

## ORIGINAL PAPER ΕΡΕΥΝΗΤΙΚΗ ΕΡΓΑΣΙΑ

### The relationship of serum ferritin level with cardiovascular risk factors in healthy men

**OBJECTIVE** The role of ferritin as a marker of inflammation in the clinical assessment of cardiovascular risk remains to be determined. The purpose of this study was to assess correlations between serum ferritin levels and some of the known cardiovascular risk factors in healthy men. **METHOD** Data from an epidemiological survey of 256 men of a Greek warship, aged 19–38 years, on behavioral and demographic characteristics, family history of premature coronary heart disease (CHD), weight and height, blood pressure and serum ferritin levels, were analyzed. **RESULTS** Serum ferritin concentration correlated significantly with age, systolic and diastolic blood pressure, body-mass index, alcohol consumption, years of smoking and cigarette pack-years. No significant association was found between serum ferritin level and smoking, aerobic exercise or family history of premature CHD. **CONCLUSIONS** A relationship was observed between the level of serum ferritin and various cardiovascular risk factors in early adulthood. Intervention and prevention measures should be targeted at the smoking behavior, blood pressure and obesity of naval personnel.

Experimental and clinical studies suggest that inflammatory processes play a role in the pathogenesis of atherosclerosis and the clinical manifestations of atherosclerotic disease.<sup>1,2</sup> However, the role of ferritin as a marker of inflammation in the clinical assessment of cardiovascular risk remains to be determined, as there is conflicting evidence regarding the relationship between iron stores and cardiovascular disease (CVD).<sup>3,4</sup>

Data which have been published on the relationship between serum ferritin and cardiovascular risk factors in early adulthood are scarce.<sup>3</sup> The purpose of this study was to assess the prevalence of some of the known cardiovascular risk factors and their correlation with serum ferritin levels in healthy young men.

#### MATERIAL AND METHOD

This study was carried out on a warship of the Greek armed forces, between February and July 1998 according to a protocol approved by the Hellenic Naval General Staff. The study

population was the military personnel of the warship (n=285 men), aged between 19 and 38 years. All subjects provided informed consent before participating in the study.

The participants were interviewed during visits to the sick-bay, using a structured questionnaire which included items on the following topics: Demographic characteristics, such as age, smoking habit [*current smokers* (smoking at least one cigarette per day) and *non-smokers* (never-smokers/former smokers)]; years of smoking and number of cigarettes per day; alcohol consumption [*abstainers* and *drinkers* (drinking at least one or more alcoholic drink during their day off)]; aerobic exercise (any type of isotonic exercise, such as jogging, cycling, swimming, etc.) during leisure time (*yes* or *no*), and finally the presence or absence (*yes* or *no*) of any history of premature coronary heart disease (CHD) among first-degree relatives (<55 years for male relatives and <65 for female relatives).

Anthropometric characteristics and blood pressure were also recorded. An apparatus (calibrated scale with an accuracy of ±0.1 kg and a fixed stadiometer) was used to measure body weight (BW) and body height (BH). Subjects were weighed without shoes and tunic. Standing BH was measured without

ARCHIVES OF HELLENIC MEDICINE 2007, 24(6):573–577  
ΑΡΧΕΙΑ ΕΛΛΗΝΙΚΗΣ ΙΑΤΡΙΚΗΣ 2007, 24(6):573–577

E.E. Mazokopakis,<sup>1,2</sup>  
J.A. Papadakis,<sup>1</sup>  
M.G. Papadomanolaki,<sup>3</sup>  
C.D. Lionis,<sup>2</sup>  
E.S. Ganotakis<sup>1</sup>

<sup>1</sup>Department of Internal Medicine,  
School of Medicine, University of Crete

<sup>2</sup>Clinic of Social and Family Medicine,  
School of Medicine, University of Crete

<sup>3</sup>Department of Sciences, Technical  
University of Crete, Crete, Greece

Συσχέτιση επιπέδων φερριτίνης  
ορού και καρδιαγγειακών  
παραγόντων κινδύνου σε υγιείς  
άνδρες

Περίληψη στο τέλος του άρθρου

#### Key words

Cardiovascular risk factors  
Ferritin  
Warship

Submitted 4.4.2006

Accepted 4.7.2006

shoes to the nearest 0.5 cm with the shoulders in relaxed position and arms hanging freely. BW and BH were measured twice and the mean of two readings calculated. The values were used to calculate body-mass index (BMI), as BW in kilograms (kg) divided by the square of BH in meters (m<sup>2</sup>). Blood pressure measurement was performed according to the recommendations of the American Society of Hypertension,<sup>5</sup> using a random-zero sphygmomanometer (model No 7076, Hawksley and Sons Limited, Sussex, England) applied on the right arm. Cuffs were chosen on the basis of the circumference of each individual's arm. The first and fifth Korotkoff sounds were recorded for systolic and diastolic readings respectively. Two readings separated by five minutes were averaged.

Venous blood was collected in the morning, after a 12 hour overnight fast, with the participant in a sitting position; a tourniquet was used but released before sampling. Blood samples taken from the participants were transported to the laboratories of the Athens Naval Hospital for blood count and measurement of the level of serum ferritin by microparticle enzyme immunoassay (MEIA), using Abbott IMX (AxSYM Ferritin). The laboratory has performed satisfactorily in external quality assurance programs.

#### Statistical analysis and presentation of results

Values were expressed as median and range. All P values were derived from two-tailed analysis, and values <0.05 were considered significant. Between group results were assessed by Mann-Whitney tests. Correlation was assessed by Spearman's correlation ( $r_s$ ).

## RESULTS

From the original number of 285 male personnel, complete answers to the questionnaire, anthropometric characteristics, blood pressure and blood samples were obtained from 256 individuals (participation rate 89.8%).

The characteristics of the participants are shown in table 1.

#### Correlations of serum ferritin

The correlations of the serum level of ferritin are shown in table 2.

*Age.* There was a significant correlation between age and serum ferritin level.

*Smoking habit.* There was no significant difference in serum ferritin level between current smokers and non-smokers [60.3 (7.9–156.0) vs 63.4 (8.1–148.2) µg/L, P>0.05]. However, among smokers serum ferritin level

**Table 1.** Characteristics of the study population (n=256).

Variables	Median value (range) or No (%)
Age (years)	23 (19–38)
Current smokers	163 (63.7%)
Years of smoking	5 (1–18)
Family history of premature CVD	39 (15.2%)
Drinkers	156 (60.9%)
Aerobic exercise	147 (57.4%)
SBP (mmHg)	115 (90–155)
DBP (mmHg)	70 (55–95)
Hypertensives	3 (1.2%)
BMI (kg/m <sup>2</sup> )	24.6 (18.0–35.9)
25.0–29.9	73 (26.6%)
≥30.0	13 (4.8%)
Ferritin (µg/L)	62.3 (7.9–156.0)
Hb (g/dL)	15.0 (11.0–17.9)
WBC (K/µL)	6.80 (4.07–11.81)
PLT (K/µL)	227 (122–394)

CVD: Cardiovascular disease; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; BMI: Body-mass index; Hb: Hemoglobin; WBC: White cell blood count; PLT: Platelets

**Table 2.** Correlations of serum ferritin level in 256 participants ( $r_s$ =Spearman's correlation).

Variables	$r_s$
Age	0.227**
Years of smoking	0.283**
Cigarette pack years	0.199*
BMI	0.166**
Systolic blood pressure	0.149*
Diastolic blood pressure	0.181**
Hb	0.154*
WBC	0.203**
PLT	0.032

BMI: Body-mass index; Hb: Hemoglobin; WBC: White cell blood count; PLT: Platelets

\* P<0.05; \*\* P<0.01

was significantly correlated with the number of years of smoking and cigarette pack-years.

*Alcohol consumption.* Drinkers had a significantly higher serum ferritin level than compared with abstainers [63.0 (11.1–156.0) vs 49.8 (7.9–148.2) µg/L, P<0.05].

*Aerobic exercise.* There was no significant difference in serum ferritin level between those who exercised dur-

ing their leisure time and those who did not [60.3 (7.9–146.6) vs 62.7 (11.6–156.0)  $\mu\text{g/L}$ ,  $P>0.05$ ].

**BMI.** Serum ferritin levels were correlated significantly with the BMI.

**Blood pressure.** Serum ferritin level was increased gradually with both systolic and diastolic blood pressure although only 3 (1.2%) men were actually hypertensive (systolic blood pressure  $>140$  mmHg and/or diastolic blood pressure  $>90$  mmHg).

**Hemoglobin (Hb), white cell count (WBC) and platelets (PLT).** Serum ferritin levels were significantly correlated with Hb and WBC, but not with PLT.

**Hb, WBC and PLT in smokers and non-smokers.** Smokers had a significantly higher WBC than non-smokers [7.12 (4.18–11.81) vs 6.57 (4.70–10.80)  $\text{K}/\mu\text{L}$ ,  $P<0.05$ ]. There was no significant difference in Hb and PLT values between smokers and non-smokers [15.0 (12.2–17.9) vs 15.0 (11.0–17.4)  $\text{g/dL}$  and 225 (122–394) vs 230 (140–332)  $\text{K}/\mu\text{L}$ , respectively].

## DISCUSSION

This study showed that several cardiovascular risk factors are associated with the serum level of ferritin among young and presumably healthy warship military personnel. Further research is needed to elucidate the significance of these findings and the possible mechanisms of iron metabolism in the development of CVD.<sup>6,7</sup>

Of interest is the age-related increase of serum ferritin, as such increases in iron stores have been linked to the pathogenesis of several common diseases, including atherosclerosis.<sup>8</sup> It has been hypothesized that iron catalyzes the formation of reactive oxygen species reactions and that the free radicals produced cause lipid peroxidation, leading to the modification of low-density lipoprotein (LDL) at the molecular level and the formation of atherosclerotic plaque.<sup>8</sup> Several earlier studies have also shown a gradual increase of serum ferritin levels with aging.<sup>9–11</sup>

The positive correlation of serum ferritin with BMI, a reliable index of obesity, has also been reported in other studies.<sup>3,4,11</sup> Considering that a high BMI implies a high energy intake, and that nutritional iron intake is proportional to the energy intake, it can be hypothesized that participants with a high BMI have a high iron intake, which in turn influences body iron stores and serum ferritin.<sup>4</sup>

Elevated blood pressure is an established cardiovascular risk factor.<sup>1</sup> This study showed a positive correlation of serum ferritin with both systolic and diastolic blood pressure. However the literature has revealed conflicting results.<sup>3,4,12</sup>

This study, as that of Hughes et al,<sup>13</sup> did not find significant difference in serum ferritin levels between current smokers and non-smokers. In contrast, a significant negative association was found among 1044 Danish men aged 30–60 years.<sup>4</sup>

Among smokers serum ferritin level was correlated with the number of years of smoking and the cigarette pack-years. Salonen et al found no association between serum ferritin level and lifetime cigarette pack-years in Finnish men.<sup>12</sup> It could be hypothesized that the observed correlation between serum ferritin level and years of smoking and cigarette pack-years was due to the known effect of age on ferritin level.<sup>9–11</sup> However, the range of age in the study population was too limited (91% of them were aged between 19 and 29 years) for this to apply. The mechanism by which smoking affects serum ferritin is not defined. It is known that the number of cigarettes smoked correlates strongly with WBC and Hb,<sup>14</sup> as this study also demonstrated. Moreover, the degree of elevation of WBC within the normal range is a marker for increased CVD risk.<sup>14</sup> The results of this study showed that serum ferritin level also had a positive correlation with WBC. Thus serum ferritin level may act as an additional marker for elevated CVD risk.

In this study, the serum ferritin level was correlated with alcohol consumption, as reported elsewhere.<sup>4,17,18</sup> Increased iron absorption and/or enhanced intracellular ferritin synthesis are the mechanisms by which alcohol may influence the serum ferritin level.<sup>15,16</sup>

Although physical inactivity is an established cardiovascular risk factor,<sup>1</sup> no association was found between aerobic exercise and serum ferritin among the naval personnel. In a study of 2235 Danes aged 30–60 years, no association was found among men, but a slightly negative association was found only in 40-year-old women.<sup>4</sup>

There are methodological limitations to the present study. Firstly, the results were derived from a cross-sectional study where the small sample size and the sampling methods raise questions about the representativeness and generalization of the study findings. In addition, the study did not evaluate established metabolic cardiovascular risk factors and other markers of inflammation (e.g., lipid levels, C-reactive protein, fibrinogen, etc.).

In conclusion, this study revealed a relationship between serum ferritin level and several cardiovascular risk factors from early adulthood. Intervention and preventive measures should be targeted at the smoking behav-

ior, blood pressure and obesity of naval personnel. These results may contribute to the ongoing debate surrounding the association between iron stores and coronary heart disease.

## ΠΕΡΙΛΗΨΗ

### Συσχέτιση επιπέδων φερριτίνης ορού και καρδιαγγειακών παραγόντων κινδύνου σε υγιείς άνδρες

H.E. MAZOKOΠAKHΣ,<sup>1,2</sup> I.A. ΠΑΠΑΔAKHΣ,<sup>1</sup> M.Γ. ΠΑΠΑΔOMANΩΛAKH,<sup>3</sup> X.Δ. ΛIONHΣ,<sup>2</sup> E.Σ. ΓANΩTAKHΣ<sup>1</sup>

<sup>1</sup>Κλινική Γενικής Παθολογίας, <sup>2</sup>Κλινική Κοινωνικής και Οικογενειακής Ιατρικής, Ιατρικό Τμήμα Σχολής Επιστημών Υγείας, Πανεπιστήμιο Κρήτης, <sup>3</sup>Πολυτεχνείο Κρήτης, Κρήτη

Αρχεία Ελληνικής Ιατρικής 2007, 24(6):573-577

**ΣΚΟΠΟΣ** Ο ρόλος της φερριτίνης, ως δείκτη φλεγμονής, στην εκτίμηση του καρδιαγγειακού κινδύνου παραμένει ακαθόριστος. Σκοπός της μελέτης ήταν ο προσδιορισμός πιθανών συσχετίσεων των επιπέδων της φερριτίνης ορού με ορισμένους καρδιαγγειακούς παράγοντες κινδύνου σε υγιείς άνδρες. **ΥΛΙΚΟ-ΜΕΘΟΔΟΣ** Τα κοινωνικοδημογραφικά στοιχεία, το οικογενειακό και το ατομικό ιστορικό (συνήθειες υγείας), το ύψος και το βάρος, η αρτηριακή πίεση και τα επίπεδα της φερριτίνης ορού 256 ανδρών ενός πολεμικού πλοίου (ΠΠ), ηλικίας 19-38 ετών, καταγράφηκαν και αναλύθηκαν. **ΑΠΟΤΕΛΕΣΜΑΤΑ** Τα επίπεδα της φερριτίνης ορού συσχετίζονταν σημαντικά με την ηλικία, τη συστολική και τη διαστολική αρτηριακή πίεση, το δείκτη μάζας σώματος, την κατανάλωση οινοπνεύματος, τα έτη καπνίσματος και τα πακέτα-έτη καπνίσματος. Δεν διαπιστώθηκε σημαντική συσχέτιση μεταξύ των επιπέδων της φερριτίνης ορού και της καπνισματικής συνήθειας, της αεροβικής σωματικής άσκησης και του οικογενειακού ιστορικού στεφανιαίας νόσου. **ΣΥΜΠΕΡΑΣΜΑΤΑ** Η παρούσα μελέτη ανάδειξε την ύπαρξη συσχετίσεων μεταξύ των επιπέδων φερριτίνης ορού και ορισμένων καρδιαγγειακών παραγόντων κινδύνου σε υγιείς άνδρες ενός ΠΠ. Προληπτικές παρεμβάσεις πρέπει να στοχεύουν στην εκτίμηση και την αντιμετώπιση καρδιαγγειακών παραγόντων κινδύνου (καπνισματικής συνήθειας, αρτηριακής υπέρτασης, παχυσαρκίας) στο προσωπικό των ΠΠ.

**Λέξεις ευρητηρίου:** Καρδιαγγειακοί παράγοντες κινδύνου, Πολεμικό πλοίο, Φερριτίνη

## References

- WOOD D. Established and emerging cardiovascular risk factors. *Am Heart J* 2001, 141:S49-S57
- MEHTA JL, SALDEEN TG, RAND K. Interactive role of infection, inflammation and traditional risk factors in atherosclerosis and coronary artery disease. *J Am Coll Cardiol* 1998, 31:1217-1225
- WILLIAMS MJ, POULTON R, WILLIAMS S. Relationship of serum ferritin with cardiovascular risk factors and inflammation in young men and women. *Atherosclerosis* 2002, 165:179-184
- MILMAN N, KIRCHHOFF M. Relationship between serum ferritin and risk factors for ischaemic heart disease in 2235 Danes aged 30-60 years. *J Intern Med* 1999, 245:423-433
- AMERICAN SOCIETY OF HYPERTENSION. Recommendations for routine blood pressure measurement by indirect cuff sphygmomanometer. *Am J Hypertens* 1992, 5:207-209
- KIECHL S, WILLEIT J, EGGER G, EGGE G, POEWE W, OBERHOLLENZER F. Body iron stores and the risk of carotid atherosclerosis; prospective results from the Bruneck study. *Circulation* 1997, 96:3300-3307
- De VALK B, MARX JJM. Iron, atherosclerosis, and ischemic heart disease. *Arch Intern Med* 1999, 159:1542-1548
- HAIDARI M, JAVADI E, SANATI A, HAJILOOI M, GHANBILI J. Association of increased ferritin with premature coronary stenosis in men. *Clin Chem* 2001, 47:1666-1672
- MILMAN N. Serum ferritin in Danes: Studies of iron status from infancy to old age, during blood donation and pregnancy. *Int J Hematol* 1996, 63:103-135
- MILMAN N, KIRCHHOFF M. Iron stores in 1433, 30- to 60-year-old Danish males. Evaluation by serum ferritin and haemoglobin. *Scand J Clin Lab Invest* 1991, 51:635-641
- GILLUM RF. Association of serum ferritin and indices of body fat distribution and obesity in Mexican American men: The Third National Health and Nutrition Examination Survey. *Int J Obes Relat Metab Disord* 2001, 25:639-645
- SALONEN JT, NYSSONEN K, KORPELA H, TUOMILEHTO J, SEPANEN R, SALONEN R. High stored iron levels are associated with excess risk of myocardial infarction in eastern Finnish men. *Circulation* 1992, 86:803-811

13. HUGHES K, CHOO M, KUPERAN P, ONG CN, AW TC. Cardiovascular risk factors in relation to cigarette smoking: A population-based survey among Asians in Singapore. *Atherosclerosis* 1998, 137:253–258
14. KANNEL WB, ANDERSON K, WILSON PW. White blood cell count and cardiovascular disease: Insights from the Framingham study. *JAMA* 1992, 267:1253–1256
15. MILMAN N, KIRCHHOFF M. Relationship between serum ferritin, alcohol intake, and social status in 2235 Danish men and women. *Ann Hematol* 1996, 72:145–151
16. MILMAN N, BYG KE, OVESEN L, KIRCHHOFF M, JURGENSEN KSL. Iron status in Danish men 1984–94: A cohort comparison of changes in iron stores and the prevalence of iron deficiency and iron overload. *Eur J Haematol* 2002, 68:332–340
17. WHITFIELD JB, ZHU G, HEATH AC, POWELL LW, MARTIN NG. Effects of alcohol consumption on indices of iron stores and of iron stores on alcohol intake markers. *Alcohol Clin Exp Res* 2001, 25:1037–1045
18. LEGGETT BA, BROWN NN, BRYANT SJ, DUPLOCK L, POWELL LW, HALLIDAY JW. Factors affecting the concentrations of serum ferritin in a healthy Australian population. *Clin Chem* 1990, 36:1350–1355

*Corresponding author:*

E. Mazokopakis, 38A Iroon Polytechniou street, GR-731 32 Chania, Greece  
e-mail: elmazokopakis@yahoo.gr