Central cooling effects in patients with hypercholesterolaemia

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ABSTRACT

1. A prospective study has been carried out, and 68 patients with hypercholesterolaemia have been investigated to study the effects of central cooling on serum lipid levels.

2. Central cooling was obtained by the exposure of the whole body to cold water. All patients were trained to gradually reduce the water temperature from 22 to 14 °C and to increase the time of exposure from 5 to 20 min over a period of 90 days. The 33 male and 35 female patients were aged between 40 and 60 years at entry with total cholesterol of 6.0 mmol/l or greater and low-density lipoprotein (LDL)-cholesterol of 4.0 mmol/l or greater. Thyroid-stimulating hormone, free thyroxine (FT4), total T3, total cholesterol, LDL-cholesterol, high-density lipoprotein (HDL)-cholesterol, triacylglycerols and total fat mass (determined by dual-energy X-ray absorptiometry scan) were obtained at baseline and after 3 months treatment with hydrotherapy.

3. Central cooling obtained by hydrotherapy results in a median fall in tympanic temperature from 0.2 °C (P < 0.001) to 0.8 °C (P < 0.001). We have observed in these patients a significant reduction in total cholesterol (−0.2 mmol/l, P < 0.006) and LDL-cholesterol (−0.2 mmol/l, P < 0.004). Serum FT4 level was higher than baseline results in 30 of these hypercholesterolaemic patients (15.5 pmol/l to 17.3 pmol/l) and there was no significant change in serum thyroid-stimulating hormone and total T3.

4. In conclusion, in our patients with hypercholesterolaemia we have observed a significant reduction of total cholesterol and LDL-cholesterol after body temperature regulation.

INTRODUCTION

Mortality from heart diseases and cerebral thrombosis increases during winter in temperate climates [1,2]. Increases in plasma cholesterol concentration which can be produced by exposure to mild cold [3,4], provide a possible explanation. On the other hand, animal experiments have revealed that cold exposure greatly increases lipolysis [5]. Little is known about the effect of central cooling on lipid metabolism in humans. Therefore a better understanding of the influence of cold on energy metabolism and substrate utilization could help to explain the possible mechanisms that increase cardiovascular mortality during winter. Thyroid hormone levels are a major determinant of energy balance and are thought to modify body composition by their effects on metabolism of lipids, carbohydrates and protein [6]. Abnormalities of thyroid function are associated with
changes in lipid concentrations and in the incidence of ischaemic heart disease (IHD) [7–15].

Subclinical hypothyroidism is found in about 7.5% of females and 3% of males. It appears to be a risk factor for atherosclerosis and for IHD [7,9,13]. Subclinical hypothyroidism has significant effects on lipid metabolism [13]. Elevated low-density lipoprotein (LDL)-cholesterol in subclinical hypothyroidism provides a likely pathophysiological explanation for the association of IHD with this syndrome [7,8].

Whether lipid concentration and thyroid function are related when thyroid function is normal, in IHD, is uncertain. Recently, in one study of euthyroid patients, the relationship between thyroid function, serum lipid levels and IHD was investigated [7]. Correlations were found between thyrotropin, total cholesterol and LDL-cholesterol in the group of euthyroid patients with IHD but not in the control group. These findings suggested that thyroid hormone within the normal range was having a significant effect on lipid levels in patients with IHD [7]. In another population study [10] it was found that 10% of subjects with a thyroid-stimulating hormone (TSH) concentration of 1.1–3.0 m-units/l had a serum cholesterol level > 7.5 mmol/l, whereas 20% of those with TSH concentrations of 3.1–5.0 m-units/l had a serum cholesterol level > 7.5 mmol/l. Until now, therapy with thyroxine has been recommended in patients with high TSH levels (above 12 m-units/l) [14]. There is no threshold below which serum cholesterol loses its association with IHD, even in populations whose levels are generally low.

Of interest, reducing the body temperature in a number of mammals induces a marked increase in serum thyroid activity [16–18], but similar studies in man have given conflicting results [19–21].

The maintenance of constant core temperature is a fundamental biological characteristic of eutherian species. The discrepancy in the results regarding the changes in thyroid hormones as an adaptive mechanism after cold exposure may be due to the use of different temperatures and time periods of cold exposure. In these experiments, exposure temperatures were low, but always above 10 °C.

The aim of the present study was to examine the effects of central cooling on lipid serum levels, thyroid function, cardiovascular risk factors and total fat mass.

PATIENTS AND METHODS

Sixty-eight patients (48.5% males and 51.5% females) with hypercholesterolaemia (total cholesterol > 6.0 mmol/l and LDL-cholesterol > 4.0 mmol/l) attending the Beatrice Research Centre as part of a health screening programme were included. All of them were euthyroid by clinical and laboratory examination, and none had goitres. None of them was on medication. On arrival at the Beatrice Research Centre, height and weight were measured and a medical history was taken by a clinician, including details of physical activity, tobacco and alcohol consumption.

The central cooling was obtained by a programme of water immersion of the whole body up to the neck in a water-filled bath, the temperature of which was gradually decreased from 22 to 14 °C, and the time of exposure increased from 5 to 20 min over a period of 90 days. At entry to the study core temperature was measured on the tympanic membrane before and after the first cold exposure (5 min at 22 °C). Core temperature was measured again after 3 months treatment with hydrotherapy before and after the final cold exposure (20 min at 14 °C). Blood samples pre- and post central cooling were obtained after a 12-h fast.

TSH, free thyroxine and total T₄ were assayed by enzyme-immunometric methods on the Immuno 1 immunochemistry analyser (Bayer Diagnostics). Coefficient of variance for total T₄ was 6% and for free T₄ it was 7.2%. Cholesterol and triacylglycerols were measured by spectrophotometric methods on the Technicon DAX 48 analyser (Bayer Diagnostics, Basingstoke, U.K.). High-density lipoprotein (HDL)-cholesterol was measured by precipitation of other cholesterol fractions with magnesium carbonate followed by assay of remaining cholesterol on the DAX 48. LDL-cholesterol was calculated using the Friedwald equation.

Total body composition was measured using Lunar DPX dual-energy X-ray absorptiometry (software version 3.6; Lunar Corps, Madison, WI, U.S.A.). Coefficient of variance for total fat mass was 1.8%.

The study was approved by the ethics committee of Beatrice Research Centre and written informed consent was obtained from every patient.

Statistical analysis was performed by using the SAS statistical package. The null hypothesis was rejected when P < 0.05.

RESULTS

The mean age of our patients was 52 years and the body mass index 26 kg/m². The median fall in core temperature was 0.2 °C (36.7 to 36.5 °C) after the first cold exposure (5 min at 22 °C), and 0.8 °C (36.8 to 35.9 °C) after the final cold exposure (20 min at 14 °C) (P < 0.001; Table 1).

The lipid profile in the 68 patients with hypercholesterolaemia was modified by body temperature regulation (BTR). After 90 days of BTR we observed a significant reduction of total cholesterol [baseline, 6.85 mmol/l; post BTR, 6.65 mmol/l (P = 0.006)] and LDL-chole-
terol [baseline, 4.8 mmol/l; post BTR, 4.6 mmol/l (P = 0.004)] (Table 2). After BTR, the levels of TSH, FT$_{3}$, and total T$_{3}$ did not show significant changes from baseline results (P < 0.005; results not shown).

The serum level of FT$_{3}$ was found to be significantly increased after central cooling [pre, 15.5 ± 2.0 pmol/l; post, 17.3 ± 3.4 pmol/l (P < 0.001)], while serum TSH [pre, 2.1 ± 1.5 m-units/l; post, 2.1 ± 1.4 m-units/l (P = 0.5)] and total T$_{3}$ showed no change [pre, 1.54 ± 0.3 nmol/l; post, 1.59 ± 0.1 nmol/l (P < 0.05)] in 30 patients with hypercholesterolaemia.

In these 30 patients the lipid profile changes were mild and not significant for triacylglycerols and HDL-cholesterol, but statistically significant for total cholesterol [pre, 6.7 ± 0.9 mmol/l; post, 6.4 ± 1.0 mmol/l (P = 0.004)] and LDL-cholesterol [pre, 4.55 ± 0.7 mmol/l; post, 4.4 ± 0.7 mmol/l (P = 0.01)].

Body weight assessed at the beginning and end of the programme changed from 75.1 to 74.2 kg (P = 0.07), and body mass index from 26 to 25.8 kg/m$^2$ (P = 0.65). Total fat mass, measured by dual-energy X-ray absorptiometry, was reduced from 24.3 to 23.7 kg (P = 0.085).

Analysis of the physical activity and nutritional habits questionnaires did not show significant differences during the treatment period.

**DISCUSSION**

Hypercholesterolaemia appears to be an important risk factor for atherosclerosis, being associated unequivocally with increased incidence of premature IHD [22]. In the Multiple Risk Factor Intervention Trial (MRFIT), men with cholesterol levels > 6 mmol/l had more than a 3-fold increased risk of death from coronary heart disease than men with cholesterol levels < 5 mmol/l [23]. Prospective studies have clearly established that risk of coronary heart disease is related to the concentration of serum cholesterol [24]. In addition, an overview of 28 cholesterol-lowering trials estimated that the risk of coronary death plus non-fatal infarction was 7% less for every 0.6 mmol/l reduction in total cholesterol in the first 2 years of treatment, and 22% less in years 3 to 5 [24].

The present study shows the effect of BTR in patients with hypercholesterolaemia. We have observed a reduction of total cholesterol (−0.2 mmol/l) and LDL-cholesterol (−0.2 mmol/l) after 90 days of BTR.

It has been observed that during cooling there is a 2-fold increase in plasma noradrenaline [20]. There is evidence that plasma catecholamines could play an important role in regulating lipid and lipoprotein metabolism in humans [25,26]. Our hypothesis is that increased central or peripheral sympathetic outflow leading to increased catecholamine-induced caloric use might influence the serum cholesterol concentrations. It is also thought that an immediate rise in circulating plasma catecholamines during cold exposure could shift substrate use towards fatty acid metabolism [27,28].

In 44% of these hypercholesterolaemic patients, lowering the core temperature also induced changes in serum free thyroxine. The thyroid gland plays an essential role in regulatory thermogenesis [29]. This mechanism controls the heat released for maintenance of body temperature during cold exposure. Heat generated during and after exposure to cold is the result of this stimulation.

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**Table 1** Tympanic temperature pre/post body temperature regulation (BTR) at 22 °C and 14 °C

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Median</th>
<th>Minimum</th>
<th>Maximum</th>
<th>Post BTR</th>
<th>Median</th>
<th>Minimum</th>
<th>Maximum</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline: 22 °C</td>
<td>36.7</td>
<td>35.5</td>
<td>37.9</td>
<td>36.5</td>
<td>35</td>
<td>37.5</td>
<td>-0.2</td>
<td>+1</td>
</tr>
<tr>
<td>Post BTR: 14 °C</td>
<td>36.8</td>
<td>35.2</td>
<td>37.6</td>
<td>35.9</td>
<td>34</td>
<td>37.3</td>
<td>-0.8</td>
<td>+0.8</td>
</tr>
</tbody>
</table>

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**Table 2** Body temperature regulation (BTR) and lipid profile in 68 patients with hypercholesterolaemia (total cholesterol > 6.0 mmol/l, LDL-cholesterol > 4.0 mmol/l)

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Median</th>
<th>Minimum</th>
<th>Maximum</th>
<th>Post BTR</th>
<th>Median</th>
<th>Minimum</th>
<th>Maximum</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>25.95</td>
<td>17.9</td>
<td>40.3</td>
<td>25.8</td>
<td>18.3</td>
<td>40.3</td>
<td>0.652</td>
<td></td>
</tr>
<tr>
<td>Post BTR</td>
<td>21.15</td>
<td>15.7</td>
<td>30.7</td>
<td>21.6</td>
<td>16.2</td>
<td>30.6</td>
<td>0.006</td>
<td></td>
</tr>
<tr>
<td>Total cholesterol (mmol/l)</td>
<td>6.85</td>
<td>6.1</td>
<td>10.5</td>
<td>6.65</td>
<td>5.2</td>
<td>10.3</td>
<td>0.004</td>
<td></td>
</tr>
<tr>
<td>LDL-cholesterol (mmol/l)</td>
<td>4.8</td>
<td>4.1</td>
<td>7.4</td>
<td>4.6</td>
<td>3.6</td>
<td>7.2</td>
<td>0.004</td>
<td></td>
</tr>
<tr>
<td>HDL-cholesterol (mmol/l)</td>
<td>1.3</td>
<td>0.7</td>
<td>2.2</td>
<td>1.3</td>
<td>0.7</td>
<td>2.2</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Triacylglycerols (mmol/l)</td>
<td>1.4</td>
<td>0.6</td>
<td>4.6</td>
<td>1.4</td>
<td>0.6</td>
<td>5.2</td>
<td>0.148</td>
<td></td>
</tr>
</tbody>
</table>
of numerous metabolic pathways including lipid metabolism [29,30]. In fact there is evidence that thyroid hormone announces the removal of LDL particles by increasing the number of LDL receptors expressed [30–32].

Soler et al. [33] examined the role of the thyroid in adaptation to cold ambient temperatures. They found increased free thyroid hormone levels in response to cold exposure. Bernal and Escobar del Rey [34] suggested that the adaptation to cold exposure includes increased $T_4$–$5'$-monodeiodination. Enhanced $T_4$ outer ring deiodination in response to cold could be mediated by catecholamines. Catecholamines, which are thought to play an important role in response to cold and interact with $T_4$ during cold adaptation [35–37], might increase iodothyronine 5'-deiodinase activity [38]. Soler et al. [33] explained that the increased serum free thyroid hormone levels imply a higher equilibrium between extracellular and intracellular $FT_4$ and $FT_3$ as a result of prolonged intermittent cold exposure.

Chronic studies provide very little insight into the role of thyroid hormones in cold responsiveness or adaptation. This may reflect differences in the length of cold stress and methodology. In these patients with hypercholesterolaemia the effects of BTR on serum levels of total and LDL-cholesterol could also play a role in reducing the risk for coronary heart disease.

In conclusion, BTR obtained by central cooling through hydrotherapy in patients with hypercholesterolaemia for a period of 3 months results in an increased lipid metabolism marked by reduced serum concentrations of total and LDL-cholesterol. In 44% of the patients with hypercholesterolaemia we found a concomitant increased level of thyroxine serum levels. Other studies are needed to confirm the long-term effects of BTR on serum lipid levels and the reduction of risk for coronary heart disease.

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