HOMOCYSTEINE TESTING THE SCREENING, DIAGNOSIS AND MANAGEMENT OF CARDIOVASCULAR DISEASE
MED207.125
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COVERAGE:

Measurement of plasma levels of homocysteine are considered experimental or investigational in the screening, evaluation and management of patients for cardiovascular disease.

DESCRIPTION:

Homocysteine is a sulfur-containing amino acid that is rapidly oxidized in plasma into homocystine and cysteine-homocysteine disulfide. Measurement of total plasma homocysteine is the sum of homocysteine and its oxidized forms. The laboratory test is referred to as either homocysteine or homocyst(e)ine.

Plasma levels of homocysteine have been actively researched as a risk factor for cardiovascular disease, initially based on the observation that patients with hereditary homocystinuria, an inborn error of metabolism associated with high plasma levels of homocysteine, had a markedly increased risk of cardiovascular disease. Subsequently, prospective epidemiologic studies were conducted to determine if elevated plasma levels of homocysteine could be used as an independent risk factor for cardiovascular disease. Interest in homocysteine as a risk factor was further stimulated by the fact that plasma levels of homocysteine would be considered a modifiable risk factor; i.e., plasma levels may be modified by diet, specifically by increased intake of vitamin B12, B6 and folate.

Determination of homocysteine may be offered as a component of a comprehensive cardiovascular risk assessment that may include evaluation of small density lipoproteins, subclassification of high density lipoproteins, evaluation of lipoprotein (a), high sensitivity C-reactive protein and genotyping of apolipoprotein E.

RATIONALE:

Evaluation of the clinical utility of a risk factor involves the following steps:

1. Standardization of the technology
2. Determination of its diagnostic performance. As a risk factor, it is important to determine whether the novel risk factor (i.e., plasma homocysteine) independently contributes to risk assessment compared to established risk factors.
3. Determination of how the novel risk assessment will be used in the management of the patient compared to standard methods of assessing risk, and whether any subsequent changes in patient management result in an improvement in patient outcome.
The above attributes are discussed below in the context of plasma homocysteine levels.

1. **Standardization of the technology.**
   Plasma measurement of homocysteine may be performed by a variety of techniques including high performance liquid chromatography, gas chromatography-mass spectrometry, and immunoassay. Studies have shown correlations between different methods and also a within-assay precision.

2. **Determination of diagnostic performance.**
   A variety of epidemiologic studies of different designs have examined the relationship between plasma homocysteine levels and cardiovascular disease. Although no optimal level of plasma homocysteine has been defined, normal levels are considered to be between 5 and 15 umol/L, while moderate, intermediate, and severe elevations are considered to be between 16 and 30 umol/L, 31 and 100 umol/L, and >100umol/L, respectively. In a 1995 meta-analysis of 27 prospective and case control studies of plasma homocysteine, it was assumed that there was a linear relationship between plasma homocysteine and risk of cardiovascular disease, i.e., there was no threshold effect and that the risk would increase incrementally with increasing plasma homocysteine levels. The odds ratio for either coronary, cerebrovascular, or peripheral vascular disease was varied among the studies, but all were greater than 1, consistent with an increased risk. The associated confidence intervals were of varying breadth, but in all but a few studies the confidence intervals were all above one, further suggesting an increased risk. A subsequent 1997 case control study of 750 patients with known cardiovascular disease and 800 control subjects also reported that increasing levels of plasma homocysteine were an independent risk factor, powerfully increasing the risk associated with smoking or hypertension.

Of perhaps greatest clinical relevance are prospective studies in which homocysteine levels are tested in asymptomatic patients, and then these patients are followed up for subsequent cardiovascular events. Several prospective studies focusing on initially asymptomatic patients have reported mixed results. For example, Fulsome and colleagues identified all patients who developed coronary heart disease among an initial cohort of 15,792 patients who participated in the Atherosclerosis Risk in Communities (ARIC) trial. The median follow-up time was 3.3 years. Plasma homocysteine was evaluated from the stored blood samples of the 232 patients plus a random sample of the rest of the cohort. Compared with non cases, participants who subsequently developed coronary heart disease tended to have a higher baseline mean level of plasma homocysteine. However, this association
was not significant after adjusting for other cardiac risk factors. Similarly, Evans and colleagues identified 240 cases of nonfatal myocardial infarction or coronary death among a cohort of 12,866 men participating in the Multiple Risk Factor Intervention Trial (MRFIT). Plasma homocysteine from stored blood samples of these patients plus 472 controlled were evaluated. With a follow-up ranging from 11 to 17 years, homocysteine levels did not appear to be an independent risk factor for coronary heart disease. In contrast, in a prospective study using similar methodology as the above studies, Wald and colleagues reported that the initial stored plasma level of homocysteine was significantly higher among 229 men who ultimately died of ischemic heart disease compared to a control group of 1,126 men, drawn from the original study of 21,520 men. Similarly, Arnesen and colleagues found homocysteine was a risk factor for coronary heart disease based on their study of 122 patients who developed coronary heart disease out of a sample of 21,826 men and women. In summary, the data derived from prospective studies are inconclusive regarding the existence and degree of cardiovascular risk associated with elevated levels of plasma homocysteine.

Other prospective studies have focused on patients with known cardiovascular disease. For example, Nygard and colleagues prospectively studied the plasma homocysteine levels in 587 patients with angiographically confirmed coronary artery disease. After a median follow-up of 4.6 years, the authors compared the initial homocysteine levels of the 64 patients (10.9%) who had died to the remaining 523 survivors. The authors reported a strong graded dose response relation between plasma homocysteine and mortality. Stubbs and colleagues evaluated the relationship between plasma homocysteine levels and prognosis (i.e., cardiac death or myocardial infarction) in 440 patients with acute coronary syndromes admitted to the hospital. Admission plasma homocysteine levels were not related to short-term outcomes at 28 days, however, in long-term follow-up, patients with homocysteine levels in the 2 highest quintiles had a 2.6-fold increase in the risk of a cardiac event. In summary, the studies cited herein suggest that plasma homocysteine levels are positively correlated with prognosis in patients with known cardiovascular disease.

3. Homocysteine levels and the management of the patient.

The above epidemiologic studies only demonstrate an association (in some studies) between homocysteine and cardiovascular risk. It is not known whether lowering plasma homocysteine levels will modify that risk, and currently there are no target levels for optimal homocysteine levels. In addition, adherence to a diet meeting the recommended daily allowance (RDA) for folate intake, i.e., a general health message not requiring measurement of folate levels, could
result in decreased levels of homocysteine. In addition, in 1996, the U.S. Food and Drug Administration (FDA) required all enriched grain products to be fortified with folic acid to reduce the risk of neural-tube defects in newborns. This fortification has been associated with a decrease in homocysteine concentration. Given the limitations of the present data, the American Heart Association does not recommend population-wide screening for homocysteine levels. This statement suggests that measurement of plasma homocysteine may have some role in patients with a personal or family history consistent with premature cardiovascular disease, with the suggestion that those with levels above 10.0umol/L be advised to increase their intake of folic acid. However the outcomes of this treatment strategy have not been addressed in controlled trials.


This report states the mechanism of the link between homocysteine and CHD is not well understood, although persons with inherited forms of severe homocystinemia have premature vascular injury and atherosclerosis. In any case the strength of association between homocysteine and CHD is not as great as that for the major risk factors. Moreover, an elevation of homocysteine is not as common as that of the major risk factors. For these reasons ATP III does not list elevated homocysteine as a major risk factor to modify LDL-cholesterol goals.

ATP III does not recommend routine measurement of homocysteine as part of risk assessment to modify LDL-cholesterol goals for primary prevention. This is based on uncertainty about the strength of the relation between homocysteine and CHD, a lack of clinical trials showing that supplemental B vitamins will reduce risk for CHD, and the relatively low prevalence of elevated homocysteine in the U.S. population. Measurement of homocysteine nonetheless remains an option in selected cases, e.g., with a strong family history of premature CHD in an otherwise low-risk patient. If elevated, the clinical approach favored by ATP III is to determine vitamin B-12 level and, if this is normal, to ensure adequate folate intake rather than modifying the LDL-cholesterol goal.

PRICING:

None

REFERENCES:
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- The Euroopean concerted Action Project. Plasma homocysteine as a risk factor for vascular disease. JAMA 1997; 277:1775-81

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