Screening primary care patients for hereditary hemochromatosis with transferrin saturation and serum ferritin level: systematic review for the American College of Physicians

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CRD summary
This review assessed the usefulness of screening for haemochromatosis in primary care using transferrin saturation and serum ferritin levels. The authors concluded that evidence does not support screening for haemochromatosis. The limited literature search might have missed some relevant studies. However, the authors' conclusions reflect the sparse and varied data presented.

Authors' objectives
To review the evidence on: the prevalence of hereditary haemochromatosis in primary care; the morbidity and mortality risks in untreated patients; the diagnostic accuracy of transferrin saturation and serum ferritin levels for identifying hereditary haemochromatosis; the efficacy of early treatment; and the efficacy of screening.

The first two questions on prevalence and risk are not considered in this abstract.

Searching
MEDLINE was searched from 1966 to April 2004 for articles published in the English language. Additional studies were sought by reviewing the references of included studies.

Study selection
Study designs of evaluations included in the review
Diagnostic accuracy studies and controlled treatment comparisons were eligible for inclusion.

Specific interventions included in the review
Studies evaluating the use of transferrin saturation and serum ferritin to screen for hereditary haemochromatosis were eligible for inclusion. The cut-off values used to define a positive test result varied between the studies. Studies evaluating the use of therapeutic phlebotomy as a treatment for haemochromatosis were also eligible.

Reference standard test against which the new test was compared
Included studies were required to define the presence of hemochromatosis by liver biopsy [A: hepatic iron concentration >30mmol/kg dry weight], or response to therapeutic phlebotomy [A: removal of >2000mg of storage iron]. The reference standard was inconsistently applied: not all patients who tested positive underwent liver biopsy, no study reported follow-up or liver biopsy on patients testing negative.

Participants included in the review
Studies of primary care patients were eligible for inclusion.

Outcomes assessed in the review
No outcome measures for diagnostic performance were specified. Included studies addressing the therapeutic effectiveness of phlebotomy were required to report one or more of the following outcomes: diabetes mellitus, congestive heart failure, arthritis, cirrhosis, hepatocellular carcinoma, survival.

How were decisions on the relevance of primary studies made?
Two reviewers independently assessed abstracts for inclusion. Any disagreements were resolved by a third reviewer.

Assessment of study quality
The authors did not conduct a formal quality assessment; issues of methodological quality in individual included studies
were highlighted in the results tables.

Data extraction
Two reviewers independently extracted the data.

Methods of synthesis
How were the studies combined?
The studies were combined in a narrative.

How were differences between studies investigated?
Differences between the studies were discussed in the text.

Results of the review
Three studies (7,315 participants) that assessed the diagnostic performance of transferrin saturation and serum ferritin levels for the identification of haemochromatosis were included in the review. One retrospective cohort (158 participants) and one before-and-after study (251 participants), both assessing the effectiveness of phlebotomy for the treatment of haemochromatosis, were also included in the review.

Diagnostic accuracy.
Data on the diagnostic performance of transferrin saturation and serum ferritin were very limited; studies varied with respect to the reference standard of diagnosis, reported no data on test-negative patients, and not all patients with values over the threshold underwent further assessment. It was therefore not possible to derive estimates of sensitivity and specificity.

Effectiveness of phlebotomy.
No randomised trials of therapeutic phlebotomy were identified. A retrospective cohort study reported greater estimated Kaplan-Meier survival for patients who were adequately phlebotomised compared with those who were not (93% versus 48% at 5 years, and 78% versus 32% at 10 years), but the clinical comparability of the patient groups could not be determined. A before-and-after study reported improved liver histology in 42 out of 185 patients after phlebotomy (deterioration was reported in 2 patients); biopsy sampling error was a potential concern in this study.

Effectiveness of screening.
Given the lack of evidence on the effectiveness of therapeutic phlebotomy, the effectiveness of screening in primary care could not be directly assessed.

Cost information
Four cost-effectiveness analyses assessed the benefits and risks of screening. However, a lack of data limited a review of cost-effectiveness.

Authors’ conclusions
The available evidence did not demonstrate the clinical-effectiveness of screening for haemochromatosis in primary care.

CRD commentary
The objectives of this review were clearly stated. However, the inclusion criteria used to identify relevant studies were not clearly defined. The limitation of the search to a single bibliographic database and English language publications might have resulted in the incomplete retrieval of relevant publications. In addition, no attempts were made to identify...
unpublished studies, thus raising the possibility of publication bias. The duplication of the study selection and data extraction processes reduces the potential for bias and errors. Although the quality of the included studies was not formally assessed, the limitations of the included studies were discussed in detail in the text. Given the sparsity and apparent heterogeneity of the available data, the use of a narrative synthesis seems appropriate. The authors’ conclusions are appropriate for the data presented.

Implications of the review for practice and research
The authors made no specific recommendations for practice or further research.

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