Journal of Metabolic Syndrome
ISSN: 2167-0943

Milwidsky, et al., J Metabolic Synd 2014, 3:3
DOI: 10.4172/2167-0943.1000151

Research Article Open Access

Multiplicity of Dysmetabolic Components in Males is Associated with Elevated Cardiac Troponin T Concentrations

Assi Milwidsky[1*], Arie Steinvil[2], Itzhak Shapira[1], Sivan Letourneau-Shesaf[1], Rona Limor[3], Sharon Greenberg[1], Shlomo Berliner[1] and OriRogowski[1]

[1]*Department of Medicine "C" and "E", of the Tel Aviv Sourasky Medical Center, Affiliated to the Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel*

[2]*Department of Cardiology, of the Tel Aviv Sourasky Medical Center, Affiliated to the Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel*

[3]*Department of Laboratory, of the Tel Aviv Sourasky Medical Center, Affiliated to the Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel*

***Corresponding author:** Dr. Assi Milwidsky, Department of Internal Medicine "E", The Tel-Aviv Sourasky Medical Center, 6 Weizman St, Tel Aviv, 64239, Israel, Tel: 972-52-7360437 ; Fax: 972-3-6973885 ; E-mail: assi_mil@hotmail.com

Received date: June 11, 2014; **Accepted date:** June 23, 2014; **Published date:** June 26, 2014

Abstract

Background: There are multiple lines of evidence to suggest that chronic myocardial stress and increased cardiovascular risk is associated with the enhanced release of cardiac troponin in patients with ischemic heart disease. However, there is a paucity of data regarding the relation of cardiac troponin to the metabolic syndrome (MetS), a leading risk factor for cardiovascular morbidity.

Methods: We determined the prevalence of measurable high sensitivity cardiac Troponin T (hs-cTnT) with a fifth generation assay and evaluated its association to the presence of the male metabolic syndrome (MetS) components in a cohort of patients undergoing a health survey in the Tel Aviv Medical Center Inflammation Survey (TAMCIS).

Results: A total of 1,641 men with no known cardiovascular disease were recruited and MetS was diagnosed in 330 (20.1%) of them. Hs-cTnT concentrations were higher in patients with MetS ($p<0.001$). The number of MetS components was associated with the concentration ofhs-cTnT ($p<0.001$ for trend). The 99th percentile concentration was 27.6 ng/l and 16.03 ng/l for those with and without the MetS, respectively. Five percent of patients with MetS had hs-cTnT concentrations higher than the 99th percentile predetermined by the manufacturer.

Conclusions: The MetS in males is associated with higher levels of hs-cTnT than the general population, with each component increasing hs-cTnT value.

Keywords: Metabolic syndrome; Troponin T; Cardiovascular risk

Introduction

There are multiple lines of evidence to suggest that chronic myocardial stress and increased cardiovascular risk is associated with the enhanced release of cardiac troponin in patients with coronary artery disease and in apparently healthy individuals [1-4]. Increased Hs-cTnT levels had been described in some of the metabolic syndrome (MetS) components [5-7] and particularly in patients with diabetes and obesity. However, there is paucity of data regarding the relation of hs-cTnT to the MetS as a complex, and whether increasing number of MetS components is associated with increased troponin concentration and elevated cardiovascular risk.

We determined the prevalence of measurable hs-cTnT with a fifth generation assay, recently introduced into the Tel-Aviv Medical Centre Inflammation Survey (TAMCIS), [8-10] a relatively large health screening program of the Tel-Aviv Medical Center in Tel-Aviv, Israel. We then evaluated associations of cTnT with the MetS and its distinctive components.

Methods

Study population

We have analyzed data that has been collected during the period of September 2010 to June 2012 in the TAMCIS, a registered data bank of the Israeli ministry of justice [8-10]. This is a relatively large cohort of individuals who attended our medical center for a routine annual check-up and who gave their written informed consent for participation according to the instructions of the local ethics committee. Included were1,891 male subjects for whom hs-cTnT were obtained. Based on the medical history found in the medical charts of TAMCIS, We later excluded 250 subjects due to any previous vascular event (myocardial infarction, pulmonary emboli, venous thromboembolism or a cerebrovascular accident), a previous diagnosis of ischemic heart disease or immunosuppressive therapy, steroidal or antibiotic treatment or recent acute infection or previous malignancy. Following these exclusions the study group was comprised of 1,641 apparently healthy males with no known cardiovascular disease.

Definition of the metabolic syndrome

The diagnosis of the metabolic syndrome was based on the joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention, National Heart, Lung, and Blood

Institute, American Heart Association, World Heart Federation, International Atherosclerosis Society, and International Association for the Study of Obesity [11]. In short, elevated waist circumference was defined as ≥94 cm (37 inches) in men as recommended for Europe and the Middle East. Elevated triglycerides (TG) were defined as ≥150 mg/dl (1.7 mmol/l) or on drug treatment for elevated triglycerides; reduced HDL-C was defined as <40 mg/dL (1.0 mmol/l, all participants were men) or on drug treatment for reduced HDL-C; elevated blood pressure was defined as ≥130 mm Hg systolic blood pressure or ≥85 mm Hg diastolic blood pressure or on antihypertensive drug treatment in a patient with a history of hypertension; elevated fasting glucose was defined as ≥100 mg/dl (5.55 mmol/l), drug treatment of elevated glucose was an alternate indicator. Smokers were defined as individuals who smoked at least 5 cigarettes per day while past smokers had quit smoking for at least 30 days prior to examination.

Laboratory methods

All blood samples were drawn following a 12 hour fasting period. Cardiac troponin T levels were measured with a novel pre-commercial highly sensitive assay (Elecsys Troponin T; Roche Diagnostics, Indianapolis, IN), as described previously [4]. The lower limit of detection of the novel assay is 3ng/L. The coefficient of variation of <10% is 13 ng/L and the 99th percentile value for cTnT published by the manufacturer is14 ng/L.

The complete blood count parameters were measured using a coulter STKS electronic counter. Quantitative fibrinogen was measured by the Claus [12] method, and the high sensitivity C-Reactive Protein (hs-CRP) was performed by using the Behring BN II Nephelometer (DADE Behring, Marburg, Germany) analyzer and a method described by Rifai et al. [13]. Triglycerides were measured by an adaptation of the fossati 3 step enzymatic reactions with the Bayer Advia 1650 chemistry analyzer. Serum triglycerides were determined calorimetrically with an enzyme that produces hydrogen peroxide [14]. HDL-C was determined by a method developed by Izawa et al as described before [15] using the Bayer Advia 1650 chemistry analyzer. LDL-C was derived from the measured concentrations of total cholesterol, HDL-C and triglycerides using the Fried wald equation: LDL-C=Total Cholesterol – HDL-C – TG/5.

Statistical Analysis

All continuous variables were displayed as mean (standard deviation [SD]), while categorical variables were displayed as number (percent) of patients within each group. Since the hs-cTnT displayed non-normal distribution, all analyses were non-parametric. Comparison of all continuous variables was done using the Mann-Whitney U analysis while for categorical variables the Fischer exact test was used.

The level of significance used for all analyses was two-tailed ($p<0.05$). The SPSS 19.0 statistical package was used to perform all statistical analyses (SSPS Inc., Chicago, IL, USA).

Results

We have presently included a total of 1,641 men, at a mean age ± SD [range] of 47.4 ± 10.1 [24-78] years. Demographic, medical history and laboratory values of subjects with and without the MetS are presented in Table 1. A diagnosis of the Metabolic Syndrome, according to the harmonized criteria was present in 330 (20.1%) subjects.

		Metabolic Syndrome		P Value
		No	Yes	
Medical history	Age	46.5	50.9	0.59
	Hypertension, %	21.7	61.2	<0.001
	Current smoking, %	11	9.4	<0.001
	Diabetes mellitus, %	1.5	15.5	<0.001
	Systolic blood pressure, mm hg	124	134	0.22
	Diastolic blood pressure, mm hg	78	84	0.49
Laboratory data	Total cholesterol, mg/dL	184	186	0.2
	HDL-C, mg/dL	51	40	<0.001
	Triglycerides, mg/dL	101	179	<0.001
	eGFR, mL/min	80.5	77.8	<0.001
	hs-CRP, mg/L	1.9	2.8	0.008
	Hemoglobin A1C, %	5.4	5.8	<0.001
Medications	Aspirin, %	4.3	14.8	<0.001
	Antihypertensive, %	10	30	<0.001
	Statins, %	14.4	28.5	<0.001

Table 1: Baseline characteristics according to the metabolic syndrome

HDL-C – high density lipoprotein cholesterol, eGFR – estimated glomerular filtration rate, hs-CRP – high sensitive C-Reactive Protein.

The percentage of subjects with one, two, three, four and five components of the MetS was 20%, 31%, 28.8%, 14% and 5.1%, respectively. Mean and percentile values of hs-cTnT were calculated for each group. The 75th percentile for hs-cTnT was3.88 ng/l and 5.4 ng/l for patients without and with MetS, respectively. The 25th and 50th percentiles were 3.0 for both. The 99th percentile was 16.03 ng/l and 27.6 ng/l for those without and with MetS, respectively. Data is presented in Table 2. Waist ≥ 94 cm (37 inches). HTN (hypertension) - ≥ 130 mm Hg systolic blood pressure or ≥ 85 mm Hg diastolic blood pressure or on antihypertensive drug treatment. IFG (Impaired Fasting Glucose) - ≥ 100 mg/dl (5.55 mmol/l) or †on glucose lowering treatment. TG (elevated triglycerides) - ≥ 150 mg/dl (1.7 mmol/l) or on drug treatment for elevated triglycerides. HDL (reduced HDL-c) was defined as <40 mg/dL (1.0 mmol/l) or on drug treatment for reduced HDL-C.

		Number of patients	Hs-cTnT concentrations ng/L					
			Min	Max	25th percentile	Median	75th percentile	99th percentile
Positive MetS comp. *	Waist	959	3.0	35.8	3.0	3.0	4.7	19.1
	HTN	783	3.0	35.8	3.0	3.0	5.0	18.9
	IFG†	120	3.0	26.6	3.0	3.2	6.9	25.0
	TG	343	3.0	35.8	3.0	3.0	4.5	27.4
	HDL	355	3.0	35.8	3.0	3.0	4.1	18.5
Number of positive MetS comp.*	0	329	3.0	43.8	3.0	3.0	3.0	10.6
	1	509	3.0	35.8	3.0	3.0	3.8	16.6
	2	473	3.0	24.6	3.0	3.0	4.7	16.3
	3	229	3.0	28.7	3.0	3.0	5.4	25.6
	4 or 5	101	3.0	35.8	3.0	3.0	6.0	35.6
MetS	No	1,311	3.0	43.8	3.0	3.0	3.9	16.0
	Yes	330	3.0	35.8	3.0	3.0	5.4	27.6

Table 2: hs-cTnT concentrations relation to Metabolic Syndrome components

Hs-cTnT: High sensitive cardiac troponin T, MetS: Metabolic syndrome, Min: Minimum, Max- maximum, Comp: components.

* Positivity of MetS components was based upon the harmonized criteria.

A graphical presentation of hs-cTnT concentrations in individuals with and without the MetS is presented in figure 1. As can be seen, subjects with the MetS had higher measurements of hs-cTnT ($p<0.001$).

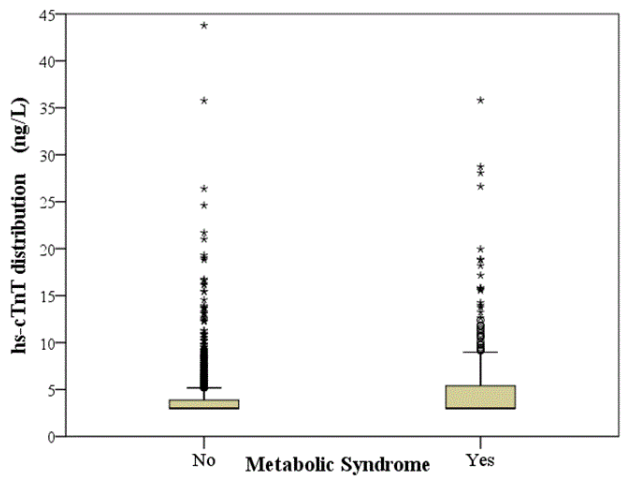

Figure 1: Increased hs-cTnT concentration for subjects with the metabolic syndrome

Box and whisker plots of the distribution of hs-cTnT: the bottom and top of the box represent the first and third quartiles (25th and 75th percentile), and the bold band inside the box is the second quartile (the median). The ends of the whiskers represent the lowest datum still within 1.5 the inter quartile range (IQR) of the lower quartile, and the highest datum still within 1.5 IQR of the upper quartile. The circles represent outliers in the range of 1.5 to 3 IQR and the stars represent extreme outliers, of more than 3 IQR.

The number of MetS components was associated with the level of hs-cTnT ($p<0.001$ for trend), with each additional component (e.g. increased waist circumference) increasing the hs-cTnT level (Figure 2).

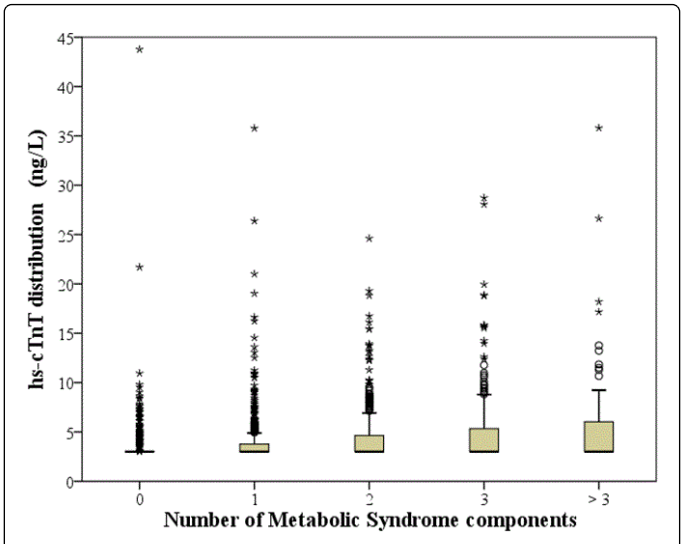

Figure 2: A trend for higher mean hs-cTnT concentration with increasing number of Metabolic syndrome components

Hs-cTnT concentrations for each of the metabolic syndrome components and according to the number of positive Mets components are presented in Table 2.

Box and whisker plots of the distribution of hs-cTnT: the bottom and top of the box represent the first and third **quartiles** (25^{th} and 75^{th} percentile), and the bold band inside the box is the second **quartile** (the **median**). The ends of the whiskers represent the lowest datum still within 1.5 the inter quartile range (IQR) of the lower quartile, and the highest datum still within 1.5 IQR of the upper quartile. The circles represent outliers in the range of 1.5 to 3 IQR and the stars represent extreme outliers, of more than 3 IQR.

Discussion

The main finding of the current study is the association of dysmetabolism with the eventual presence of chronic myocardial stress, expressed by elevated hs-cTnT concentrations in males with no known cardiovascular disease.

This is the first large report suggesting that the MetS is associated with elevated hs-cTnT concentrations in adult men. The findings are consistent with a previous work studying the relation of hs-cTnT and the MetS in children and adolescents [6], showing that circulating concentrations of hs-cTnT in obese children with MetS are higher than those without the MetS and the non-obese children. A previous work in adults [16] found that hs-cTnT was directly associated with metabolic risk (P<0.001). However the study did not compare levels of cardiac troponin between those with and without the MetS, nor did it use the harmonized criteria of the metabolic syndrome, currently the most widespread definition used.

We have presently shown that the baseline concentrations of hs-cTnT are influenced by the components of the MetS, a factor not currently included in the depiction of troponin elevation.

Hs-cTnT concentration was above the 99th percentile for almost 5% of patients with the MetS and for

Concentrations increase in relation to increasing number of MetS components, which was statistically significant (p<0.001 for trend). In accordance with the finding of Wallace et al. of four predictors of elevated cTnT levels, one of which was diabetes mellitus [17] The above association might raise a multiple-hit theory for the presence of increased cTnT concentrations in apparently healthy individuals, meaning that MetS components may have an additive value in increasing hs-cTnT levels, a marker of myocardial stress. Despite of being too limited to find out what is the main determinant for the presence of enhanced cTnT concentrations in the peripheral blood, the results do point toward a multiple-hit possibility. Looking at the potential contributors for the metabolic health, one might accept that similar factors are those patients the 99th percentile was 27.6 ng/l, substantially higher than that determined by the manufacturer, at 14 ng/l. This finding is consistent with a previous work by Saunders et.al. [4] who found that actual 99th percentile concentrations were substantially higher than those determined by the manufacturer, a fact that further stresses that need to calibrate threshold values based on local empiric observations.

An additional significant finding of the present study is the association between multiplicities of dysmetabolic risk factors with absolute hs-cTnT concentrations. Although troponin levels were mildly lower in the group with 5 MetS components compared to those with 4 components, this group comprised of only 84 (5.1%) participants, thus the statistical significance of such minor variability could not be reliably analyzed. Therefore we determined the trend for hs-cTnT involved in the process of cardiomyocytes damage.

Limitations

Only male patients were included in the current analysis because most of the TAMCIS survey population consists of males, unfortunately we were under powered to include females in the study. In the statistical analysis we were unable to exclude factors closely related to the metabolic syndrome (e.g. hypertension, dyslipidemia and diabetes) or use a control group that would isolate their influence on troponin concentration without omitting major influences of the MetS itself. However, we examined patients with MetS as a group with multiple comorbidities by definition, thus an attempt to isolate one of its' critical components seems not necessary.

Conclusion

Elevated concentrations of cTnT might be present in the peripheral blood of men with the metabolic syndrome. The association with multiplicity of dysmetabolic risk factors point toward the possibility of a multiple-hit mechanism that is involved in cardiomyocytes damage. No one dysmetabolic component could be singled out as the most dominant in this report, suggesting the need to improve most, if not all, of the dysmetabolic components in order to protect against cardiomyocytes damage.

References

1. Wang TJ, Wollert KC, Larson MG, Coglianese E, McCabe EL, et al. (2012) Prognostic utility of novel biomarkers of cardiovascular stress: the Framingham Heart Study. Circulation 126: 1596-1604.
2. Omland T, de Lemos JA, Sabatine MS, Christophi CA, Rice MM, et al. (2009) A sensitive cardiac troponin T assay in stable coronary artery disease. N Engl J Med 361: 2538-2547.
3. Leistner DM, Klotsche J, Pieper L, Stalla GK, Lehnert H, et al. (2012) Circulating troponin as measured by a sensitive assay for cardiovascular risk assessment in primary prevention. Clin Chem 58: 200-208.
4. Saunders JT, Nambi V, de Lemos JA, Chambless LE, Virani SS, et al. (2011) Cardiac troponin T measured by a highly sensitive assay predicts coronary heart disease, heart failure, and mortality in the Atherosclerosis Risk in Communities Study. Circulation 123: 1367-1376.
5. de Lemos JA, Drazner MH, Omland T, Ayers CR, Khera A, et al. (2010) Association of troponin T detected with a highly sensitive assay and cardiac structure and mortality risk in the general population. JAMA 304: 2503-2512.
6. Pervanidou P, Akalestos A, Bastaki D, Apostolakou F, Papassotiriou I, et al. (2013) Increased circulating High-Sensitivity Troponin T concentrations in children and adolescents with obesity and the metabolic syndrome: a marker for early cardiac damage? Metabolism 62: 527-531.
7. Zheng J, Ye P, Luo L, Xiao W, Xu R, et al. (2012) Association between blood glucose levels and high-sensitivity cardiac troponin T in an overt cardiovascular disease-free community-based study. Diabetes Res Clin Pract 97: 139-45.
8. Rogowski O, Shapira I, Peretz H, Berliner S (2008) Glycohaemoglobin as a determinant of increased fibrinogen concentrations and low-grade inflammation in apparently healthy nondiabetic individuals. Clin Endocrinol (Oxf) 68: 182-189.
9. Rogowski O, Shapira I, Shirom A, Melamed S, Toker S, et al. (2007) Heart rate and microinflammation in men: a relevant atherothrombotic link. Heart 93: 940-944.

10. Steinvil A, Shirom A, Melamed S, Toker S, Justo D, et al. (2008) Relation of educational level to inflammation-sensitive biomarker level. Am J Cardiol 102: 1034-1039.
11. Alberti KG, Eckel RH, Grundy SM, et al. (2009) Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation 120: 1640-1645.
12. CLAUSS A (1957) [Rapid physiological coagulation method in determination of fibrinogen]. Acta Haematol 17: 237-246.
13. Rifai N, Tracy RP, Ridker PM (1999) Clinical efficacy of an automated high-sensitivity C-reactive protein assay. Clin Chem 45: 2136-2141.
14. Fossati P, Prencipe L (1982) Serum triglycerides determined colorimetrically with an enzyme that produces hydrogen peroxide. Clin Chem 28: 2077-2080.
15. Steinvil A, Shapira I, Ben-Bassat OK, Cohen M, Vered Y, et al. (2010) The association of higher levels of within-normal-limits liver enzymes and the prevalence of the metabolic syndrome. Cardiovasc Diabetol 9: 30.
16. Siervo M, Ruggiero D, Sorice R, Nutile T, Aversano M, et al. (2010) Angiogenesis and biomarkers of cardiovascular risk in adults with metabolic syndrome. J Intern Med 268: 338-347.
17. Wallace TW1, Abdullah SM, Drazner MH, Das SR, Khera A, et al. (2006) Prevalence and determinants of troponin T elevation in the general population. Circulation 113: 1958-1965.