 25.1 kg/m²). Patients with both DTC and T2DM received higher cumulative doses of radioiodine (200 mCi ± 25) over a longer duration (14 months) compared to patients with DTC and without T2DM (180 mCi ± 20, 12 months). The prevalence of hypertension, arrhythmias, and myocardial infarctions was higher in patients with DTC and without T2DM than in patients with both DTC and T2DM. Statistical analysis revealed significant variations in hypertension incidence ($p < 0.001$) and myocardial infarction occurrence ($p = 0.03$) between the groups. Multivariate regression analysis showed an independent association of T2DM with a higher risk of hypertension ($p < 0.001$) and myocardial infarction ($p = 0.015$) among DTC patients.

Conclusion:
The study highlights the importance of considering cardiovascular risks associated with radioiodine therapy in DTC patients, particularly those with T2DM. Personalized treatment strategies balancing cancer management and cardiovascular risk mitigation are crucial for optimizing patient outcomes.

Recommendations:
Clinicians should adopt a multidisciplinary approach integrating endocrinology, oncology, and cardiology to optimize the management of DTC patients with T2DM.

Keywords: *Differentiated Thyroid Cancer, Radioiodine Therapy, Type 2 Diabetes Mellitus, Cardiovascular Risks*
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INTRODUCTION.

The interplay between differentiated thyroid cancer (DTC), type 2 diabetes mellitus (T2DM), and the cardiovascular implications of cumulative radioiodine doses presents a complex clinical scenario that necessitates a nuanced understanding of endocrinology, oncology, and cardiology. DTC, the most common form of thyroid malignancy, often requires a therapeutic approach that includes radioiodine therapy for remnant ablation or treatment of metastatic disease [1]. However, the cumulative doses of radioiodine used in these treatments have raised concerns regarding potential cardiovascular risks, especially in people with pre-existing conditions such as T2DM, a known risk factor for cardiovascular diseases (CVD).

T2DM exacerbates the risk of developing cardiovascular complications due to a combination of hyperglycemia, insulin resistance, and the presence of other cardiovascular risk factors such as dyslipidemia and hypertension. The management of DTC in people with T2DM thus requires careful consideration of the potential cardiovascular risks associated with cumulative radioiodine doses. Research indicates that radioiodine therapy, while effective for the treatment of DTC, may contribute to oxidative stress, inflammation, and endothelial dysfunction, all of which are pivotal in the pathogenesis of atherosclerosis and subsequent cardiovascular events [1, 2].

Furthermore, studies have proposed that the cardiovascular risk related to radioiodine therapy may be dose-dependent, with higher cumulative doses leading to an elevated risk of cardiovascular morbidity and mortality. This is particularly relevant for patients with T2DM, who already have an elevated baseline risk for cardiovascular complications [3, 4].

The management strategies for DTC in the context of T2DM, therefore, often involve a careful balance between the effective treatment of thyroid cancer and the minimization of cardiovascular risks, highlighting the importance of personalized medicine and the need for ongoing research into safer and more effective therapeutic approaches. The cardiovascular implications of cumulative radioiodine doses in individuals with DTC and T2DM represent a significant concern that requires a multidisciplinary approach to patient care.

The study aims to investigate the cardiovascular effects related to cumulative doses of radioiodine therapy in patients diagnosed with differentiated thyroid cancer and comorbid Type 2 diabetes mellitus, with a focus on elucidating potential risks and outcomes for this patient population.

METHODOLOGY.

Study Design.

A retrospective cohort design.

Study Setting.

The study was conducted at Katihar Medical College, utilizing patient records from August 2022 to September 2023 for data collection.

Participants.

The study included 75 participants after implementing all the selection criteria.

Intervention.

- Category I: 60 females with DTC and without T2DM (DTC/−T2DM).
- Category II: 15 females with both DTC and T2DM (DTC/+T2DM).

Inclusion Criteria.

- Female patients diagnosed with DTC.
- Availability of complete medical records, including thyroid cancer treatment history and cardiovascular outcomes.
- Age range: 40 to 70 years.
- Non-smokers

Exclusion Criteria.

- Patients with a history of other types of thyroid cancer.
- Patients with pre-existing cardiovascular diseases before thyroid cancer diagnosis.
- Patients with incomplete medical records.

Bias.

To minimize bias, data collection, and analysis were conducted by researchers blinded to patient identities and specific treatment details.

Variables.

Variables included cumulative doses of radioiodine therapy, cardiovascular outcomes (e.g., hypertension, arrhythmias,

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myocardial infarction), age, BMI, thyroid cancer stage, duration of diabetes, and other relevant comorbidities.

Data Collection.

Patient data were gathered from electronic medical records, including demographic information, thyroid cancer diagnosis details, radioiodine therapy regimens, diabetes status, cardiovascular outcomes, and relevant clinical parameters. The total oral dosage of ThyroTop (131I sodium iodide) was more than 150 mCi (5.55 GBq). This total dosage was given across four rounds of 131I treatment, with an average duration of 12 months. ThyroTop131 was utilized in the treatment protocol. The dosage of 131I administered to this patient cohort adhered to clinical and diagnostic imaging recommendations outlined in the ATA (American Thyroid Association) and ETA (European Thyroid Association) guidelines [5, 6], ensuring compliance with safety measures [7].

Additionally, demographic data such as age, smoking habits, hypertension status, and body mass index (BMI), alongside records of daily levothyroxine dose per patient, blood count, ECG assessments of left ventricular function, and serum biochemical parameters including triglycerides, total cholesterol, alkaline phosphatase (ALP), total lipids, and ionized calcium (Ca2+), were collected from medical history. These data corresponded to the most current hospitalization, occurring six months after the last therapeutic dose of 131I. All hypertensive patients included received treatment with antihypertensive drugs, ensuring that their blood pressure remained within the normal range.

Statistical Analysis.

SPSS software version 18 was utilized for data analysis. Comparative analysis between two groups was performed using appropriate statistical tests (t-tests, chi-square tests). Multivariate regression analysis may be employed to adjust for potential confounders. Statistical significance was set at $p < 0.05$.

Ethical considerations.

The study protocol was approved by the Ethics Committee and written informed consent was received from all the participants.

RESULTS.

Table 1: Clinical features of the study population.

Characteristic	Category I	Category II	p-values
Age (years)	55 ± 5.2	60 ± 6.3	0.04
Body Mass Index (BMI)	25.1 kg/m²	28.5 kg/m²	<0.00,
Daily Levothyroxine Dose	100 mcg	150 mcg	0.02
Left Ventricular Function	Normal	Reduced	0.01
Blood Count	Within Normal Range	Mild Anemia	0.05
Total Cholesterol (mg/dL)	180	220	0.003
Triglycerides (mg/dL)	120	160	0.007
Total Lipids (mg/dL)	200	250	0.015
Alkaline Phosphatase (ALP)	70	80	0.10
Ionized Calcium (Ca^{2+})	4.5	4.6	0.25

The study enrolled a total of 75 female participants, categorized into two categories based on their diagnoses: 60 patients with DTC/−T2DM (Category I) and 15 patients diagnosed with both DTC/+T2DM (Category II).

In terms of demographic characteristics, the mean age of patients in Category I was 55 years (±5.2), while Category II had a mean age of 60 years, with a (±6.3). The BMI also varied between the two categories, with category I average BMI of 25.1 kg/m² and category II averaging 28.5 kg/m².

Regarding radioiodine therapy, patients in category I received a total dose of 131I sodium iodide ThyroTop averaging 180 mCi, (± 20), while those in category II received an average cumulative dose of 200 mCi (± 25). The duration of radioiodine therapy was slightly longer in category II, averaging 14 months compared to 12 months in category I.

In terms of cardiovascular outcomes, the incidence of hypertension, arrhythmias, and myocardial infarctions differed between the two categories. In category I, 16.7% of patients developed hypertension, 8.3% experienced arrhythmias, and 3.3% had myocardial infarctions. On the other hand, in category II, the prevalence of hypertension was notably higher at 53.3%, with 40.0% experiencing arrhythmias and 20.0% having myocardial infarctions.

Statistical analyses revealed significant differences between the groups. A chi-square test demonstrated a significant discrepancy in hypertension incidence between both categories, with a p-value less than 0.001. Nonetheless, there

had been no statistically significant difference in the incidence of arrhythmias among the two groups. Nonetheless, the occurrence of myocardial infarctions exhibited a significant difference, with a p-value of 0.03.
Further analysis using multivariate regression, adjusting for age, BMI, and duration of diabetes, indicated that the presence of T2DM was independently related to a greater risk of developing hypertension ($p < 0.001$) and myocardial infarction ($p = 0.015$) among patients with DTC.

DISCUSSION.

The study enrolled 75 female participants, divided into two categories based on their diagnoses: 60 patients with DTC/−T2DM (Category I) and 15 patients diagnosed with both DTC/+T2DM (Category II). Category II patients exhibited a higher average age (60 years ± 6.3) compared to Category I (55 years ± 5.2) and had a higher average BMI (28.5 kg/m²) than Category I (25.1 kg/m²).
Patients in Category II received a slightly higher cumulative dose of radioiodine therapy (200 mCi ± 25) over a longer duration (14 months) compared to Category I (180 mCi ± 20 over 12 months). Significant differences were observed in cardiovascular outcomes, with Category II displaying notably higher incidences of hypertension (53.3%), arrhythmias (40.0%), and myocardial infarctions (20.0%) compared to Category I.
Statistical analyses confirmed these differences, with a significant discrepancy in hypertension incidence between both categories ($p < 0.001$) and a significant difference in myocardial infarction occurrence ($p = 0.03$). These outcomes underscore the importance of considering comorbidities like T2DM in the management of thyroid cancer patients, especially regarding cardiovascular health.
Recent studies have shed light on the cardiovascular implications of cumulative radioiodine doses in individuals with DTC, particularly those with concurrent T2DM. One study highlighted the differential cardiovascular effects of elevated total doses of 131I in people with DTC with and without T2DM, underscoring the need for tailored therapeutic approaches in this patient population [8]. Another investigation delved into the inflammatory response to radioiodine therapy in women, revealing that the interplay between neutrophils and obesity might limit 131I uptake, suggesting a complex association between prescribed radioiodine activity, blood radioactivity, BMI, and inflammatory markers in patients with both DTC and T2DM [9].
Further research explored the role of peripheral circulating free DNA and the platelet-to-lymphocyte ratio in individuals undergoing radioiodine therapy, indicating potential biomarkers for assessing therapy outcomes in this unique cohort [10]. Additionally, a case report and literature review on late renal toxicity in patients treated with lenvatinib for radioiodine-refractory DTC highlighted the importance of cautious treatment initiation in people with pre-existing diabetes to prevent renal toxicity, suggesting an intricate balance between effective cancer treatment and the management of comorbid conditions [11].

GENERALIZABILITY.

Generalizing findings from this retrospective cohort study focused on female participants with differentiated thyroid cancer (DTC) and comorbid Type 2 diabetes mellitus (T2DM), necessitates caution due to its single-center design and reliance on medical records. Although valuable insights into cardiovascular outcomes associated with cumulative radioiodine therapy in this population were provided, broader applicability may be limited. Future research should replicate these findings in larger, multicenter studies involving diverse patient demographics to enhance generalizability.

CONCLUSION.

The study sheds light on the intricate correlation between DTC, T2DM, and the cardiovascular implications of cumulative radioiodine therapy. The findings underscore the importance of personalized treatment approaches that carefully balance cancer management with cardiovascular risk mitigation in DTC patients, particularly those with T2DM. The significantly higher prevalence of hypertension and myocardial infarction in DTC patients with T2DM highlights the need for vigilant cardiovascular monitoring and intervention strategies in this patient population. A multidisciplinary approach integrating endocrinology, oncology, and cardiology is essential for optimizing patient outcomes and minimizing cardiovascular morbidity and mortality in DTC patients with T2DM. Further research is warranted to explore novel therapeutic modalities aimed at mitigating cardiovascular risks associated with radioiodine therapy in this context.

LIMITATIONS.

The limitations of this study include a small sample population who were included in this study. The findings of this study cannot be generalized for a larger sample population. Furthermore, the lack of a comparison group also poses a limitation for this study's findings.

RECOMMENDATION.

Clinicians should adopt a multidisciplinary approach integrating endocrinology, oncology, and cardiology to

optimize the management of DTC patients with T2DM. Further research is warranted to explore safer and more effective therapeutic approaches addressing the cardiovascular implications of radioiodine therapy in this patient population.

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LIST OF ABBREVIATIONS.

DTC: Differentiated thyroid cancer
T2DM: Type 2 diabetes mellitus
CVD: Cardiovascular disease
BMI: Body Mass Index
ATA: American Thyroid Association
ETA: European Thyroid Association

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No funding was received.

CONFLICT OF INTEREST.

The authors have no competing interests to declare.

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