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Relationship between pro-anti-inflammatory cytokines, T-cell activation and CA 125 in obese patients with heart failure

Authors' Contribution:
A Study Design
B Data Collection
C Statistical Analysis
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Summary

Background: This researcher previously found that serum levels of some inflammatory cytokines are elevated in patients with cardiovascular disease (CVD). Hence, this study investigated the relationship between circulating levels of pro-anti-inflammatory cytokines, T-cell activation marker and carbohydrate antigen 125 (CA 125) for the first time in obese Egyptian patients with heart failure (HF).

Material/Methods: This study included 60 HF patients, and 30 normal controls, with age range 50–70 years. HF patients were divided into 2 groups: non-obese mild HF according to clinical status (New York Heart Association Class) (NYHA class I/II) (n =20) and obese severe HF (NYHA class III/IV) (n=40). Serum pro-anti-inflammatory cytokine levels (TNF-α, IL-6, and IL-10), T-cell activation marker (sIL-2R/CD25), and CA 125; tumor marker were measured by ELISA.

Results: Serum levels of TNF-α, IL-6, and IL-10 as pro-anti-inflammatory cytokines, sIL-2R/CD25 as T-cell activation marker, and CA 125 as tumor marker were significantly higher in HF patients than in normal controls. Moreover, serum levels of TNF-α, IL-6, sIL-2R/CD25, and IL-10, as well as CA 125 were significantly higher in the obese than in the non-obese mild HF patients. Correlation analysis showed that CA 125 was positively related to BMI, TNF-α, IL-6, and sIL-2R/CD25 in the HF patients group.

Conclusions: These findings show that CA 125 is markedly elevated in HF patients, and is correlated with serum TNF-α, IL-6, and sIL-2R/CD25 levels. Therefore, we can conclude that CA125, being a tumor marker, is closely related to the cytokine system.

key words: heart failure • obesity • pro-anti-inflammatory cytokines • T-cell activation • CA 125

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Background

CA 125 is a tumor marker classically associated with ovarian cancer, and recent studies have reported increased serum CA125 levels in HF patients [1]. Due to their pivotal role in inflammation, cytokines are classified as pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), and anti-inflammatory cytokines, such as IL-10 [2,3]. The specificity of cytokine action is provided by their unique receptors, where interaction of cytokines with cytokine receptors is a necessary component of their physiologic role; moreover, cytokine receptors exist in either membrane-bound and/or soluble forms [4].

Activated T-cells release IL-2 and a soluble form of the IL-2 receptor, consisting of the α chain of the αβγ complex that constitutes the functional membrane receptor. sIL-2R/CD25 has a low affinity for IL-2 and its anti-inflammatory activity is still poorly defined. It represents, however, a reliable marker of T-lymphocyte activation [5].

A recent study by Perik et al. [6] reported that circulating levels of the pro-inflammatory cytokines as TNF-α are elevated in patients with HF, that these proteins are associated with HF severity, and that increased levels of pro-anti-inflammatory cytokines have been shown to be associated with CVD, but no report has yet shown that inflammatory cytokines themselves lead to or are related to elevated serum CA 125 in obese HF patients. Therefore, our study aimed to measure blood levels of CA 125 and the pro-anti-inflammatory cytokine, together with T-cell activation marker sIL-2R/CD25, in patients with HF, and to determine the potential relationship between this tumor marker and the severity of HF in obese subjects. Furthermore, we sought to determine whether sIL-2R/CD25 is a marker of autoimmune involvement or of non-specific inflammation in advanced HF. This study is one of our group's multiple studies on HF in Egypt, exploring the mechanisms and consequences related to this disorder in a developing country, as well as to find the best diagnostic and/or prognostic tests.

To optimize the cost-benefit ratio, we need to refine our tools for identifying patients with increased cardiovascular risk harboring plaques prone to rupture. Ideally, high-resolution plaque imaging is combined with 1 or several emerging biomarkers that provide incremental information about plaque biology and patient prognosis. Adding to the wealth of experimental, clinical, and epidemiological evidence that identified inflammation as an integral element throughout the different stages of atherosclerosis, biomarkers of inflammation have been validated in clinical trials.

Material and Methods

Subjects

The present study included 60 consecutive HF patients (average age 61.5 years, range 53–70 years) admitted to the Department of Cardiology, Ain Shams University, El-Demerdash Hospital, Cairo, Egypt. On admission, the diagnosis of CVD was based on medical history and initial work-up, which included physical examination, electrocardiogram, chest X-ray, and echocardiographic evaluation. Etiology of heart failure was ischemic heart disease (IHD) in 19 patients and dilated cardiomyopathy (CMP) in 41 patients.

Patients with renal failure, myocardial infarction within the previous 6 months, diabetes mellitus, infection or any inflammatory illness such as sepsis, malignancy, arthritis or connective tissue disease were excluded.

At the time of the evaluation, patients were being treated with angiotensin-converting enzyme (ACE) inhibitors, diuretics, aldosterone receptor antagonists, digoxin and/or nitrates. None were receiving antibiotics or anti-inflammatory drugs.

Thirty healthy age- and sex-matched volunteers served as a control group (average age 60 years, range 50–70 years). None of the healthy volunteers had any concomitant disease, and all physical and laboratory examination parameters were normal (Table 1).

Body mass index (BMI) was calculated as an index of the weight in kilograms divided by the square of the height in meters. Detailed characteristics of the study groups are presented in Table 1.

The study protocol was approved by the hospital ethics committee; all participants gave informed signed consent to participate in the study. The investigation conformed to the principles outlined in the Declaration of Helsinki.

After protocol approval, the study was conducted from February 2010 to July 2010.

Sample collection and blood tests

Blood was systematically taken from an antecubital vein shortly after admission to the hospital. Sera were aliquoted, a portion for FBG and creatinine determination as well as anti-cardiolipin-IgG by ORGENTEC Diagnostika (Germany), and another portion was stored at –80°C until assay.

Measurement of serum pro-anti-inflammatory cytokines

Serum cytokine levels were measured using commercially available enzyme-linked immuno-sorbent assay (ELISA) kits; TNF-α, IL-6, and IL-10 by AviBion, Helsinki (Finland), and sIL-2R/CD25 by Invitrogen Corporation, Carlsbad, California, USA.

Measurement of CA 125

Serum levels of CA 125 were measured using ELISA procedures carried out according to the manufacturer's instructions (Monobind Inc., USA).

Echocardiographic assessment

All patients underwent a 2-dimensional Doppler echocardiographic examination for measurement of left ventricular ejection fraction (LVEF) using the Simpson method and checking for the presence of pericardial fluid. All patients had a left ventricular ejection fraction of <40%. CHF was defined as typical chest pain on admission and typical ECG changes (ST segment depression ≥2 mm in at least 2 leads and/or negative T waves in at least 2 leads). Signs and symptoms of heart failure were classified according to

the New York Heart Association (NYHA) functional classes (I–IV), as presented in Table 1.

Statistical analysis

Data are presented as mean ±SD. Analysis of group differences was performed using the Mann–Whitney U test for continuous variables and the χ^2 test for categorical variables. Coefficients of correlation (r) were calculated by the Spearman's rank test. Probability values are 2-sided and considered significant when $p \leq 0.05$. Multiple linear regression analysis was then performed to determine the independent predictors and to discover whether pro-anti-inflammatory cytokines independently predicted the levels of CA 125 and sIL-2R/CD25. All statistical analyses were performed using the SPSS version 17 software package.

Results

Baseline characteristics

The HF patients did not differ from the normal controls with regard to age, sex, FBG, creatinine and anti-cardiolipin-IgG (Table 1).

Serum levels of TNF-α, IL-6, sIL-2R/CD25, and CA 125

Serum levels of TNF-α, IL-6, sIL-2R/CD25, and CA 125 in the patient group were significantly higher than in the control group (Table 2); however, there was no difference between the study groups in IL-10 levels. Compared to the control group, patients with elevated CA 125 had significantly higher BMI (Table 2).

Correlation analysis (Table 3) showed that BMI was significantly associated with pro-inflammatory cytokines, as well as with sIL-2R/CD25, and moreover, with CA 125 ($P<0.001$). Pro-inflammatory cytokines and sIL-2R/CD25 influenced each other and CA 125 positively ($P<0.001$).

After adjustments of pro-anti-inflammatory cytokines in HF patients, either obese or non-obese (n=60), only TNF-α, but not IL-6 or IL-10 ($P>0.05$), was an independent statistically significant predictive factor for CA 125 and sIL-2R/CD25 ($P<0.001$) (Table 4).

Discussion

The relationship between serum cytokines (pro-anti) and tumor marker(s) in HF is an area of increasing interest. Certain cytokines play an important role in the pathogenesis of chronic HF and its prognosis [2], and inflammation participates in all phases of the development of atherosclerosis [7,8]. Therefore, the pivotal role of cytokines in immune regulation has recently been explored in a variety of medical conditions, including CVD [9]. Until now, there was no data available on the relationship between pro- and anti-inflammatory cytokines with CA 125 in patients with chronic or obese HF. To our knowledge, ours is the first study to investigate the potential relationship between these cytokines and CA 125 in obese HF patients.

Collectively, the present study shows that HF patients have markedly elevated serum levels of TNF-α, IL-6, and sIL-2R/CD25 as compared to normal controls, and that this increase parallels the severity of HF. These findings are consistent with the findings of other investigators [1].

It has been reported that IL-6 reflects cardiovascular risk factors in a model that is similar to that of CRP, and its levels increase with age [7]. In our study, IL-6 was elevated in the patient group compared to the control group, implicating IL-6 as an important immune cell activator capable of participation in destabilization of the atherosclerotic plaque. IL-10 is an anti-inflammatory cytokine that inhibits the production of several inflammatory cytokines, such as IL-2 and IFN-gamma, and is strongly associated with a better prognosis among those patients with acute ischemic syndromes [7]. IL-10 levels were not different between the patient group and the control group, and its levels did not change with the severity of HF; hence, it raised the value of the combined inflammatory marker evaluation. Due to the complexity of the inflammatory process, the interrelations with cytokines and the response of acute-phase proteins, it is likely that no single marker contains all the important risk information. The typical cytokine cascade includes induction of an early class of cytokines, which then leads to increased production of later cytokines [8]. Accordingly, our study showed a significant correlation between IL-6, TNF-α and sIL-2R/CD25.

There is great interest in the study of inflammatory markers as cardiovascular risk predictors; however, its impact on the prediction of cardiovascular risk is limited by the fact that inflammation participates in the physiopathological processes of many chronic conditions, including depression, osteoporosis, arthritis, periodontal disease, chronic obstructive pulmonary disease, and cognitive impairment [7].

Since serum cytokines may be elevated due to acute or chronic infections and inflammation, we excluded these conditions. In addition, in order to minimize the effect of medication, patients receiving antibiotic or anti-inflammatory agents were not included in the study.

Recent evidence suggests that cardiomyopathy (CMP), as a cause of HF, may be an autoimmune disorder in some patients [10]. An elevated sIL-2R/CD25 level represents a marker of T lymphocyte activation and has been reported in CMP (HF). Selective elevation of sIL-2R/CD25 in mild ischemia suggests activation and, hence, involvement of antigen-specific T-lymphocytes in this condition. It may be that the overall effect of any cytokine depends on the timing of cytokine release, the local milieu in which it acts, the presence of competing or synergistic elements, cytokine receptor density, and tissue responsiveness to each cytokine.

The adverse effects of obesity on overall cardiovascular health, including HF, are numerous. Because advanced HF is a catabolic state, obese patients with HF may have more metabolic reserve [11]. In the course of CA 125 (a tumor marker) evaluation we observed its high serum levels in our HF patients compared with controls. The increase in serum CA 125 levels was significant in patients with obese severe HF (NYHA III–IV) compared to those with non-obese mild HF (NYHA class I–II). Serum CA 125 levels increased in parallel with the severity of HF, which is consistent with the findings of previous studies [12,13].

Table 1. Clinical and hemodynamic characteristics of subjects evaluated.

Groups	Control	HF	P value *
n	30	60	
Age (years)	60.3±5.8	61.5±6	NS
Sex (M/F)	20 (67%)/10 (33%)	41 (68%)/19 (32%)	NS
HTN	Non	6 (10%)	
Smoking	Non	6 (10%)	
Obesity (%)	Non	20 (33%)/40 (67%)	
NYHA functional class (%)			
I		6 (10%)	
II		14 (23%)	
III		19 (32%)	
IV		21 (35%)	
Duration of heart disease (years)		5±0.5	
LVEF (%)		<40%	
Etiology (%) CMP/IHD		41 (68%)/19 (32%)	
Medication:			
ACEI		50 (83%)	
ARB		20 (33%)	
Digoxin		30 (50%)	
Statins		45 (75%)	
Diuretics		60 (100%)	
Anticoagulants		45 (75%)	
FBG (mg%)	83.5±5.4	83±5.6	NS
Creatinine (mg%)	1±0.1	1±0.11	NS
Anticardiolipin-IgG (U/mL)	6.7±0.53	7.4±0.7	NS

HTN – Hypertension; NYHA – New York Heart Association; LVEF – Left ventricular ejection fraction; CMP/IHD – Cardiomyopathy/Ischemic heart disease; ACEI – Angiotensine converting enzyme inhibitors; ARB – Aldosterone receptor blocker; FBG – Fasting blood glucose.
a Data are given as mean ±SD. NS – not significant. * p values are for the comparison between the control and the study groups.

Since all women were of postmenopausal age (60–70 years), the same reference interval was used for both men and women.

Elevated CA 125 levels have been reported in ovarian cancer, lymphoma, and in gastrointestinal tract, lung, and uterine malignancies [14,15]. Previous studies have shown that high levels of serum CA 125 are associated with the presence of benign and malignant serosal fluids [16,17]. Turk et al. [18] found that serum CA 125 levels were significantly higher in HF patients with pleural effusion than in those without pleural effusion. A recent study by Varol et al. [13] reported that serum CA 125 levels may be related to the presence and severity of HF, as well as the presence of pericardial effusion. These reports suggest that serosal fluids occurring in patients with HF are directly responsible for elevated serum CA 125 levels, and that the presence of serosal fluid, rather than its cytopathological content, may stimulate its release, suggesting that the increase in serum CA 125 levels may be due to production by mesothelial cells and non-mesothelial cells as a consequence of inflammation, stasis or other stimulatory mechanisms. Duman et al. [19] found that in HF patients with mitral stenosis, elevated CA 125 levels may be due to venous congestion and activation of peritoneal mesothelial cells or increased signal peptides. Likewise, because they were clinically stable, the majority of our patients with high CA 125 did not have pleural effusion. Recently, Kosar et al. [3] demonstrated that high CA 125 levels in HF patients were correlated with inflammatory cytokines levels, suggesting a relationship between CA 125 and cytokines.

Multiple independent pathways of evidence now pinpoint inflammation as a key regulatory process that links altered arterial biology with multiple risk factors for atherosclerosis and its complications [20].

This study showed that, in addition to the elevation in advanced HF patients, serum CA 125 levels were significantly increased in the mild HF patients, indicating that elevated serum CA 125 levels may be dependent on inflammation as a consequence of cytokine network activation.

The most striking finding of this study was that the increase in serum CA 125 levels was positively correlated with serum TNF-α and IL-6 levels, suggesting that serum CA 125 levels have a strong positive relationship with serum TNF-α and IL-6, and that levels in HF patients, being produced by the adipose

Table 2. Comparison of serum pro-anti-inflammatory cytokines and CA 125 levels in normal controls and in HF patients.

Parameters	Control	Non-obese mild HF	Obese sever HF	*P**
n	30	20	40	
BMI (Kg/m^2)	22.6±1.65	22.8±1.6	28.65±1[a,b]	<0.001
TNF-α (pg/mL)	12.8±0.6	35.5±0.7[a]	108.3±0.85[a,b]	<0.001
IL-6 (pg/mL)	4.7±0.6	11.6±1.6[a]	18.5±1.4[a,b]	<0.001
IL-10 (pg/mL)	18.7±1.3	18.5±1.14	18±0.9	NS
sIL-2R/CD25 (pg/mL)	1116.6±129	2965±81.2[a]	3555±254[a,b]	<0.001
CA 125 (U/mL)	20.9±2.7	25.8±2.5[a]	77.4±5.4[a,b]	<0.001

TNF-α – tumor necrosis factor-alpha; IL-6 – Interleukin-6; IL-10 – Interleukin-10; sIL-2R/CD25 – Interleukin-2 soluble receptor.
Data are presented as mean ±SD. NS – not significant. * P values are for the comparison between the control and the study groups.
[a,b] significant difference from control and Non-obese mild HF NYHA class I/II groups, respectively.

Table 3. Correlation coefficients (r) of different parameters in CHF patients (obese and non-obese) (n=60).

	BMI	TNF-α	IL-6	IL-10	sIL-2R/CD25	CA 125
BMI		0.914***				
TNF-α	0.914***		0.913***	–0.278**		0.982***
IL-6	0.863***					
sIL-2R/CD25	0.707***	NS	0.739***			0.757***
IL-10	NS		NS		NS	
CA 125	0.875***		0.886***	NS		

r = Spearman's rank correlation coefficients. **, *** Correlation is significant at the 0.05, 0.001 level. NS – Non significant correlation.

Table 4. Predictive values of CHF patients (obese and non-obese) (n=60).

	sIL-2R/CD25	CA 125
TNF-α	B=1.619,P=0.002	B=1.258, P=0.001
IL-6	NS	NS
IL-10	NS	NS
sIL-2R/CD25		NS
CA 125	NS	

Evaluated by multiple regressions; B – standardized coefficients;
NS – Non significant correlation.

tissue, especially excessive abdominal fat [21]. Our study supports the hypothesis that elevated serum CA 125 levels are closely associated with inflammatory mediators or cytokines.

Previous reports have suggested that CA 125 is produced by and secreted from ovarian epithelial tumor cells and lymphoma when stimulated by cytokines such as TNF-α and IL-6 [22,23]. Therefore, we can speculate that in HF pro-anti-inflammatory cytokines such as TNF-α, IL-6, and IL-10 may either permit expression of CA 125 or predispose to contributory factors for the production of CA 125. T-lymphocyte activation appears to be independent from classic clinical predictors and independent from the acute phase reaction (Table 4). Further studies are required to confirm our data suggesting a role of T-lymphocytes in promoting HF, and to evaluate the potential diagnostic value of elevated sIL-2R/CD25 levels.

It is only a matter of time until determination of risk factors after HF will become, like EF assessment, a routine method [8].

The strength of the results and conclusions of this study is limited by the small number of patients in the study groups.

Conclusions

1. The influence of pro-anti-inflammatory markers and T-cell activation marker(s) on the development of atherosclerotic disease is well established, and they are useful in the prediction of elevated cardiac risk among middle-aged individuals.

2. The evaluation of patients with HF should be multifaceted and should include the assessment of hemodynamic left ventricular function and the assessment of humoral risk factors.

3. Serum CA 125 levels are elevated in patients with HF and that this increase in serum CA 125 levels correlates with BMI, pro-anti-inflammatory cytokines and T-cell activation marker(s).

4. These data suggest that a link may exist between cytokines, T-cell activation, and CA 125 in HF patients; obese or non-obese. Elevated serum CA 125 levels may be secondary to the activation of these cytokines in obese HF patients.

5. Further studies are required to determine the predictive value of plasma CA 125 in forecasting the risk of premature death or the need for cardiac transplantation.

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Conflict of interest

No conflict of interest relevant to this article was reported.

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Study association

This study is an independent basic regular research paper and not a part of any thesis.

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