Factors That Affect Serum Levels of Ferritin in Australian Adults and Implications for Follow-up

Elizabeth J. McKinnon,[*] Enrico Rossi,[‡] John P. Beilby,[‡,§] Debbie Trinder,[‖,¶] and John K. Olynyk[*,#,**]

*Institute for Immunology and Infectious Diseases, Murdoch University, Murdoch, Western Australia; ‡PathWest, Perth, Western Australia; §School of Pathology and Laboratory Medicine, University of Western Australia, Nedlands, Western Australia; ‖School of Medicine and Pharmacology, Fremantle Hospital, University of Western Australia, Fremantle, Western Australia; ¶Western Australian Institute of Medical Research, Perth, Western Australia; #Department of Gastroenterology, Fremantle Hospital, Fremantle, Western Australia; and **Curtin Health Innovation Research Institute, Curtin University, Bentley, Western Australia, Australia

BACKGROUND & AIMS: **Serum levels of ferritin are commonly measured to assess iron stores but are affected by factors such as obesity and chronic disease. Published reference ranges have not changed in decades, and the number of patients whose levels exceed the upper limits has been increasing. As a result, more patients are evaluated for iron overload.**

METHODS: **We compared serum levels of ferritin in 1188 Australian adults who participated in the 2005 Busselton Population Survey with levels from the 1995 survey. Parametric regression was used to assess the effects of body weight and biochemical parameters on serum level of ferritin to derive contemporary population-appropriate reference ranges.**

RESULTS: **In 2005, age-adjusted levels of ferritin were 21% higher in men ($P < .0001$) and 10% higher in women ($P = .01$) than in 1995; 31% of men exceeded levels of 300 μg/L, compared with 23% in 1995. Body mass index (BMI) ≥25 kg/m^2 was associated with higher levels of ferritin in men ≥35 years old and in postmenopausal women ($P \leq .002$). Serum level of γ-glutamyltransferase (GGT) correlated with serum level of ferritin ($P < .0001$). In men, the estimated 95th percentiles ranged from 353 to 495 μg/L (<35 years), from 350 to 511 μg/L (≥35 years, BMI <25 kg/m^2), and from 413 to 696 μg/L (≥35 years, BMI ≥25 kg/m^2) when GGT levels were 10–75 IU/L. In women, the 95th percentiles ranged from 106 to 235 μg/L (premenopausal), from 222 to 323 μg/L (postmenopausal, BMI <25 kg/m^2), and from 249 to 422 μg/L (postmenopausal, BMI ≥25 kg/m^2) when GGT levels were 8–45 IU/L.**

CONCLUSION: **Serum levels of ferritin increased significantly between 1995 and 2005. Reference ranges that accommodate demographic and biomedical variations will assist clinicians in identifying individuals who require further evaluation for iron overload.**

Keywords: Hyperferritinemia; Risk Factor; Population-based Study; Overweight.

Measurements of serum ferritin levels provide important information regarding body iron stores. Serum ferritin levels ≤20 μg/L are present in about 12% of women and 2% of men in the adult population and are suggestive of iron depletion,[1,2] requiring assessment of physiological or pathologic causality.[3] Elevation of serum ferritin levels to values ≥300 μg/L is also commonplace, affecting 4% of women and 23% of men in an Australian population surveyed in 1995.[4]

Increasing ascertainment of adults with elevated serum ferritin levels has resulted in escalating rates of referral for evaluation or treatment of possible iron overload. Indeed, 36% of all referrals to the Australian Red Cross Blood Service for therapeutic phlebotomy in Australia are for such individuals.[5,6] However, serum ferritin levels are strongly influenced by dietary intake of iron-containing products, alcohol consumption, and body mass index (BMI),[2] and hyperferritinemia is observed not only in iron overload syndromes but also in subjects with other chronic liver diseases and non-hepatic inflammatory disorders.[7–10] The predictive

Abbreviations used in this paper: BMI, body mass index; GGT, γ-glutamyltransferase; HOMA-IR, homeostasis model assessment-estimated insulin resistance.

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value of elevated serum ferritin levels for iron overload is highest in those individuals with a history of exposure to exogenously administered iron or blood products, or individuals of northern European descent who are homozygous for the C282Y mutation in the HFE gene.[11] In such individuals, serum ferritin levels >1000 μg/L indicate an increased risk of disease affecting the liver, joints, and other organs.[12–14] It has been clearly demonstrated that hyperferritinemia outside of these clinical settings is associated with either normal or minimal elevation of hepatic iron concentration to levels not usually associated with iron-overload disease.[11,14] Although interest exists in iron reduction therapy for amelioration of cancer risk, improvement of insulin sensitivity in metabolic syndrome, and management of fatty liver disease, at the current time phlebotomy therapy is of no proven value in this group of individuals.[15–18]

Published reference ranges for serum ferritin levels were often derived many years ago, and the upper limits of normal, which are mostly in the vicinity of 300–400 μg/L (Supplementary Table 1), are progressively being exceeded by greater numbers of individuals, prompting evaluation for potential iron overload. Differences in published reference ranges are most evident in the upper limit, and it is not clear whether ranges are based on values of historical or clinical relevance or determined from observed population central ranges. Because of the increasing rates of obesity and metabolic syndrome in most Western populations,[19] it is quite likely that the previously determined reference ranges for serum ferritin within our population have changed over time.[2,4,20] The aims of this study were to (1) characterize how serum ferritin levels have changed over time, (2) define the upper limit of a population-appropriate reference range for serum ferritin, and (3) determine the effect of body weight and biochemical parameters including glucose, insulin, lipid, and liver biochemistry on the reference range in a community-based study of adults.

Materials and Methods

Population and Subjects

Busselton is a town in the southwest of Western Australia that has been prospectively surveyed since 1966 and is in many respects similar to the Framingham population.[21] Approximately 95% of the adult Busselton population is white, predominantly of Anglo-Celtic ancestry, and 1.5% Indigenous Australian (2006 census). Of residents born overseas (15.2%), nearly three-fourths have emigrated from Europe, mostly the United Kingdom and Western Europe. In 2005, 6544 adults aged 20–79 years were randomly selected from the electoral roll and invited to participate, and data were collected from 2549 (39.0%). Of these participants, 81% were born in Australia, 16% in Europe, and 1% in New Zealand. For the study presented here the cohort was stratified by age, with 100 men and 100 women of the 2549 adults randomly selected from each decade between 20 and 80 years, with the exception of men aged 20–29 where only 89 participants were available. Comparisons were made with data from 2991 randomly selected participants (51% male) of a 1995 study conducted as a follow-up to earlier surveys; 87% of this cohort were born in Australia and 11% in Europe. Permission was granted for this study by the Busselton Population Medical Research Foundation and the Committee for Human Rights at the University of Western Australia.

Biochemical and Clinical Measurements

The conduct of the Busselton health surveys has been described previously.[2,4,22,23] In brief, survey participants were asked to complete a comprehensive health and lifestyle questionnaire and to undergo various clinical measurements and tests. Anthropometric measures (waist circumference, weight, and height, from which BMI was calculated) were obtained by trained survey staff who used standardized protocols.

All blood samples were obtained from fasting participants in the early morning. Serum alkaline phosphatase, alanine aminotransferase and γ-glutamyltransferase (GGT) enzyme activities, total bilirubin and C-reactive protein, cholesterol and high-density cholesterol concentrations were determined at the time of the survey by using a Hitachi 917 automated biochemical analyzer (Hitachi, Tokyo, Japan). Serum ferritin concentrations of the 2005 cohort were determined in 2012 on sera retrieved from cryofacility storage at −80°C by using a chemiluminescent microparticle immunoassay technology on an Abbott Architect 16200 automated analyzer (Abbott, Abbott Park, IL). Ferritin assay performance was assessed by calculating between assay analytical variations (CV_A) from the mean and standard deviation of results for 3 quality control sera assayed daily during a 3-month period. The CV_A values for ferritin were 5.3%, 3.3%, and 4.4% at concentrations of 7, 59, and 440 μg/L, respectively. Ferritin analysis of the 1995 dataset used as a comparator had been performed in 1998 by a Chiron ACS-180 analyzer (Ciba-Corning, Medfield, MA), with CV_A values for ferritin of 4.2%, 9.5%, and 5.2% at concentrations of 9, 78, and 327 μg/L, respectively. Internal laboratory assessment of between-machine variation detected a downward bias in readings obtained from the later Architect machine, with readings estimated to be approximately 20% lower than if analyzed by the ACS machine used earlier.

Statistical Analysis

Cohort summaries used nonparametric statistics, including group medians and interquartile ranges,

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