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Research Article

Leptin and Adiponectin and their Relationship to Drugs, Hypertension, Diabetes, and Body Mass Index in Left Ventricular Heart Failure Patients

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Abstract

Background: Heart failure is a burgeoning healthcare problem.

Objective: Evaluating leptin and adiponectin, proteins which have opposite effects on the cardiovascular system, as predictors of left ventricular systolic heart failure severity.

Methods: Blood samples were collected from 60 subjects with mild-to-severe heart failure and 14 healthy volunteers after 12-hour fasting. Serum leptin and adiponectin levels were assessed by quantitative sandwich enzyme immunoassay.

Result: Significant positive correlations were observed between serum adiponectin and EF (r = 0.372, p = 0.003), statin intake (simvastatin and atorvastatin; r = 0.273, p = 0.025) and beta blocker intake (bisoprolol and carvedilol; r = 0.276, p = 0.033). Adiponectin showed significant positive correlation with age (r = 0.609, p = 0.035), metformin (r = 0.993, p = 0.044), in subjects with hyperleptinemia and consumption of clopidogrel (r = 0.648, p = 0.019) and statin (r = 0.126, p = 0.049) in those with hypoleptinemia. Diabetes mellitus patients showed, significant positive correlations between the leptin/adiponectin ratio with gender (r = 0.386, p = 0.018) and EF (r = 0.369, p = 0.029). Hypertensive patients (n = 28) showed, significant positive correlations were observed with serum leptin and BMI (r = 0.16, p = 0.005), and with serum adiponectin and EF (r = 0.372, p = 0.003), statin (r = 0.272, p = 0.035) and beta-blocker (r = 0.276, p = 0.033).

Conclusion: Different parameters were similar in both groups; differences were seen only when the patients were clustered in groups based on other factors, for e.g., diabetes.

Keywords: *Adiponectin; Diabetes; Heart Failure; Hypertension; Leptin*

Introduction

Heart failure (HF) is a burgeoning health and healthcare problem. Currently about 26 million individuals worldwide have HF [1]. It is a clinical syndrome that results from various structural or functional disorders, which impair the ability of the ventricles to fill (diastole) or eject blood (systole), thus rendering the heart unable to pump blood at a rate sufficient to meet the metabolic demands of the body [2]. Although there is no single cause for HF, several risk factors like increasing age, male gender, family history, hypertension, coronary heart disease (CHD), valvular heart disease, left ventricular hypertrophy, hyperlipidemia, overweight/obesity and diabetes increase the chances of its development [3,4].

Leptin is a 167-amino acid protein with a molecular mass of 16 kDa. Its name is derived from the Greek word 'leptos' which means 'thin'. Leptin, an important signal in regulation of adipose tissue mass and body weight, operates by inhibiting or stimulating food intake and energy expenditure through the release of several neurotransmitters by acting on the receptors sites in the hypothalamus [5,6]. Leptin may be structurally similar to proteins of the long-chain helical cytokine family, including IL-2, IL-12 and growth hormone [7]. It is involved in the regulation of reproduction, immune function, blood pressure, renal function, bone formation, angiogenesis and vascular disorders [8]. The biologic activities of leptin on target tissues are carried out through selective binding to a specific leptin receptor [9].

Plasma leptin and its soluble receptor exhibit elevated levels in patients with advanced congestive heart failure, indicating that leptin may participate in the catabolic state [10]. It has also been postulated that it could play a major role in cardiovascular disease (CVD) through the activation of the sympathetic nervous system [11]. Leptin has potentially atherogenic, thrombotic and angiogenic effects [12,13]. Further, it stimulates vascular inflammation, causes oxidative stress, and vascular smooth muscle hypertrophy that may contribute to the pathogenesis of type 2 diabetes mellitus, hypertension, atherosclerosis, and coronary heart disease [12,14,15].

Adiponectin is synthesized predominantly not only by adipocytes but also by skeletal muscle, endothelial cells (EC) and cardiomyocytes. It is abundant in the plasma representing 0.01% of plasma proteins (3 - 30 mg/ml) [16]. It is a 244 amino acid protein belonging to the collagen superfamily [17]. It exists as a 30 kDa molecule (high-molecular-weight form, HMW) or as smaller globular fragments. The HMW version predominates in plasma [18]. Adiponectin have anti-inflammatory, antidiabetic, anti-obesity, and antiatherogenic properties [19], in addition to improving vascular function and modulating pathologic cardiac remodeling [20]. Adiponectin levels are reduced in obesity, coronary artery disease (CAD), hypertension, and insulin resistance [20]. However, increased adiponectin levels are seen in patients with chronic heart failure, which might reflect greater cardiovascular risk and inflammation [21]. The release of adiponectin into the circulation is associated with the severity of HF symptoms [22], disease severity, and mortality [23]. Elevated adiponectin levels likely reflect an attempt to mitigate proinflammatory or impaired metabolic states and demonstrate a balance between the protective and harmful pathways in left ventricular (LV) systolic dysfunction and HF. The current study was conducted to assess the role of leptin and adiponectin as predictors of left ventricular systolic heart failure severity in Libyan patients.

Subjects and Methods

This study was carried out in Biochemistry Department, Faculty of Medicine, Benghazi University from January 2014 to 2015. Ethical committee clearance was obtained from the Benghazi University Ethics Committee, and informed consent was obtained from all the subjects.

Subjects with mild-to-severe heart failure diagnosed according to WHO criteria and who had visited the Benghazi Cardiac Center were included in the study. The control group comprised of apparently healthy individuals and were recruited from the University of Benghazi. A total of 60 subjects fulfilled the inclusion criteria (46 males and 14 females) and were included in the study (cases) and 14 healthy individuals (5 females and 9 males) constituted the control group. In all study subjects, ejection fraction (EF) was assessed by echocardiography either on the day of recruitment or at a time interval not exceeding 6 months. Subjects with heart failure with concomitant renal failure were excluded from the study.

Demographic and anthropometric parameters were recorded. Blood samples collected from all subjects after an overnight fast (12hr). Blood samples (5 mL each) were drawn into vacutainer and plastic tubes. The blood was allowed to clot, centrifuged at 500 g for 15 minutes within 30 min of sample collection and serum was collected and stored at (60°C) until assayed. Serum leptin and adiponectin levels were assessed by quantitative sandwich enzyme immunoassay.

Results

The baseline characteristics were similar in both study groups, as shown in table 1. No significant difference in any of the parameters including BMI, serum leptin and serum adiponectin levels between the two case and control groups. When comparing serum leptin and adiponectin levels in relation with ejection fraction (EF), adiponectin shows a significant correlation with respect to EF however, the serum leptin levels were inconsistent and non-significant with respect to EF as shown in table 2. Among cases, a significant positive correlation was observed between serum adiponectin and EF (r = 0.372, p = 0.003], statin intake (simvastatin and atorvastatin; r = 0.273, p = 0.025) and beta blocker intake (bisoprolol and carvedilol; r = 0.276, p = 0.033]. There was a significant positive correlation between leptin adiponectin ratio and EF (r = 0.348, p = 0.006), gender (r = 0.316, p = 0.014) and IDCM (r = 0.334, p = 0.009; Table 3).

Parameter	Cases (N = 60)	Control (N = 14)	CI 95%	p-value
BMI	28.52 ± 4.09	20.49 ± 5.62	5.42 - 10.63	0.0001*
Leptin	10.27 ± 6.69	13.31 ± 1.51	-0.64 - 0.56	0.0969NS
Adiponectin	21.67 ± 13.6	19.51 ± 4.2	-5.20 - 9.52	0.5604NS

Tables 1: *Levels of Leptin and Adiponectin in cases and controls.*

	EF > 35	EF < 35	CI 95%	p-value
Adiponectin	13.55 ± 6.57	24.24 ± 11.85	-15.86 - -5.51	0.0001
Leptin	11.04 ± 5.43	8.71 ± 7.28	-1.08 - 5.74	0.1172

Table 2: *Leptin and Adiponectin levels in relation with Ejection fraction.*

	Adiponectin		Leptin adiponectin Ratio	
	R	P	R	P
Ejection fraction	0.372	0.003	0.348	0.006
Statin	0.273	0.025	0.091	0.448
Beta blocker	0.276	0.033	0.170	0.194
Gender	0.198	0.130	0.316	0.014
IDCM	0.170	0.193	0.334	0.009

Table 3: *Correlation of serum adiponectin and leptin adiponectin ratio with EF, statin, beta blocker, gender and IDCM.*

In patients with diabetes and non-diabetic individuals, adiponectin showed non-significant correlations (p = .7133), while leptin showed a significant correlation (p = .0013) as shown in table 4. Further, in subjects with diabetes mellitus, a significant positive correlation was observed between the leptin/adiponectin ratio with gender (r = 0.386, p = 0.018) and EF (r = 0.369, p = 0.029), while in those who did not have diabetes mellitus, there was a significant positive correlation only with EF (r = 0.563, p = 0.005; Table 5). In subjects with hypertension (n = 28), a significant positive correlation was observed with serum leptin and BMI (r = 0.16, p = 0.005), and with serum adiponectin and EF (r = 0.372, p = 0.003), statin (r = 0.272, p = 0.035) and beta blocker (r = 0.276, p = 0.033; Table 6). When comparing serum adiponectin (p = 0.3080) and leptin (p = 0.9863) levels in hypertensive patient and non-hypertensive individuals, there is a non-significant correlation as shown in table 7.

	Diabetic	Non-Diabetic	CI 95%	p-value
Adiponectin	22.47 ± 15.43	21.13 ± 10.77	-5.92 - 8.60	0.7133
Leptin	16.36 ± 6.55	10.37 ± 6.17	2.44 - 9.53	0.0013

Table 4: *Serum Adiponectin and Leptin levels in relation with Diabetes.*

	Subjects with diabetes mellitus (n = 36)		Subjects without diabetes mellitus (n = 24)	
	R	P value	R	P value
Gender	.386	.018	0.223	0.294
IDCM	.344	.037	0.254	0.231
EF	.369	.029	.563	.005

Table 5: *Correlation of leptin/adiponectin ratio with gender, IDCM and EF in subjects with diabetes mellitus vs. those without.*

	Serum leptin		Serum adiponectin	
	R	P value	R	P value
BMI	0.16	0.005	0.084	0.523
EF	0.097	0.459	0.372	0.003
Statin	0.061	0.646	0.273	0.035
Beta-blocker	0.130	0.320	0.276	0.033

Table 6: *Correlation of serum leptin and serum adiponectin with BMI, EF, statins and beta-blockers.*

	HTN	Non HTN	CI 95%	p-value
Adiponectin	19.73 ± 10.46	23.37 ± 15.96	-10.72 - 3.44	0.3080
Leptin	10.50 ± 6.46	10.47 ± 6.96	-3.45 - 3.51	0.9863

Table 7: *Serum Adiponectin and Leptin levels in relation with Hypertension.*

In subjects without hypertension, there was a significant correlation of serum adiponectin with EF (p = 0.002). Further, the leptin/adiponectin ratio had a positive significant correlation with gender (r = 0.316, p = 0.014), IDCM (r = 0.334, p = 0.009) and EF (r = 0.348, p = 0.006) in subjects with hypertension, and with EF (r = 0.434, p = 0.017) and beta-blockers (r = 0.391, p = 0.027) in those with no hypertension (Table 8).

	Subjects with no hypertension		Subjects with hypertension	
	R	P value	R	P value
Gender	.217	.233	0.316	0.014
IDCM	.192	.291	0.334	0.009
EF	.434	.017	0.348	0.006
Beta-blocker	.391	.027	0.170	0.194

Table 8: *Correlation of leptin/adiponectin ratio with gender, IDCM, EF, beta-blockers in subjects with hypertension vs. those without hypertension.*

Discussion

The results of our study demonstrate that in patients with chronic, stable systolic HF, beta-blocker therapy correlated significantly with lower adiponectin levels, especially in non-obese patients. Statin and LVEF were also significant determinants of adiponectin values. In a study by Tengiz., *et al*. [24] the presence of significant correlation between adiponectin levels and LVEF was demonstrated. Further, the authors emphasize the need to take into account the impact of medications, particularly beta-blockers and statins, when evaluating adiponectin levels in patients with heart failure.

In chronic heart failure, adiponectin levels are increased as a compensatory mechanism to overcome insulin resistance and exaggerated energy expenditure [25,26]. In heart failure subjects, there is increased glucose oxidation and decreased fatty acid oxidation, while in normal subjects, the heart uses fatty acids as main energy source, which provides 60 - 70% of the energy needed to maintain cardiac work [27]. Therefore, in the failing human heart, there is a shift from fatty acids to glucose utilization as a source of energy. However, if this shift is inadequate, the failing heart suffers from a state of chronic energy deprivation. Therefore, adiponectin may be released by adipose tissue to compensate for this impaired metabolic state [26]. Adiponectin regulates metabolism and insulin sensitivity, at least in part, by promoting the phosphorylation and activation of AMP-activated protein kinase (AMPK) (a stress-responsive kinase) in skeletal muscle, liver, and adipocytes. Use of beta-blockers, especially with vasodilating properties in HF patients may improve the metabolic profile by improving insulin sensitivity [28].

Further, beta-blockers decrease adiponectin levels in heart failure. Previous studies have demonstrated that carvedilol-induced improved LVEF correlated with changes in BMI [28]. In a pilot study by Lainscak., *et al*. [29] there was a significant increase in body fat following 6 months of beta-blocker treatment, with a decreased in the adiponectin levels.

The present study demonstrated the positive effects of simvastatin and atorvastatin on adiponectin values. These findings are in line with those of previous studies, which reported that simvastatin therapy significantly decreased adiponectin levels without corresponding change in BMI8 and there was a reduction in the serum adiponectin levels with atorvastatin [30].

In the current study, we observed that in hyperleptinemia subjects, there was a significant positive correlation of serum adiponectin levels with age and metformin, while in hypoleptinemia subjects, this correlation was with clopidogrel and statins. These findings are similar to the study by Schautz., *et al*. excepting clopidogrel [31]. Schautz., *et al*. further demonstrated that age-related changes in leptin and adiponectin levels are opposite to each other and partly independent of adiposity and body fat distribution. Studies have also reported that treatment with metformin lowers circulating adiponectin levels [32,33].

We also observed that serum adiponectin level has a statistically significant correlation with BMI in hyperadiponectinemia. Takiguchi., *et al*. demonstrated that lower BMI was associated with higher circulating levels of adiponectin [34]. In subjects with IDCM and CAD, serum adiponectin has a significant positive correlation with EF, aspirin, and statin treatment. A study by Agnieszka Kaplon-Cieslicka., *et al.* is the first study as per our knowledge to demonstrate an association of lower serum adiponectin concentration with higher serum thromboxane B2 level in patients treated with aspirin [35], these findings further substantiate the results of our study.

In the present study, we compared between subjects with diabetes mellitus with those without. Serum adiponectin and leptin in subjects with diabetes have a non-significant positive correlation with all parameters assessed in this study. The findings of a study by Baldasseroni., *et al*. [36] confirms our observations that adiponectin increased across the different ACC/AHA chronic HF stages, but this change is less evident in subjects with diabetes. In subjects with no diabetes mellitus, treatment with clopidogrel, aspirin and statins significantly reduced serum adiponectin level. In a study by Aprahamian., *et al.* [37] high levels of adiponectin were observed in subjects with heart failure and hypertension, while in the present study, there was a significant positive correlation between serum adiponectin and LVEF in subjects with and without hypertension, but this correlation was observed with treatment with statins and beta-blockers in only those with hypertension.

In human heart failure, circulating leptin is increased independently of weight [38]. Our study confirms these observations. In our study, we also assessed the correlation between serum leptin and adiponectin levels and the other parameters in subjects with EF < 35 and > 35. A significant positive correlation was observed between serum leptin levels and metformin treatment in subjects with EF < 35 and with gender in those with EF > 35. A significant positive correlation was observed with serum adiponectin and normal coronary arteries in subjects with EF > 35, similar to the findings of the study by Nakamura., *et al*. [39] which demonstrated that serum adiponectin levels are significantly lower in patients with acute coronary syndrome compared to patients with stable angina and healthy controls. Further, we observed that in our study, there was a significant correlation between leptin/adiponectin ratio and gender, LVEF and IDCM subjects with heart failure with hypertension and with beta-blockers in those without hypertension.

Conclusion

It is apparent from the present study that the different parameters measured are similar in patients and control subjects. The differences were seen only when the patients were clustered in groups based on other factors, for instance, those that were diabetics compared to those that were non-diabetics. In addition, correlation studies showed effects of different factors on leptin, adiponectin and on one another. Therefore, more extensive studies are required, recruiting more patients to have the ability to fix a group of factors and study one factor at a time.

Conflict of Interests

The authors declare that there are no conflicts of interest regarding this manuscript.

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