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Research Article

Genito-Thyroid Index: A Global Systems Approach to the Neutrophil-to-Lymphocyte Ratio According to the Theory of Endobiogeny Applied to Ambulatory Patients with Chronic Heart Failure

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Abstract

Background: Chronic heart failure (CHF) is an inflammatory disorder. Elevated Neutrophil-to-Lymphocyte ratio (NLR) is associated with inflammation and increased morbidity and mortality in various disorders including CHF. NLR is a non-specific, quantitative biomarker assessment. It does not allow for a personalized approach to treatment. A global systems approach to biomarker assessment is quantitative and qualitative, contextualizing basic data into larger sets of meaning. Such a system may provide greater meaning to the NLR, increasing its clinical utility in CHF. Endobiogeny is a global systems theory. It claims to be able to model complex physiology through biomarkers, offering context-rich interpretations of data for meaningful clinical applicability. In Endobiogeny, NLR is referred to as the Genito-Thyroid index (GT).

Aim: The NLR has never been studied in ambulatory CHF patients. The first aim of this study was to determine if NLR is elevated for ambulatory CHF patients versus controls. The second was to determine if the endobiogenic interpretation of the NLR as the GT index is consistent with current pathophysiologic models.

Methods: A retrospective observational case-controlled study was performed in 93 patients with New York Heart Association class II-III heart failure patients and 104 individuals with no cardiovascular pathology as a control group. Two biomarkers, percent neutrophils and percent lymphocytes, were entered into the Biology of Functions modeling software, from which a direct index was produced to model an aspect of the heart failure terrain. All calculations were performed using SPSS Inc. (version 22.0) and analyzed by univariate or multivariate analysis of covariance.

Results: NLR or, GT index (normal 1.5-2.5) was elevated in CHF patients vs. control (2.81 vs 2.01, $p<0.001$).

Conclusions: NLR, or, GT index, when elevated reflects a hyperimmune response to an aggression. CHF is associated with elevated immune activity. Ambulatory CHF patients show signs of a hyperimmune response even when clinically stable. The endobiogenic explanation of the NLR is consistent with current pathophysiological models of CHF. Future studies should explore if a certain cutoff value of the GT index is predictive of future deterioration in CHF patients. Future studies should evaluate other endobiogenic indexes for their clinical relevance in CHF.

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ABBREVIATIONS

CHF: Chronic Heart Failure; NLR: Neutrophil-to-Lymphocyte Ratio; GT: Genito-Thyroid; BOF: Biology of Functions

INTRODUCTION

The neutrophil-to-lymphocyte ratio (NLR) has been widely studied. Elevated NLR is believed to reflect a systemic inflammatory terrain, and correlated with increased morbidity and mortality. It is inexpensive and often performed but remains infrequently used in clinical practice due to lack of specificity. If there were a way to reinterpret the NLR as a more precise expression of physiologic activity, it may have a greater value in clinical practice. Biomarkers are evaluated independent of each other, infrequently contextualized to the etiologic or compensatory mechanisms within the patient. Direct ratios are an attempt to contextualize two or more pieces of data in a qualitative way: one level of activity relative to another. The NRL is one example: %Neutrophils ÷ %Lymphocytes. Other examples include hematocrit (red blood cells/hemoglobin) and the blood urea nitrogen/creatinine ratio. This approach contextualizes two or more levels of function but doesn't address etiological or teleological concerns such as "what caused it to appear?" and, "what is the clinical implication?".

Systems theory seeks to answer these questions by introducing the concept of upstream regulators and downstream output. In a case such as the NLR, the neutrophils and lymphocytes are downstream output from bone marrow. The question then becomes: "What are the upstream factors that influenced the production or mobilization of these factors?" and, "If NLR reflects systemic inflammation, what are the factors that augment or diminish this tendency?" Answering these questions would open a new level of understanding of cause and effect and beyond mechanisms of action for all biomarkers, including the NLR.

Endobiogeny is a global systems theory rooted in clinical practice. It claims to assess human physiology in a manner that contextualizes upstream and downstream events. The theory of endobiogeny considers the neuroendocrine system as the manager of metabolism, thus, the manager of the global terrain [1]. Biomarkers are considered the downstream metabolic output of tissues that were regulated upstream by neuroendocrine factors. From the theory of endobiogeny, a series of direct and indirect ratios of biomarkers have been developed called the Biology of Functions (BoF), [2] discussed in detail elsewhere [2]. In the BoF, the NLR is referred to as the Genito-thyroid ratio (GT) for reasons discussed below. For the remainder of the article, the NLR will be referred to in both ways: NLR (GT).

We hypothesized that in ambulatory patients with chronic heart failure (CHF), NLR (GT) would be elevated versus control subjects, reflecting the inflammatory terrain of CHF patients. A secondary hypothesis was that the theory of Endobiogeny could contextualize the NLR (GT) values in CHF patients based on currently accepted notions of the CHF terrain.

METHODS

Study Participants

A retrospective observational case-controlled study was performed. The study sample consisted of 93 patients diagnosed with New York Heart Association (NYHA) classes II through III heart failure and 104 individuals with no cardiovascular pathology as a control group. Patients were recruited from the San Diego Veterans Affairs Medical Center Cardiology Clinic and the University of California, San Diego (UCSD) Medical Center Advanced Heart Failure Program as part of a larger study on the effects of depression on cellular adhesion and inflammation in HF. We included the non-CHF control sample from the local community via advertisements (e.g., newspapers, flyers, brochures, and websites) and word of mouth referrals.

Inclusion criteria for all study participants were age between 30 and 85 years. Additional inclusion criteria for CHF patients included symptoms of CHF for at least 3 months that had been optimally treated with beta blockers, diuretics, and Angiotensin-converting enzyme (ACE) inhibitors. Left ventricular ejection fraction (LVEF) was assessed by echocardiography as part of the patient's routine medical evaluation. Exclusion criteria included recent myocardial infarction (1 month), recent stroke or significant cerebral neurological impairment, severe chronic obstructive pulmonary disease, and psychiatric illness other than depression and co-morbid anxiety. Subjects were instructed to abstain from taking aspirin for 24 hours prior to the testing session.

The investigation conformed to the principles outlined in the Declaration of Helsinki. The University of California, San Diego Institutional Review Board, approved the study. All subjects gave informed written consent.

Biochemical Analyses

Blood was drawn into ethylendiaminetetra acetic acid (EDTA)-coated vacutainer tubes (BD Biosciences, San Jose, California) for complete blood count with differential and platelets, which was determined at the Clinical Laboratory at the UCSD Medical Center.

Statistical Analyses

All calculations were performed using SPSS Inc. (version22.0) software package (SPSS, Chicago, Illinois). Data are presented as mean ± SEM or ± SD. Results were considered statistically significant at the $p \leq .05$ level and tests were either univariate or multivariate analysis of covariance (ANCOVA). In both groups, normal distribution of data was verified prior to statistical analyses using the Kolmogorov-Smirnov test. We calculated mean arterial pressure (MAP) from resting BP readings (1/3 systolic BP + 2/3 diastolic BP) and body mass index (BMI) was calculated by the formula weight in kg/ (height in m2).

Value of the NLR

In this study the normal range of NLR (GT) was considered to be 1.5-2.5, as proposed by the originator of the theory of Endobiogeny, Dr. Christian Duraffourd.

RESULTS

Sociodemographic and medical characteristics of the study subjects are presented in Table (1). CHF patients were older ($p<0.01$) and heavier ($p<0.01$) than non-CHF subjects and had lower mean blood pressure ($p<0.01$).

A multivariate ANCOVA examining CHF vs. control group differences in NLR ratio within a CBC with differential, controlling for age, body mass index (BMI), mean arterial pressure (MAP) and gender was significant (F=10.59; p<0.001). Both age (F=4.90; p<0.001) and gender (F=7.54; p<0.001) were significant covariates; BMI (F=1.28; p=0.251) and mean blood pressure (F=1.51; p=0.147) were not significant covariates (Table 1). Subsequent individual univariate ANCOVAs, controlling for age and gender, showed CHF group differences for % neutrophils, % lymphocytes, and NLR (GT) as indicated in (Table 1).

A multivariate ANCOVA was conducted on the NLR (GT) ratio as dependent variables and controlling for age, BMI, MAP and gender. The overall model was significant for the CHF grouping variable (F=8.98; p<0.001). Additionally, age (F=4.02; p<0.001) and gender (F=6.77; p<0.001) were significant covariates; BMI and mean blood pressure were not significant covariates.

DISCUSSION

The theory of Endobiogeny considers the neuroendocrine system to be the manager of the terrain because it regulates metabolism. Therefore neuroendocrine activity is the primary area of investigation for most disorders regardless of the specific mechanisms of disease expression. The NLR is referred to as the Genito-thyroid index in the BoF. It is so called because it is hypothesized to reflect a qualitative physiologic relationship between the gonadotropic hormone estrogen derived from the genitals (genito-) and the thyrotropic hormone TSH (thyroid). The index is defined as "the relative activity of estrogens in relationship to that of TSH regardless of the absolute activity of peripheral thyroid hormones" (Figure 1).

Recall that the NLR (GT) is %Neutrophils ÷ %Lymphocytes. Neutrophils, in the numerator, are hypothesized to represent the activity of estrogens. Estrogens (upstream) stimulate the production of neutrophils (downstream) in the bone marrow. Estrogens prolong neutrophils in circulation [3,4] Neutrophils play a key role in the immune response and inflammation [5-8]. The greater the relative estrogenism, the greater the relative neutrophilia, the greater the inflammatory activity of neutrophils will be.

In the denominator is lymphocytes. Estrogens in general stimulate anabolic tissue construction [9-15]. They also stimulate TSH to calibrate thyroid hormone output to augment production of ATP [16-18]. TSH also stimulates maturation of lymphocytes in the thymus [19,20]. The more efficient TSH and thyroid response is to estrogen demand, the lower the % Lymphocyte count, and the greater the relative degree of immune activity and systemic inflammation [21-23].

To summarize, the higher the value of NLR (GT), the greater the relative neutrophilia is in relationship to lymphocytosis—regardless of their absolute values. The greater the ratio, the greater the number of pro-inflammatory cells are (reflected in the neutrophil count) and the greater the activity of those immune cells to release inflammatory mediators (inversely proportional to the lymphocyte count). The greater the ratio is, the greater the catabolic thyrotropic activity is relative to the anabolic estrogenic demand. Thus from the theory of endobiogeny, the NLR (GT) is contextualized to endocrine management of the immune response in adaptation during an aggression (Figure 2).

Prior studies have hypothesized elevated NLR (GT) to be a general indicator of systemic inflammation in a wide variety of disorders such as bacteremia, [24] pneumonia, [25] diabetes [26], cancer, [27,28] and critical illness [29]. CHF is a disorder associated with a chronic inflammatory terrain. Neutrophil-derived cytokines, such as interleukin-6 and tumor necrosis factor alpha are associated with severity of CHF [30-34]. Other aspects of neutrophil activity are also associated with CHF [35,36]. Lymphocyte count has been inversely correlated with adverse outcomes in CHF patients [37]. Finally, a large-scale

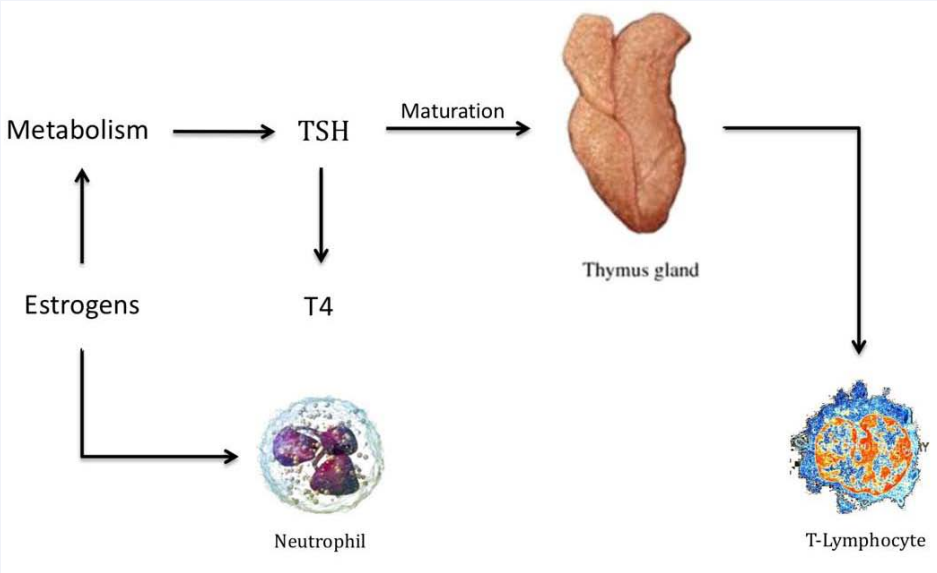

Figure 1 Genito-Thyroid index: relationship to endocrine action on the terrain.

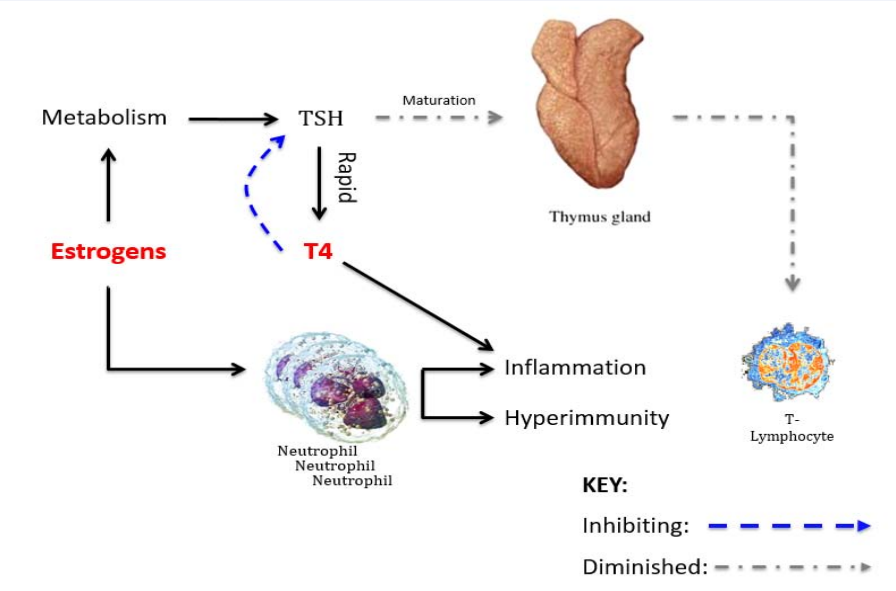

Figure 2 Elevated Genito-Thyroid index: implications in the endocrine terrain.

Table 1: Sociodemographic and Medical Characteristics of the Study Subjects.

(mean ± SD)	Heart Failure	Non-Heart Failure	p-value
N	93	104	
Age (years) **	55.9 (12)	49.2 (14)	<0.01
Gender (# Women / # Men)	15 / 78	12 / 92	NS
Body Mass Index (kg/m^2) **	31.9 (8.2)	28.8 (6.4)	<0.01
Mean arterial pressure (mm Hg) *	80.0 (9.5)	90.5 (10.1)	<0.001
LVEF (%)	32.1%	---	
Neutrophil % **	62.6 (10.1)	57.8 (7.82)	<0.01
Lymphocyte % *	25.3 (8.91)	30.9 (6.85)	<0.001
Genito-Thyroid (1.5-2.5) *	2.81 ± 1.04	2.01 ± 0.75	<0.001
Medications:			
ACE inhibitors	73 %	0 %	
Beta blockers	95 %	0 %	
Calcium channel blockers	5 %	0 %	
Statin	56 %	0 %	
Aspirin	54 %	7 %	
Diuretics	90 %	0 %	
Anti-arrhythmics	9 %	0 %	
Digoxin	61 %	0 %	

Abbreviations: **CBC: Complete Blood Count; ACE: Angiotensin-Converting-Enzyme, NS: Not significant**

analysis of over 1300 hospitalized elderly patients with CHF found a strong correlation between the NLR (GT), chronic renal disease and major cardiac events [38].

Our study is the first to establish that the NLR (GT) is also elevated in ambulatory stage 2 and stage 3 CHF patients. It is also the first study to propose a theory of what the relevance of the NLR is to CHF based on a global systems theory. Other studies support the value of a qualitative analysis over a strictly quantitative one. A 2010 study by de Jager et al., noted that the NLR (GT) with absolute lymphopenia were better predictors of bacteremia than total WBC count, neutrophil percentage or C-reactive protein [24]. A 2012 study by de Jager et al., found similar results in adults admitted to the hospital for pneumonia, including risk of mortality [25].

The challenges in accepting the results of this study arise from the binary and quantitative modalities of modern biomedical

investigations. This approach seeks to measure output and actions of individual actors rather than the functional activity of multiple ones. The theory of endobiogeny describes endocrine relationships in regulating metabolism more akin to physics or engineering, such as efficiency of response, pulsatility of output, etc. The conceptual nature of global systems theory, such as Endobiogeny, requires clinical correlation with diagnosis and prognosis of clinical conditions.

This study represents an initial step in applying global systems theory to clinical medicine. It offers an explanation of the upstream origins of systemic inflammation reflected by an elevated NLR (GT). A limitation of this study is that it was not able to offer insights into clinical therapies or outcomes. Future studies should investigate this in a prospective fashion. Other indexes of the BoF that reflect more concrete physiologic activity related to CHF should be evaluated in future studies, such as those evaluating cortisol, catabolism, and sympathetic function.

CONCLUSION

The neutrophil-to-lymphocyte ratio, also known as the genito-thyroid index, is a marker correlated with systemic inflammation and poor outcomes in various disorders, including hospitalized patients with CHF. Our study was the first to demonstrate that it is elevated in ambulatory patients with CHF. Using a global systems theory, Endobiogeny, we hypothesized what upstream endocrine factors may be related to the origin of elevated neutrophils and diminished lymphocytes and the relevance of those factors to the adaptation response. With this contextualization, this simple, inexpensive ratio may offer greater insight into the origins and progression of chronic heart failure at the global metabolic level.

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Conflict of Interest

The Corresponding Author has the right to grant on behalf of all authors and does grant on behalf of all authors, an exclusive license on a worldwide basis to the Journal of Cardiology and Clinical Research to permit this article (if accepted) to be published in the Journal of Cardiology and Clinical Research editions and any other products and sublicenses such use and exploit all subsidiary rights, as set out in our license.

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