Reference Distributions for Apolipoproteins AI and B and B/AI Ratios: Comparison of a Large Cohort to the World's Literature

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Limiting the clinical utility of apolipoproteins AI (apo AI) and B (apo B) and the apo B/AI ratios until the last decade has been the lack of satisfactory methods for quantifying serum levels and credible reference materials. Great technological strides have been made in the last few years. The remaining barrier to more relevant and cost-effective use of serum protein data for diagnosis and prognosis has been the availability of widely recognized reliable reference intervals from birth to old age for both males and females. A total of 82 publications reporting reference intervals have been identified that meet most of the same inclusion criteria used in our prior six studies. These have been analyzed statistically and

compared to similar studies, i.e., sufficient number, listed subject criteria, method, and reference material, in general terms. Published smaller studies with constrained age ranges, agree on average with our large series of life-long reference intervals that range from less than one year to over 80 years. This study was performed to assess the degree of agreement between smaller reference interval studies to our large population analysis. This meta-analysis provides support and reassurance that many of the smaller reference intervals published previously fall within reasonable limits of our large population. *J. Clin. Lab. Anal.* 20:218–226, 2006. © 2006 Wiley-Liss, Inc.

Key words: reference intervals; Caucasian; apolipoprotein AI; apolipoprotein B; apolipoprotein B/AI ratio; SP1-01; SP3-07

INTRODUCTION

The acute phase response can induce upregulation of synthesis of some serum proteins, downregulation of others, and accelerated catabolism of others. However, its effect on apolipoproteins (apo) AI and B has not been carefully studied. The inflammatory response, especially when intense, can affect both synthesis, destruction, and distribution within the body. In other words, increased synthesis can be masked by apparent accelerated loss with resulting levels remaining within the normal range. Diagnostic and prognostic application of these measurements has previously been largely limited to assessing whether serum levels change with evolving or overt atherosclerotic cardiovascular disease, the nephrotic syndrome, and certain metabolic disorders, without taking into consideration other coexisting problems.

The two proteins examined in this study, lipoproteins AI and B, and the B/AI ratio represent the major lipid transport moieties believed to be important in the inception and evolution of atherogenic heart disease, a major public health issue. This study, like its predecessors (1–6), aims to identify publications that provided reference data for these measurements and satisfied minimal acceptance criteria. A total of 82 publications from the period between 1972 and 2003 were identified and reviewed (7–88).

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MATERIAL AND METHODS

Identification of Published Reference Data

Briefly, the methods used to search for relevant publication were the same as for the previous studies

(1–6) with the key-word headings and the analyte specific terms using PubMed (<http://www.ncbi.nlm.nih.gov/PubMed>) and MEDLINE CD-ROM searches (OVID Technologies, New York, NY). Methodological

Fig. 1. A summary of published apo AI and B median reference values. The published central estimates for apo AI (A), and apo B (B), and the apo B/AI ratio (C) are displayed on the logarithmic vertical axis vs. the mean (or median) age on the logarithmic horizontal axis. The three symbol sizes represent the number of observations in each group (small, medium, and large circles, representing over 100, 50 to 99, and 10 to 49 observations, respectively). The solid (male) and dashed (female) lines are the regressed median levels from our large cohort study (98).

Fig. 1. Continued.

papers or those that only examined patients with specific diseases were excluded. Articles were considered acceptable if they: 1) identified the assay method; 2) provided minimum details of the study population such as age; and 3) provided sufficient numerical information for statistical analysis. Our previous meta-analyses required that a credible reference material be named; however, in this analysis this was not feasible since the reference material of choice did not become available until the 1990s. Instead we elected to accept all reference materials if one was listed.

Estimating the Central Estimate and Reference Intervals from Published Studies

The mean, median, or geometric mean was used as the estimate of the center of the distribution. If not directly available, these values were computed using observed or smoothed centiles (e.g., between the 2.5th and 97.5th centile). If none of these were available, the study was excluded. Observed 95% reference intervals were used for the reference interval analysis. If the interval was estimated from parameters or was other than the 95% interval, the study was excluded from the reference interval analysis.

Reported Results Assigned to Single Reference Materials

Results from the most recent papers in this study had been standardized against SP1-01 for apo AI and

SP3-07 for apo B, as previously described (89–93). This material was released by the International Federation of Clinical Chemists (IFCC), the Community Bureau of Reference (BCR) in Brussels, Belgium (94,95). Recent publications, however, raise some doubt on the issue of commercially available reference materials processed by protocols that are not in accordance with recommendations, which are thus unstable and produce unreliable results (96,97).

RESULTS

Number of Studies Available for Analysis

A total of 82 publications were identified that contained information on apo AI and/or B and in a smaller number of cases, the apo B/AI ratios, in apparently healthy individuals (7–45,47–88). A total of 66 papers had enough data to calculate central estimates and 28 papers supplied sufficient information for calculating the reference intervals for one or more of the values (Figs. 1 and 2).

Of the 82 publications identified that contained information on apo AI and/or B or the apo B/AI ratios, 73 had information on apo AI, 75 on apo B, and 25 on the apo B/AI ratio. Of these, sufficient information for calculating central estimates was available in 64, 66, and 18 publications, respectively. A total of 28, 25, and 11 publications supplied sufficient information for calculating individual reference intervals for apo AI,

apo B, and the B/AI ratio, respectively. A small number of publications with the fewest cases or older technology were excluded from Figs. 1 and 2 due to space constraints.

Comparison of the Central Estimates

Figure 1 shows the central estimates of apo AI (Fig. 1A), apo B (Fig. 1B), and the apo B/AI ratios (Fig. 1C). The reported mean (or median) age of the study population is shown on the logarithmic horizontal axis vs. the central estimates on the logarithmic vertical

axis. Each observation is shown as a circle, with the smallest and darkest circles representing the more reliable estimates (over 100 observations). If a published observation was based on less than 10 observations, it was combined with an adjacent age group from the same publication, if possible, otherwise it was not shown. For purposes of comparison, the solid and dashed lines represent the median levels found for males and females, respectively, in our companion study (98).

Figure 1A shows the reported apo AI median values from the 64 published studies considered acceptable. In adults, the range is at least two-fold for the majority

Fig. 2. Reference intervals from published studies. The bars represent the interval between the 2.5th and 97.5th centile for each study with the number of subjects above the bar. The horizontal axis shows the reference number for each study. The selected centiles have been presented as multiples of the median (MoM), compensating for age, gender, and reference material differences between studies. The analyses for apo AI (**A**) and apo B (**B**) measurements, and the apo B/AI ratios (**C**), on identical logarithmic vertical axes. The horizontal dotted lines display the weighted consensus value at the 2.5th centile and the 97.5th centile for previously published studies. The broken bars represent the observed and predicted reference intervals from our large cohort study (57). (In certain instances the number of cases differs from the published information, as the result of portions of the data not meeting our full criteria.)

Fig. 2. Continued.

of the studies. Our median levels for apo AI are in the midrange of values from a number of published estimates. The estimates of our median apo B levels (Fig. 1B) are also in the midrange of the 66 published studies. Our median apo B/AI ratios (Fig. 1C) are somewhat lower than the 18 published studies.

Comparison of the Reference Intervals

It is possible that our reference intervals may be wider than other smaller studies because we relied on the diagnosis provided on the laboratory requisition slip (99). For that reason, we compared our 95% reference limits with those published. The reference intervals reported in the studies used in the above analyses were sometimes based on a small number of observations; however, 40 of 73 studies of apo AI, 25 of 75 studies of apo B, and 15 of 25 studies of the apo B/AI ratio included 100 or more observations. Therefore, verification of the health status of each individual was usually possible; however, our observed reference intervals were each based on over 27,000 (out of over 37,000) observations, and verification was not possible for each individual. Figure 2 shows other published studies after conversion to multiples of the median (e.g., each study's reference limits divided by their own population medians). The reference numbers are shown on the horizontal axis; sorted by decreasing 95% reference interval width. The weighted average of the upper and lower limits of the ranges reported in the literature (excluding our study) is shown by two thin horizontal dashed lines. The 95% reference intervals for our study (both observed and predicted from the popula-

tion parameters) are represented as thick dashed lines. Figure 2A–C shows the analysis for apo AI, apo B, and the B/AI ratio reference intervals, respectively. For both analytes and the B/AI ratio, the width of our reference values fall in the middle of those found in the literature.

Ethnic Group–Specific Reference Intervals

Of the 83 studies included in these analyses, 25 publications provided values on racial or ethnic groups. Only six stated categorically that the subjects were only Caucasian (14,40,57,58,60,78,79). Three reported results in both Caucasian and black African Americans without distinction (18,19,81); three gave data on blacks and Caucasians separately (84–86); one reported on a large cohort of Caucasians, blacks, and Hispanic individuals (58); one reported on black Africans; two described values for restricted ethnic groups (42,44,83,87); and seven reported on Asians (28,29,43,63,65,75,77). The remaining 58 did not provide racial composition of their study subjects. There was no apparent difference in the levels of apo AI, apo B, or the apo B/AI ratio in racial or ethnic cohorts, as illustrated in Fig. 2.

DISCUSSION

This is the seventh in a series of meta-analyses for serum protein reference intervals. Our practical approach applied to published population data produces many reference intervals comparable to our companion study (98), which reported reference data for apo AI, apo B, and the B/AI ratio based on over 27,000 observations.

The current meta-analysis, like the previous six, shows our median levels and reference interval widths to be consistent with published studies indicating that local laboratory reference intervals may already be close to optimal if the intervals have been previously calibrated to SP1-01 and/or SP3-07.

The availability of a robust set of reference data for both sexes and throughout life facilitates more reliable incorporation of serum protein values into diagnostic and prognostic patient evaluation. These intervals also set the stage for studying possible differences in population subgroups (e.g., racial/genetically predisposed (81,85,86,100) or geographic). By employing recommended protocols (101,102) local populations can now be compared more easily and with smaller study groups, since variations by age and sex can be taken into account prior to population comparisons.

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