Normal cholesterol measurements in white collar workers still at cardiovascular risk?

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Low serum total cholesterol (TC) in workers has been taken to indicate absence of cardiovascular (CV) risk. In angiographically confirmed coronary artery disease TC has been shown to be less poignant than compound indices of cardiovascular risk in separating patients from controls. The implications for prevention in an industrial medical setting of relying on TC measurements are discussed. Employees (n=229) tested by an occupational health service in a non-manufacturing firm were dichotomized as low and high cardiovascular risk subjects either by the level of total cholesterol, or by two compound indices of blood lipid components. The compound indices were: the TC/HDLc-ratio, and an 'atherogenic index' (ATH-index) defined as 

\[
\frac{(TC-HDLc) \times (apo B)}{(HDLc) \times (apo A)}
\]

(apo A= apolipoprotein A-I, apo B= apolipoprotein B). Cut-off values to separate between low- and high-risk subjects were defined as TC=6.0 mmol/l, HDLc=0.9 mmol/l, apo A=1.8 g/l and apo B=1.3 g/l, based on clinical guidelines in Norway. These individual cut-off values gave TC/HDLc and ATH-index cut-off values of 6.7 and 4.1, respectively. Assuming a more correct discrimination between persons at low- and high-risk, using compound lipid indices, both the number of persons given unnecessary advice on lifestyle changes or urged to take TC reducing medication, and the number of persons not treated on the basis of normal TC levels, would be reduced. Percentages of persons classified as TC-level-low risk, were adjusted using empirical data on sensitivity and specificity of the compound indices. Among employees with TC <6.0mmol/l, 15% and 23% of women, and 12% and 19% of men would be classified as high-risk persons using the TC/HDLc-ratio or the ATH-index, respectively. Lack of prospective data on compound indices suggests cautious interpretation. TC values in spurious testing, as often applied in occupational health service without due regard to other lipid fractions, would increase the probability of unnecessarily treating persons not at CV risk and withholding people at probable CV risk from treatment. Although prospective studies are needed to confirm findings, the changes observed suggest avoiding measurements of some single lipid factors.

INTRODUCTION

Screening persons above 40 years for cardiovascular (CV) risk is considered a useful preventive measure, and measuring total cholesterol (TC) once before the age of 40 has been advocated by preventive cardiologists. Occupational health service is conveniently in contact with all employees, including persons not visiting general practitioners regularly. Total cholesterol reduction, blood pressure regulation and cessation of smoking have been major aims of preventive cardiology.1 Whereas blood pressure normalization has reduced the prevalence of cardiovascular mortality, and smoking cessation also favourably influences cardiovascular risk,2 reduction in total cholesterol levels, both by dietary and pharmacologically initiated programmes, have not unequivocally been associated with reduced CV mortality3-6

Predictive value of serum total cholesterol may be as low as <2%, reducing the value of TC as a gold
standard method. The finding of an increase in mortality after 15 years of TC reducing efforts in a group of Finnish businessmen supports this view.

Extended knowledge of lipid metabolism has increased our laboratory armamentarium to assess CV risk, even in the non-fasting state, and will presumably also provide improved diagnostic possibilities. Although TC measurements are not considered by many as diagnostic of future CV disease, the busy GP may often rely on such simple measurements as a guideline when also other risk factors are present. In a Swedish study of management of hyperlipidaemia, general practitioners, industrial medical officers and internists were asked about their assessment of CV risk tests. TC tests were considered to be the most important indicator by 42%, 23% and 26% respectively, whereas 46%, 63% and 56% respectively, considered the LDL/HDLc-index test to be the best. Drug treatment was started at a lower level of TC by industrial medical officers engaged in primary prevention, maybe suggesting a fear of not reacting due to false negative tests. Although multiple predictors of cardiovascular disease are already well accepted as superior to total cholesterol measurements alone, the above-mentioned study indicates that the activity of practitioners still may lag somewhat behind this level of knowledge. In another study, Norwegian general practitioners did not change their former treatment decisions for hyperlipidaemia at TC levels >7.2 mmol/l at a follow-up inquiry 3 months after a National Cholesterol Campaign, a fact also substantiated in a Canadian study.

The aim of the study would then be to indicate the variability of normal total cholesterol measurements done in occupational health service compared with lipid indices including HDL-cholesterol and apolipoprotein measurements.

Compound indices and total cholesterol measurements

The positive relationship between serum cholesterol levels in a population and the cardiovascular mortality rate is impressive, but its value as a guideline in individual counselling may be less impressive. A more detailed understanding of lipid metabolism has urged many researchers to look for compound indices, which are presumed to discriminate better between persons at low- and high-risk of cardiovascular disease. A reason for this is the appreciation that other lipid components in blood may significantly influence the overall lipid balance, and hence the risk of CV. Recommending measurement of other lipid components than TC only before the age of 40 may improve the predictive value of the advice given.

The relative amount of the apolipoprotein B (apo B) and cholesterol in low density lipoprotein (LDL) in blood can be different in CV disease cases and controls. As reported by Sniderman, et al. patients may have hyper-betalipoproteinemia with fairly normal levels of total cholesterol. In line with this, it may be hypothesized that variations in the relative amounts of apolipoprotein A (apo A) and cholesterol in the antiatherogenic high density lipoproteins (HDLc) may also contribute to augment separation of patients and controls, when using compound indices as compared to TC. Even if compound indices separate better, none of the proposed indices are at present suitable as a gold standard in preventive cardiology.

It was previously shown, in a comparison between angiographically defined coronary patients and controls, that an atherogenic index (ATH-index), calculated as

\[
\text{ATH-index} = \frac{\left(\frac{\text{[TC]} - \text{[HDLc]}}{\text{[apo B]}}\right) \times \text{[apo B]}}{\text{[apo A]}} \times \text{[HDLc]}
\]

yielded better separation than TC, TC/HDLc and other indices. In a study of heart transplant recipients, the post-operative increase in TC was compared in patients given lovastatin and controls. The ATH-index separated better, showing a 61% reduction, than TC (19%) and LDL (24%). The long-term metabolic effects of n-3 polyunsaturated fatty acids in patients after bypass surgery showed a reduction in the ATH-index which was not apparent according to TC or LDL levels.

MATERIALS

In a study of 229 healthy employed men (n=112) and women (117) TC was compared with two compound indices, TC/HDLc-ratio and the ATH-index. Mean ages (sd) in men and women were 39.8 (10.7) and 40.1 (13.0) respectively. Employees with known hypertensive, other cardiovascular or renal disorders were excluded, and none refused to participate. Sixty-eight per cent of the employees had TC <6.0 mmol/l. Only 10 employees had a TC >8.0 mmol/l, and 73 persons (32%) had a TC value above 6.0 mmol/l (Figure 1). Laboratory methods are described elsewhere.

A cut-off between low- and high-risk was defined, based on current clinical laboratory reference values for TC, HDLc and the apolipoproteins. As an upper, normal limit of TC, 6.0 mmol/l was chosen, which would be in agreement with current recommendations. Similarly a lower limit for HDLc was set at 0.9 mmol/l. On the basis of reference values from clinical laboratories in Norway, a cut-off for apo B was set at 1.3 g/l and for apo A at 1.8 g/l. The cut-off values between low- and high-risk thus calculated were 6.7 and 4.1 for the TC/HDLc and the ATH-index, respectively.

RESULTS

Among employees with a TC-value below 6.0 mmol/l, the TC/HDLc and the ATH-index would have allocated 97% and 75% (Table 1), respectively, to a
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Figure 1. Distribution of total cholesterol values (mmol/l) among healthy employees in a non-manufacturing firm, n=229. Line indicates division between low- and high-CV risk.

<table>
<thead>
<tr>
<th>Level of total cholesterol</th>
<th>Total cholesterol mmol/l</th>
<th>TC/HDLc-index</th>
<th>ATH-index</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;3</td>
<td>&lt;6.0</td>
<td>97</td>
<td>75</td>
</tr>
<tr>
<td>3-3.5</td>
<td>55.4 TN*</td>
<td>15.1 FN</td>
<td>47.6 TN</td>
</tr>
<tr>
<td>3.5-4</td>
<td>19.9 FP</td>
<td>9.6 TP</td>
<td>10.4 FP</td>
</tr>
<tr>
<td>4-4.5</td>
<td>25.0 FP</td>
<td>14.0 TP</td>
<td>28.0 TP</td>
</tr>
<tr>
<td>4.5-5</td>
<td>29.5% of sample</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-5.5</td>
<td>44.6 TN</td>
<td>12.2 TN</td>
<td>38.3 TN</td>
</tr>
<tr>
<td>5.5-6</td>
<td>43.2% of sample</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6-6.5</td>
<td>43.6 TN</td>
<td>12.2 FN</td>
<td>47.6 TN</td>
</tr>
<tr>
<td>6.5-7</td>
<td>20.8 FP</td>
<td>9.6 TP</td>
<td>10.4 FP</td>
</tr>
<tr>
<td>7-7.5</td>
<td>28.0 TP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7.5-8</td>
<td>32.4% of sample</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8-8.5</td>
<td>36.0 TN</td>
<td>12.2 FN</td>
<td>38.3 TN</td>
</tr>
<tr>
<td>8.5-9</td>
<td>39.4% of sample</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;9</td>
<td>55.4 TN</td>
<td>15.1 FN</td>
<td>47.6 TN</td>
</tr>
</tbody>
</table>

Table 1. Fraction of persons classified as low-risk individuals measured by two indices of cardiovascular risk, according to their total cholesterol value using TC values as a 'gold standard'.

<table>
<thead>
<tr>
<th>Total cholesterol mmol/l</th>
<th>TC/HDLc-index</th>
<th>ATH-index</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>&lt;6.0</td>
<td>97</td>
</tr>
<tr>
<td>Group 2</td>
<td>≥6.0</td>
<td>64*</td>
</tr>
</tbody>
</table>

† See second footnote, Table 2.

Table 2. Percentages of persons classified as low-risk individuals (negative test) measured by two compound indices of cardiovascular risk, grouped according to their total cholesterol value and sex. The percentages are recalculated using the sensitivity and specificity of the two compound indices as found by Høstmark, et al. in a study of the separation of coronary angiography-confirmed patients from controls. TC/HDLc-index: Sensitivity 90% and specificity 90%; ATH-index: Sensitivity 81% and specificity 90%.

<table>
<thead>
<tr>
<th>TC/HDLc-index</th>
<th>ATH-index</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women</td>
<td></td>
</tr>
<tr>
<td>Group 1</td>
<td></td>
</tr>
<tr>
<td>&lt;TC 6.0mmol/l</td>
<td>55.4 TN*</td>
</tr>
<tr>
<td>70.5% of sample</td>
<td></td>
</tr>
<tr>
<td>Group 2</td>
<td></td>
</tr>
<tr>
<td>≥TC 6.0mmol/l</td>
<td>19.9 FP</td>
</tr>
<tr>
<td>29.5% of sample</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td></td>
</tr>
<tr>
<td>Group 1</td>
<td></td>
</tr>
<tr>
<td>&lt;TC 6.0mmol/l</td>
<td>44.6 TN</td>
</tr>
<tr>
<td>56.8% of sample</td>
<td></td>
</tr>
<tr>
<td>Group 2</td>
<td></td>
</tr>
<tr>
<td>≥TC 6.0mmol/l</td>
<td>29.2 FP</td>
</tr>
<tr>
<td>43.2% of sample</td>
<td></td>
</tr>
</tbody>
</table>

* TN = True negative, i.e. not in need of advice or treatment, which is also the conclusion by TC measurements; FN = False negative, i.e. in need of advice or treatment, which is not the conclusion by TC measurements; FP = False positive, i.e. not in need of advice or treatment, but judged in need by TC measurements; TP = True positive, i.e. in need of advice or treatment.

† This entry was calculated as follows: The number of true positives 36% from Table 1 for the TC/HDLc-index must be adjusted according to the 90% specificity of this index: 32.4% is the adjusted value. There are 29.5% women with a TC-value above 6.0 mmol/l in the reference population. Thus 32.4% of 29.5% is 9.5% as the fraction of true positive women with TC >6.0mmol/l. The other entries are calculated similarly.

With the above assumptions, the number of persons at low- and high-risk would vary considerably, depending on the index-variables used, i.e. TC, TC/HDLc, or the ATH-index. As much as 25% of employees with a TC value <6.0 mmol/l would have an ATH-index value above the cut-off between low- and high-risk (Figure 2). Thus, by TC measurements alone they would barely be allocated to advice on lifestyle changes, or to medical treatment. However, by looking at the ATH-index value, these 25% would probably be allocated to such advice. Similarly, 28% of employees with a TC value above 6.0 mmol/l would be judged by the ATH-index to have a low risk, thus not being candidates for preventive measures.

A similar kind of reasoning suggests (Figure 3) that by the TC/HDLc index, 3% and 64% respectively would be allocated to probable under/over treatment if only TC measurements were used.

An indication of the ability of these two compound indices to separate better between angiographically confirmed atherosclerosis and normal controls may be obtained from the above-mentioned study, where coronary artery disease patients were compared with angiographically and clinically normal persons. Sensitivity and specificity in this study were 90% and 90% for the ATH-index, and 81% and 90% for the TC/HDLc index. Prospective studies of various ratios between the components of the indices indicate a relationship to CV mortality. The observations of Figures 2 and 3 may be recalculated taking the empirical validity percentages of the indices into account. Table 2 gives the calculated percentages with an explanation of the calculations in a footnote. Female employees with TCmmol/l would be judged as high-risk in 15% and 23% of cases with the TC/HDLc-ratio and the ATH-index, respectively. Male employees with
**Figure 2.** Distribution of ATH-index* values among healthy employees in a non-manufacturing firm, n=229.

ATH-index = ([TC-HDLc] × [apo B]) + ([HDLc] × [apo A]).

**Figure 3.** Distribution of TC/HDLc-ratio* values among healthy employees in a non-manufacturing firm, n=229.

TC/HDLc-ratio = [TC]/[HDLc] = TCHDL.

A higher percentage of high-risk persons also according to TC measurements, would likewise in 12% and 19% be judged as high-risk with the TC/HDLc-ratio and the ATH-index.

**DISCUSSION**

The number of misclassified persons pertinent to CV risk from this medium sized company indicate that the continued conviction of some practitioners in TC measurements may increase the risk of some of their patients. This was eloquently shown in the study by Danielsson, et al., which also indicated that new guidelines are of meagre help if not employed.

Epidemiological evidence exists connecting several blood lipid factors to cardiovascular disease development. The Scandinavian simvastatin study indicated that patients with coronary heart disease had improved survival when treated with cholesterol-lowering medication even at total cholesterol levels as low as 6 mmol/l. As our calculations have shown, some of the persons not judged to be at high-risk, would be so, when more complex indices are used. Focusing on total cholesterol levels may misclassify persons even in this group of persons having lived through a myocardial infarction.

The composite nature of cholesterol transport in humans may be an explanation of the lack of success in programmes aimed at cholesterol-lowering through diet and medication, in spite of overwhelming epidemiological evidence of a positive relationship between level of total cholesterol in a population and its mortality rate from all causes and coronary heart disease. The 4S study may be an exception in a post-MI population. A high level of HDL-cholesterol seems to be beneficial to overall risk. On the other hand the cholesterol-content of the apolipoproteins does not parallel the TC-levels, as indicated by the increased spread of the ATH-index in Figure 2 and the observed rise in discriminatory power of the ATH-index in coronary patients. Although to date apolipoprotein levels in blood may not be influenced separately, the incorporation of them in compound indices may give CV risk evaluation a higher predictive value. Prospective studies including the compound indices may, however, be necessary to confirm this.

The gains from an extended screening procedure would include the lowering of unnecessary expenses, reduction in quality of life and the allocation to treatment, in cases of false positive tests. Today the cost of an extended screening (ATH-index=265Nkr=£25) is much higher than the TC measurement (TC= 27Nkr =£2.6) alone. But a cost analysis comparing cheap and expensive screening alternatives may end up in favour of the expensive, if the efficacy of the latter is higher. This may be the case according to Table 2.

In a non-manufacturing firm as in the present study, the employees would probably profit from a better screening, the knowledge of which in its own right might reduce the atherogenic index by increasing social support, as shown with TC by John Cassel in 1963. Persons with a false negative TC result would, to our knowledge, benefit from advice on a change in lifestyle. Even if disclosure of a false negative test resulted in only a prolongation of some months of life, many employees would value this information much higher than the cost to obtain it.

**CONCLUSION**

Compound tests discussed in this study are suitable in occupational health service as no fasting procedures must be followed. The development of cheaper apolipoprotein tests would appreciably reduce the cost of compound screening tests. Postponing a decision to employ compound indices until prospective studies are done, would probably do more harm than good to patients. The cheap and standardized TC tests employed should not be an argument against compound indices, as the number of misclassified persons...
would be significant. Studies based on the improved separation attained by compound indices would still require an investigating of the predictive value of compound indices. An interesting extension of the use of compound indices would be a comparison of other multifactorial indices of CV risk, as blood pressure, diabetes, smoking and physical activity, with the ATH-index.

REFERENCES


