Serum Leptin in Ischemic Heart Disease Patients with and without Significant Diastolic Dysfunction in Lean and Obese Patients; Cross-Sectional Study

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ABSTRACT
Background: Ischemic heart disease is a major cause of heart failure and has a poor prognosis. Addressing behavioral risk factors like obesity and overweight helps avoid most cardiovascular illnesses. The satiety hormone leptin reduces appetite and regulates energy. **Aim of the study**: Leptin levels in lean and obese patients with ischemic heart disease, with or without diastolic dysfunction, were compared.
Methods and Patients: Between June 2019 and November 2020, 140 ischemic patients from Ain Shams University hospitals were included. History, examination, Duke Coronary Artery Disease score, Body Mass Index, serum leptin, and echocardiography were recorded. Patients were placed into four BMI and diastolic function groups plus the control group. A: lean ischemic patients without significant diastolic dysfunction, B: lean ischemic patients with diastolic dysfunction (II-IV), C: obese ischemic patients without significant diastolic dysfunction, Group D: obese ischemic patients with diastolic dysfunction, and E was a control group.
Results: A positive correlation was seen between serum leptin and Duke score in all ischemia groups (n=140) ($p<0.001$). Serum leptin was higher in diastolic dysfunction groups (n=70) than in non-dysfunction groups (N=70) (Group B 25.7%, Group D 28.6% vs Group A 5.7%, Group C 8.6%, and Control Group (n=35) 0.0%).
Conclusion: Leptin independently increases CAD risk. In CAD patients, elevated leptin was related to diastolic dysfunction.
Keywords: Serum leptin, Diastolic dysfunction, coronary artery disease.

INTRODUCTION
The satiety hormone leptin inhibits hunger and regulates energy balance, so the body does not elicit hunger reactions when it does not need energy [1,2]. One of the most essential adipocytokines, it regulates energy balance and appetite [3].

Most authors showed that leptin fights obesity. Leptin therapy may prevent obesity, hypertension, and diabetes even before they occur [4]. Leptin regulates blood pressure, lipolysis, immunological modulation, wound healing, and angiogenesis in addition to metabolism [5]. Leptin triggers the sympathetic nervous system, thrombosis, and platelet aggregation, which causes ischemic heart disease [6]. Males had higher serum leptin levels in ischemic heart disease than females, according to a 2014 meta-analysis [7].

However, **Puurunen et al.** found that hyperleptinemia is linked to left ventricular diastolic dysfunction in ischemic heart disease patients and may be the sole cause of congestive heart failure in obese people. Leptin modulation triggers inflammatory response by activating TNF-α via p38 and JNK MAPK pathways, perhaps linked to recurrent myocardial infarction and death [8].

AIM OF STUDY
Measuring and comparing serum leptin levels in ischemic heart disease patients with and without diastolic dysfunction, in both obese and lean patients.

PATIENTS AND METHODS
From June 2019 to November 2019, 140 ischemic patients and 35 control subjects were enrolled from two centers (Ain Shams University, Cardiology Department wards, and outpatient clinic, and Misr University for Science and Technology, Cardiology Department wards and outpatient clinic) in a cross-sectional study.

Unstable ischemic patients, diabetic patients, uncontrolled hypertensive patients, impaired function EF < 50 % and patients with pulmonary hypertension were not enrolled in the study.

Ethical Considerations
- **The research protocol was following the declaration of Helsinki.**
- **Approval was obtained from the Ethical Committee at Ain Shams University.**
- **All participants had informed written consent with consideration of adequate privacy and confidentiality.**

History taking, with particular emphasis on:
Risk factors include hypertension, diabetes, smoking, etc.

Investigations confirming ischemia: CA, MSCT, or history of PCI, then Duke modified score was calculated to detect the degree of ischemia.

Duke CAD index:
The Duke CAD index, originally developed by David F. Kong, is an angiographic score that hierarchically assigns prognostic weights (0-100) based on the anatomic location, stenotic severity, and extent of coronary artery lesions in an individual patient [9].

Table (1) Duke CAD index: Angiographic scoring system.

Extent of CAD	Prognostic Weight (0-100)
No CAD ≥50%	0
1 VD 50%-74%	19
>1 VD 50%-74%	23
1 VD (75%)	23
1 VD (≥95%)	32
2 VD	37
2 VD (both ≥95%)	42
1 VD, ≥95% proximal LAD	48
2 VD, ≥95% LAD	48
2 VD, ≥95% proximal LAD	56
3 VD	56
3 VD, ≥95% in at least one	63
3 VD, 75% proximal LAD	67
3 VD, ≥95% proximal LAD	74
Left main (75%)	82
Left main (≥95%)	100

CAD indicates coronary artery disease; VD, vessel disease; and LAD, left anterior descending coronary artery.

General examination, with particular emphasis on:
BMI, as normal weight and obese. The cut-off range for BMI is as follows: normal weight (18.5-22.99); obese patient was considered in our study >30. BMI was calculated using the formula (Weight (Kg)/Height (m^2). Blood pressure was measured using a mercury sphygmomanometer.

Cardiac examination including inspection, palpation, and auscultation.
Full laboratory investigations including Random blood samples (5 mL) were taken for CBC, lipid profile, KFTs, cardiac enzymes, HbA1c, and serum leptin. Blood was allowed to clot, then withdrawn and centrifuged at 3500 rpm for 10 minutes. Serum was isolated and kept at −80°C using a standard technique. The mean serum leptin concentration in obese individuals was 52.8±24.6 ng/mL (range 28.2-77.4 ng/mL; P<0.001), while in lean patients, it was 12.7±6.1 ng/mL (range 6.6-18.8 ng/mL) as found by previous study[10].

12 lead surface ECG was recorded for all the patients included in the study population as well as the controls.

Echocardiography with particular emphasis on diastolic dysfunction grading:
Grade I (impaired relaxation): Reduced E wave velocity causes E/A reversal (ratio < 1.0). The E wave deceleration time exceeds 200 ms. While tissue Doppler e/e' ratio is normal, Grade I diastolic dysfunction may occur in adults over 60 as a non-pathological result.

Pathological Grade II (pseudonormal): High left atrial pressures. The E/A ratio is normal (0.8 +- 1.5), the deceleration time is normal (160-200 ms), however the e/e' ratio is high (8-15). The E/A ratio is <1 with Valsalva.

Grade III (reversible restrictive): High left atrial pressures. A "restrictive filling pattern" is characterized by an E/A ratio > 2.0, a deceleration duration < 160 ms, and an e/e' ratio >15. The E/A ratio decreases to < 1.0 with Valsalva.

Grade IV (fixed restrictive): Poor prognosis and high left atrial pressures. The E/A ratio is >2.0, deceleration time is minimal, and e/e' is >15 [11].

Significant diastolic dysfunction was defined as diastolic dysfunction grade (II–IV).

After a full assessment of each individual, patients were divided into five groups: Group A lean ischemic patients without significant diastolic dysfunction, Group B lean ischemic patients with diastolic dysfunction (II-IV), Group C obese ischemic patients without significant diastolic dysfunction, Group D obese ischemic patients with diastolic dysfunction (II-IV), Group E was a control group lean nonischemic without diastolic dysfunction.

Statistical Analysis
- The SPSS software version 29 was used.
- Numerical variables were expressed as mean, standard deviation (SD), and range.
- Qualitative variables were expressed as frequency and percentage.
- Statistical significance was set at a level of $p < 0.05$; and ≤ 0.001 was considered highly significant.

RESULTS
In our study, higher leptin levels were related to higher E/E' independent of BMI: (10.0 vs 15.0) in the lean group, (10.0 vs 21.0) in the obese group, and (5.0 vs 7.0) in the control group. The E/A ratio and leptin level were positively correlated regardless of BMI E/A (0.7 vs. 2.5) in the lean group, 0.6 vs. 1.9 in the obese group, and 0.4 vs. 0.8 in the control group. We found that CAD patients with higher plasma leptin levels have reduced left ventricular diastolic performance regardless of BMI.

There were no significant differences between the studied groups regarding **Age and sex**.

Table (2): Age and sex among the study groups

Variables		Group-A Lean IND (N=35)	Group-B Lean ID (N=35)	Group-C Obese IND (N=35)	Group-D Obese ID (N=35)	Group-E Control INID (N=35)	p
Age (years)	Mean±SD	55.0±8.4	53.7±7.2	55.1±8.8	57.6±7.5	56.8±8.5	^
	Range	39.0–75.0	40.0–70.0	40.0–74.0	44.0–71.0	43.0–77.0	0.259
Sex	Male	23 (65.7%)	27 (77.1%)	26 (74.3%)	22 (62.9%)	24 (68.6%)	#
	Female	12 (34.3%)	8 (22.9%)	9 (25.7%)	13 (37.1%)	11 (31.4%)	0.676

^ANOVA test, #Chi square test

The body mass index (BMI) was significantly higher in the obese patient groups compared to the lean groups.

Table (3): BMI (kg/m^2) among the study groups

Measures	Group-A Lean IND (N=35)	Group-B Lean ID (N=35)	Group-C Obese IND (N=35)	Group-D Obese ID (N=35)	Group-E Control INID (N=35)	p
Mean±SD	23.1±0.8b	22.8±1.0b	32.4±1.0a	32.0±1.0a	22.9±0.9b	^
Range	20.7–24.5	20.7–24.5	30.5–34.1	30.6–34.2	21.1–24.8	<0.001*

^ANOVA test, #Chi square test, *Significant. Homogenous groups by post-hoc Bonferroni test had the same letter

Serum Leptin levels were significantly higher in the obese patient groups as well as with diastolic dysfunction.

Table (4): Serum leptin (ng/mL) among the study groups

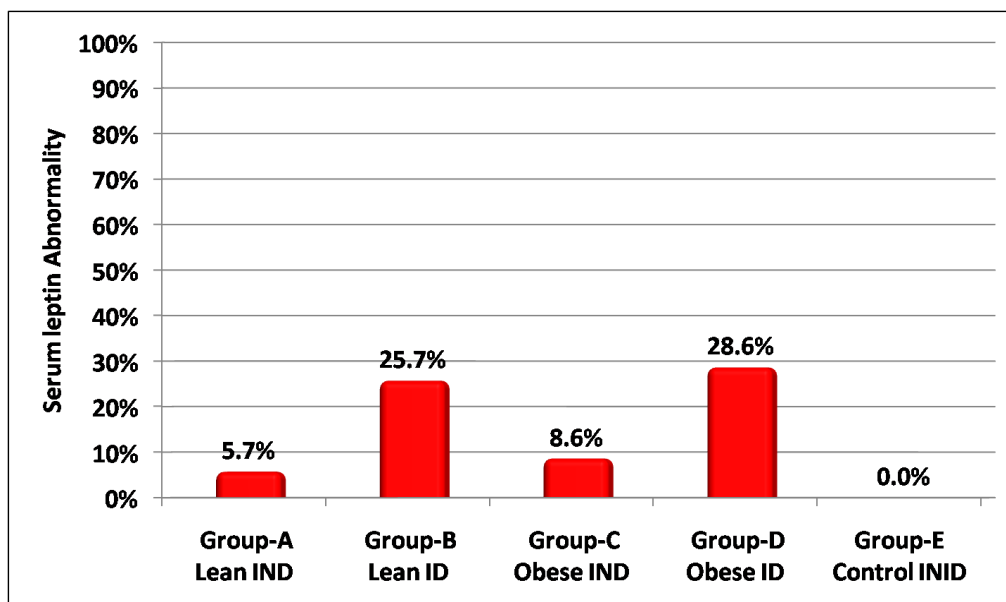| Measures	Group-A Lean IND (N=35)	Group-B Lean ID (N=35)	Group-C Obese IND (N=35)	Group-D Obese ID (N=35)	Group-E Control INID (N=35)	^p
Mean±SD	17.8±2.1d	23.4±1.1c	55.4±10.9b	65.2±9.8a	13.1±2.7e	<0.001*
#P-values of factors effects						
Ischemia	0.023*	Dysfunction	<0.001*	Obesity		<0.001*

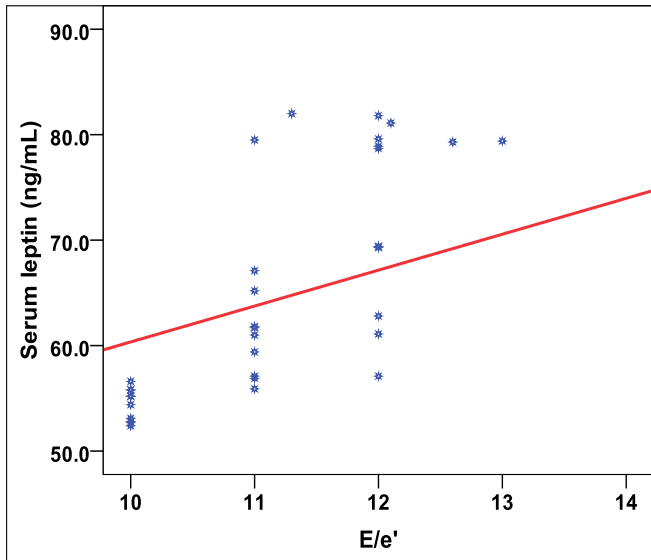**Figure (1): Serum leptin abnormality among the study groups**

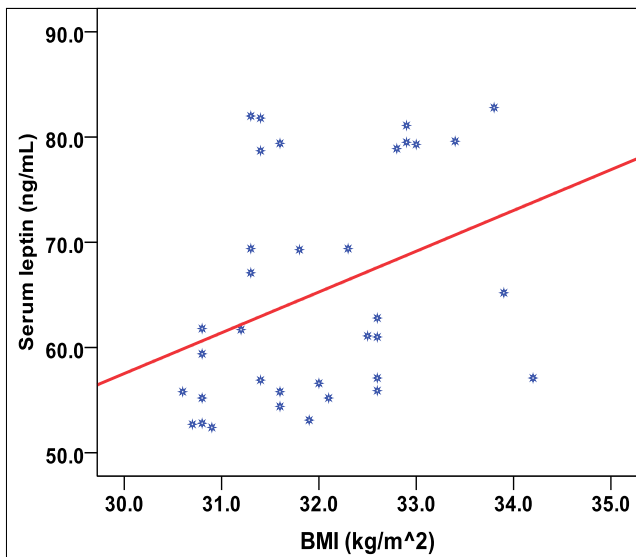**Figure (2): Correlation between serum leptin and E/e' in the obese dysfunction group.**

Figure (3): Correlation between serum leptin and BMI in the obese dysfunction group

DISCUSSION

The biggest cause of death worldwide is cardiovascular disease. Ischemic heart disease is a major cause of heart failure and has a grave prognosis. Addressing behavioral risk factors like obesity and overweight helps avoid most cardiovascular illnesses. The satiety hormone leptin reduces appetite and regulates energy [1].

In our study, higher leptin levels were related to higher E/E' independent of BMI: (10.0 vs 15.0) in the lean group, (10.0 vs 21.0) in the obese group, and (5.0 vs 7.0) in the control group. The E/A ratio and leptin level were positively correlated regardless of BMI E/A (0.7 vs. 2.5) in the lean group, 0.6 vs. 1.9 in the obese group, and 0.4 vs. 0.8 in the control group. We found that CAD patients with higher plasma leptin levels have

reduced left ventricular diastolic performance regardless of BMI.

In another study, **Puurunen et al.** examined plasma leptin and performed echocardiography on 1,601 CAD patients, 42% of whom had type 2 diabetes. Higher leptin levels were associated with greater E/E' (9.43 vs. 11.94 in the lowest and highest leptin quartile, respectively; p=0.018 for trend) but not LV dimensions or ejection fraction. E/A decreased (1.15 vs. 1.06; p=0.037). Obesity and other confounding variables did not affect these correlations [8].

Fontes-Carvalho et al. also found similar results. However, they believed leptin and diastolic dysfunction were sex-specific. Diastolic dysfunction was more likely in women with the highest leptin tertile after multivariate correction (adjusted odds ratio: 3.06; 95% CI: 1.44–6.49). They also found that leptin secretion is linked to obesity, diastolic dysfunction, and heart failure [9].

A cross-sectional study by **Nugraha et al.** found a significant positive association (r= 0.5892, p<0.001) between leptin levels and E/mean e' in young adult obese patients with a mean age of 30.75±7.25 years. In our multicenter investigation, the mean age was 56.8±9.5 years, with a substantial positive correlation (r=0.599, p<0.001) between leptin level and E/e' score, with a mean score of 11.4±1.9 and leptin levels of 65.2±10.8 ng/ml [10].

CONCLUSION

Leptin has been identified as a distinct and autonomous risk factor for the development of coronary heart disease. Furthermore, there is a correlation between increased levels of leptin in the bloodstream and compromised diastolic function of the left ventricle in individuals with coronary artery disease (CAD), regardless of their obese status and other factors that may influence the results.

Limitations It is imperative to conduct well-designed prospective cohort studies rather than relying on cross-sectional research to assess if leptin has a role as either a consequence or a causative factor in coronary heart disorders.

- **Conflicts of Interest:** None of the authors have a conflict of interest to declare.

- **Funding resources:** No funding was received from any institution.

REFERENCES
1. **Behairy N, Homos M, Ramadan A et al. (2014):** Evaluation of the left ventricle diastolic dysfunction in ischemic heart disease by CMR: Correlation with echocardiography and myocardial scarring. The

Egyptian Journal of Radiology and Nuclear Medicine, 45:1099-1104.

2. **Larsen B, Laughlin G, Cummins K *et al.* (2017):** Adipokines and severity and progression of coronary artery calcium: findings from the Rancho Bernardo study. Atherosclerosis, 265:1-6.

3. **Karthick R, Nalini D, Manohar G *et al.* (2012):** Obesity, inflammation, and acute myocardial infarction - Expression of leptin, IL-6, and high sensitivity-CRP in Chennai based population. Thromb J.,10:1–6.

4. **Gumanova N, Grilova N, Chernushevich O *et al.* (2017):** Ratios of leptin to insulin and adiponectin to endothelin are sex-dependently associated with the extent of coronary atherosclerosis. Biomarkers, 22: 239-245.

5. **Chen M, Hsu B, Lee C. (2016):** Hyperleptinemia positively correlates with cardiometabolic syndrome in hypertensive patients. Int J Clin Exp Pathol., 9: 12959-12967.

6. **Chen M, Wang J, Hsu B. (2018):** Association between hyperleptinemia and cardiovascular outcomes in patients with coronary artery diseases. The Clin Risk Manag., 14: 1855-1862.

7. **Chai S, Feng S, Xiao L *et al.* (2014):** Leptin and coronary heart disease: a systematic review and meta-analysis. The International Journal of Applied and Basic Nutrition Sciences, 2014, 11: 324-331.

8. **Puurunen V, Lepojarvi E, Piira (2016):** High plasma leptin levels are associated with diastolic function in patients with coronary artery disease. Peptides, 84:17-21.

9. **Miller J, Carlos D, Marc A *et al*. (2008):** Diagnostic Performance of Coronary Angiography by 64-Row CT. The New England journal of medicine, 359: 2324-2336.

10. **Fontes-Carvalho R, Pimenta J, Bettencourt P *et al.* (2015):** Association between plasma leptin and adiponectin levels and diastolic function in the general population. Expert Opin Ther Targets, 19:1283-91.

11. **Nugraha F, Akbar M, Toni M *et al.* (2019):** Correlation between leptin with diastolic function in young adult obesity. Acta Cardiologia Indonesiana, 5: 54-61.