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High Sensitivity Cardiac Troponin T in Patients with Type 2 Diabetes Mellitus, Relation to Cardiac Metabolic Risk Factors: Hypertension and Truncal Obesity

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ABSTRACT
Background: Diabetes mellitus type 2 (T2DM) is a prevalent metabolic disease that predisposes to diabetic cardiomyopathy and cardiovascular diseases (CVD). High sensitivity cardiac troponin T (hs-cTnT) can determine who is most at risk for developing cardiovascular issues and diabetes.
Objective: To evaluate the relation between high-sensitive cardiac troponin T and cardiac metabolic risks (hypertension and truncal obesity) in patient with T2DM.
Patients and Methods: A prospective cohort study included 50 diabetic patients reached at the emergency units of Mansoura University Hospital and Al-Azhar University Hospital in Egypt, for one year-duration from May 2021 to May 2022. All of the patients had been subjected to physical examination, medical and family diabetes history. Laboratory tests, included hs-cTnT, and truncal obesity measurement also were reported.
Results: The biomarker hs-cTnT was found in 32 (64%) of the patients. A strong significant correlation was detected between hs-cTnT and systolic blood pressure (SBP), diastolic blood pressure (DBP), hypertension, and truncal fat by dual-emission X-ray absorptiometry (DXA); with *p-value* (0.007, 0.006, 0.006, 0.001) respectively. Besides, no significant correlation was detected between hs-cTnT and the duration of diabetes, RBG, HBA1c, and BMI. Furthermore, the mean truncal fat of study population that detected by DXA scan was ranged from 8 Kg to 24 Kg with mean $\pm$ SD = 14.5 $\pm$ 4.51 Kg. **Conclusion:** The biomarker hs-cTnT and truncal fat might be associated with cardiac metabolic risks in patient with T2DM.
Keywords: hs-cTnT, Truncal fat, Troponin T, T2DM, CVD.

INTRODUCTION
Type 2 diabetes mellitus (T2DM) is spreading more widely around the world, and it is strongly linked to atherosclerotic cardiovascular disease (CVD) [(1)]. A greater resting heart rate has recently been linked to an increased risk of mortality and cardiovascular issues in those with type 2 diabetes [(2)]. According to international diabetes federation (IDF), almost 537 million people ranged from (20-79 years) worldwide were living with diabetes in 2022 [(3)].

Furthermore, a higher risk of CVD was also associated with the duration of diabetes, hypertension, smoking, being underweight, overweight, or obese, and hypoglycemia [(4)]. Therefore, recent research suggests that in addition to glucose management, broad, adaptable intervention strategies, such as lifestyle modifications, hypertension control, and cholesterol lowering, are required for reducing morbidity and mortality associated with macrovascular disease [(5)].

A frequent biomarker for myocardial infarction is cardiac troponin T (cTnT) [(6)]. Because cTnI is only found in cardiac muscles, serum cTnI is employed as a specific cardiac damage diagnostic for acute myocardial infarction (AMI) [(7)]. However, it is raised not only in acute pathogenic situations, but also in chronic pathogenic conditions. Increasing cTnI levels have recently been spotted in patients with cardiomyopathy or chronic HF in the general population [(8)].
Furthermore, several studies have demonstrated a correlation between high-sensitivity cardiac troponin T (hs-cTnT) levels and the prevalence of atrial fibrillation (AF), in the general population, vascular risk factors and structural heart disease [(9-11)].
Measuring hs-cTnT may reveal an underlying pathophysiologic overlap between CVD and diabetes that other common risk variables could miss. Participants with higher baseline hs-cTnT levels had a higher incidence of diabetes [(12-13)].
In this study we aimed to evaluate the relation between high-sensitive cardiac troponin T and cardiac metabolic risks (hypertension and truncal obesity) in patient with T2DM.

PATIENTS AND METHODS
The study involved 50 patients with T2DM who were receiving antidiabetic treatment and arrived at the Emergency Departments of both Mansoura and Al-Azhar University Hospitals over a twelve months period (May 2021-May 2021).

The inclusion criteria of our study included patients with T2DM who were receiving antidiabetic treatment and presenting with acute coronary syndrome from both sexes. On the other hand, the exclusion criteria specified patients with chronic kidney, type 1 diabetes mellitus, cardiovascular system diseases history, and patients who were refusing enrollments in the study. All participants in the current study had a medical and family history of diabetes taking, physical examination, including general conditions (appearance, consciousness and decubitus), vital signs, regional examination, radiological tests, and laboratory investigation such as determination of hs-cTnT and measurement of truncal obesity.

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Estimation high-sensitive cardiac troponin (hs-cTnT) assay

It is a modification of the hs-cTnT test from the fourth generation. There was no modification made to the biotinylated capture antibody. The monoclonal mouse FAB fragment's constant C1 region was switched out for a human IgG C1 region to genetically change the detection antibody. A mouse-human chimeric detection antibody was the outcome [(14)].

By making this alteration, the sensitivity to interference from heterophilic antibodies was intended to be further decreased. The detecting antibody's variable region matched that of the fourth-generation test exactly. By raising the sample volume from 15 L to 50 L, the ruthenium concentration of the detection antibody, and reducing the background signal by altering the buffer, the analytical sensitivity was enhanced. The LoD (Limit of detection) was reduced to 0.003 ng/mL (3 ng/L), the 99th percentile cut-off point was raised to 0.014 ng/mL (14 ng/L), and the CV was reduced to 10% at 0.013 ng/mL (13 ng/L), all of which significantly improved the hs-cTnT assay's analytical performance [(9)]. Due to a lower LoD and greater accuracy, the hs-cTnT test was able to detect more moderate increases indicative of cardiac injury.

Cardiac troponin I was estimated using VIDAS® high-sensitive troponin I (TNHS), VIDAS®

Sensitivity high troponin I is a quantitative automated test that uses the ELFA technique and VIDAS® series hardware to measure human cardiac troponin I in human serum or plasma (Enzyme Linked Fluorescent Assay). A one-step enzyme immunoassay sandwich method is used in the test, along with a final fluorescence detection (ELFA). The Solid Phase Receptacle (SPR®) houses both the solid phase and the pipetting apparatus. The pre-dispensed, ready-to-use reagents for the experiment are included in the sealed reagent strips.

Estimation of truncal obesity

A Hologic Discovery A DXA scanner (Hologic Inc., Waltham, MA) was used to perform whole-body DXA scans, and Hologic APEX software, version 3.0, was used to analyse the results. The patient was instructed to lie face down on the scanning bed with their arms by their sides during the scan. The scanner's performance was tracked in accordance with a quality assurance process, and it was calibrated every day using a spine phantom. Total body fat, body fat percentage, and trunk fat mass were all factors in determining body composition. Total body fat minus trunk fat mass was used to compute non-trunk fat mass [(15)].

Ethical approval:

The study gained approval from the local Ethical Committee of Al-Azhar University Hospital and Mansoura University Hospital. All patients felt free to withdraw from the study at any time point, according to their request. Patient confidentiality was preserved, and the collected data were used only for scientific purposes. In addition, an informed written consent was obtained from all participants. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis

Statistical Package for the Social Sciences version 22 was used to evaluate the data collected (SPSS). Tables and graph were used to display the data. Continuous quantitative variables were expressed as the mean, standard deviation (SD), and range. Relative and absolute frequencies were used to express categorical qualitative variables (percentage). Pearson's correlation coefficient was calculated. P value < 0.05 was considered significant.

RESULTS

The current study included 50 (ranged from 36 to 72 years old) patients admitted to ICU, 32 (64%) of the patients were females and 18 (36%) were males. Furthermore, 14 (28%) of the patients were using insulin, 36 (72%) were using hypoglycemic drugs, 7 (14%) were using statin and 17 (34%) were using RAS inhibitor. The duration of diabetes ranged from 7 years to 30 years with mean $\pm$ SD = 12.6 $\pm$ 5.10 years.

The biomarker hs-cTnT was found in 32 (64%) of the patients. Correlations was done between hs-cTnT and various clinical parameters. A strong significant correlation was detected between hs-cTnT and SBP; DBP, hypertension, and truncal fat by DXA. In addition, there was no significant correlation was detected between hs-cTnT and the duration of diabetes, RBG, HBA1c, and BMI **(Table 1).**

Table (1): Correlation between hs-cTnT and clinical parameters in hs-cTnT detectable patients

Parameter	Pearson's r	p-value
DM duration	0.058	0.691
RBG	0.190	0.211
HA1C	0.100	0.489
BMI	0.159	0.271
SBP	0.375	0.007*
DBP	0.381	0.006*
Hypertension	0.384	0.006*
Truncal Fat by DXA	0.492	<0.001*

*: Significant

In addition, the mean truncal fat of study population that was detected by DXA scan is shown in table 2 and figure 1.

Table (2): Truncal fat of study population that was detected by DXA scan

Truncal fat by DXA	Minimum	Maximum	Mean + SD
	8	24	14.5 $\pm$ 4.51

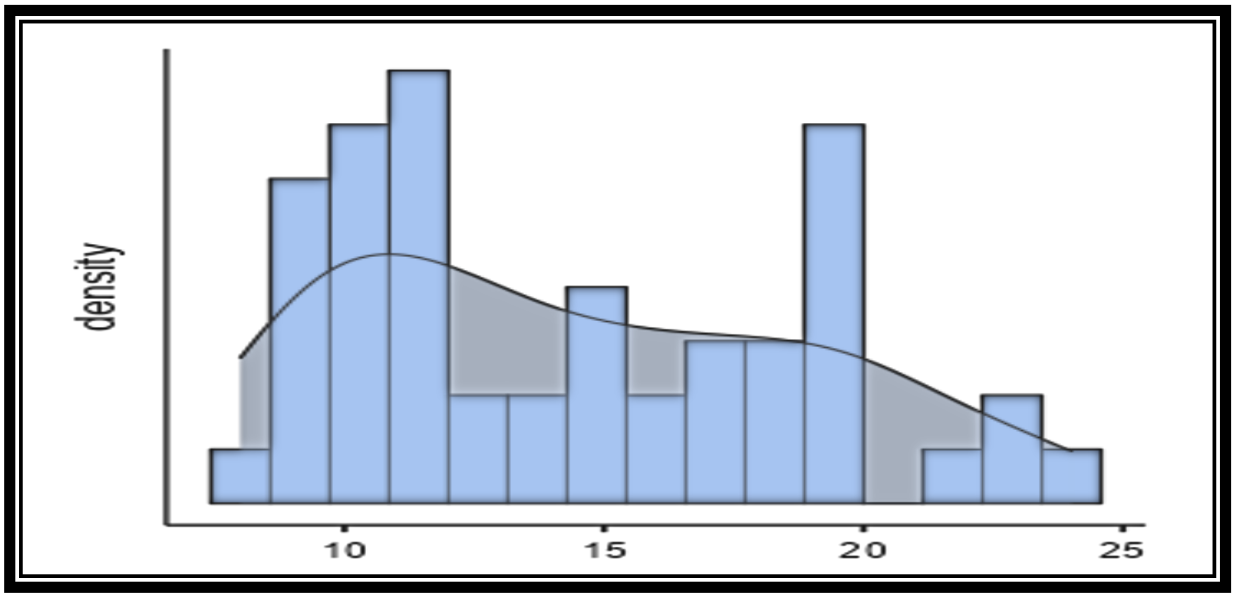

Figure (1): Truncal fat of study population by DXA Scan.

DISCUSSION

Chronically elevated troponin levels are an elevated risk of cardiovascular events and a symptom of subclinical myocardial damage, overall mortality, and a number of illnesses, including (pre) diabetes [13, 16].

The aim of the present study was to evaluate the relationship between high-sensitive cardiac troponin T and cardiac metabolic risks (hypertension and truncal obesity) in patient with type 2 DM.

50 patients with type 2 diabetes were enrolled in this prospective observational study (the mean duration of diabetes ranged from 7 years to 30 years with mean ± SD = 12.6 ±5.10 years) who received anti-diabetic medications (28% of cases were on insulin, 72% of cases received hypoglycemic drugs, 14% of cases received statins and 34% received RAS-inhibitor). They were recruited and assessed for eligibility from the Emergency Department of both Al-Azhar and Mansoura University Hospitals.

Our study showed that the mean age of the study population ranged from 36 years old to 72 years old with mean ± SD = 53.7 ± 10 years old. The majority of cases were females representing 64% of the patients and 36% were males. The mean days of hospital stay ranged from 2 to 3 days with mean ± SD = 2.3 ± 0.47 days.

Similar findings were found in **Hitsumoto's** [17] study on the factors that may be linked to elevated blood levels of hs-cTnT in 280 patients with type 2 DM, which showed that female patients made up 60.4% of the population and male patients made up 39.6%. However, the mean age of the recruited patients was higher than that of the current study (71±9-years-old). Additionally, **Bloomgarden** [18] found that people with diabetes have a 3-fold higher likelihood of being hospitalised than people without the condition.

The current study demonstrated that high sensitivity troponin-T (hs-cTnT) was detected in 32 (64%) of the patients. Chronic hyperglycemia reduces glomerular filtration, which in turn reduces troponin clearance. It also affects the heart's microcirculation, which causes microvascular damage and, in turn, ischemia, all of which contribute to an increase in troponin concentration.

Hitsumoto's [17] study on 280 patients with type 2 DM indicated that hs-cTnT was discovered in 244 (87.1%) patients, indicating a greater prevalence of increased hs-cTnT. In addition, a prior investigation by **Hallén *et al.*** [19] found that 131 participants (90%) had detectable hs-cTnT at baseline, and that 22 of these subjects (18% of the population overall) had levels that were higher than the 99th percentile for healthy controls (13.5 ng/L). Baseline levels were connected to traditional CV risk variables (age, renal function, gender). Additionally, **Everett *et al.*** [20] study on 512 diabetic women reported that hs-cTnT was detectable (≥0.003 μg/L) in 45.5% of diabetic women.

With a median level of 13 ng/L, **Witkowski *et al.*** [13] showed that prediabetics had a high prevalence of hs-cTnT. Also, a greater risk of long-term unfavourable cardiovascular events was also demonstrated in stable prediabetic subjects with subclinical myocardial necrosis as determined by hs-cTnT. Furthermore, **Takahashi *et al.*** [21] population-based cohort analysis on 30193 Japanese cases revealed that patients with hypertension and diabetes mellitus had greater hs-cTnT levels than persons without these diseases.

A study by **Hendriks *et al.*** [22] on 1133 type 2 diabetic patients reported that 513 patients (45%) passed away during the median follow-up of 11 (7–14) years, 218 (42%) of them passed away from cardiovascular reasons. Only 23% of patients with undetectable levels of hs-cTnT (3 ng/L) passed away,

compared to 58% of patients with low detectable levels (3–14 ng/L) and 84% of patients with elevated levels (14 ng/L).

Hillis *et al.* [23] found that 18% of 3862 type 2 diabetic patients had a significant cardiovascular event (combined cardiovascular mortality, nonfatal myocardial infarction, or nonfatal stroke), and 18% passed away within a median of 5 years of follow-up. For hs-cTnT, the hazard ratio for cardiovascular events and mortality was 1.50 (95% CI 1.36, 1.65) and 1.52 (95% CI 1.37, 1.67), respectively.

Our study revealed no significant correlation was detected between hs-cTnT and the duration of diabetes (p value>0.05).

Hallén *et al.* [19] found a substantial association between hs-cTnT levels at two-time intervals (baseline and 2-year follow-up) ($r = 0.92$, p value > 0.001). Furthermore, the probability of hospitalisation increased stepwise by quartiles of hs-cTnT assessed at baseline ($p = 0.058$).

Similarly, a previous study by **Fu *et al.* [24]** found a significant connection between type 2 diabetes and high hs-cTnT levels in models of multivariate logistic regression (p value < 0.05). In multivariate linear regression models, elevated levels of postprandial blood glucose ($p < 0.05$) rather than fasting blood glucose ($p > 0.05$) discovered the important relationship with higher hs-cTnT levels.

Zheng *et al.* [25] found that the patients with diabetes mellitus were substantially more likely to have detectable hs-cTnT (3.0 pg/mL) and increased hs-cTnT (13.3 pg/mL) than patients with normal glucose tolerance or impaired glucose control, and hs-cTnT was predicted by fasting blood glucose level independently.

However, **Rubin *et al.* [26]** discovered that higher HbA1c levels are connected to heightened hs-cTnT levels in people who do not have clinically evident coronary heart disease, indicating that hyperglycemia has implications on the development of clinical atherosclerotic coronary disease as well as myocardial damage.

A study by **Whelton *et al.* [12]** previously observed that patients who had raised baseline hs-cTnT levels had a higher likelihood of developing diabetes, suggesting that hs-cTnT testing may reveal an underlying pathophysiologic connection between diabetes and cardiovascular diseases. Similarly, **Madan *et al.* [27]** reported that isolated systolic hypertension was independently associated with hs-cTnT.

Moreover, **Høiseth *et al.* [28]** discovered a substantial association between arterial hypertension and hs-cTnT. Elevated hs-cTnT levels, coupled with vascular remodeling and increased pressure, may compromise microvascular function in patients with hypertension (even in the absence of ischemic heart disease).

CONCLUSION

The biomarker hs-cTnT was not shown to significantly correlate with the duration of diabetes, RBG, HBA1c, and BMI. In addition, a substantial association was shown to exist between hs-cTnT and SBP; DBP, hypertension, and truncal fat.

Conflict of interest: We confirm for the submission's originality and confirm that it is not already being considered by another publisher.

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