EFFECT OF AGING ON LIPID METABOLISM

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ABSTRACT

The effects of aging upon lipid metabolism were analysed on the facts obtained by epidemiological and experimental studies. The mean cholesterol and triglyceride concentrations increased with age up to the age of 55, then gradually fell as age advanced. Between the subjects grouped by the age under 50 and over 60 years, no difference was seen in the response of blood glucose, FFA, and IRI to oral glucose loading, and also in post-heparin lipolytic activity. But the mean dietary intake in terms of total calorie and carbohydrate intake, and also the FFA release from abdominal adipose tissue decreased, though slightly, in the aged. These indicated that the decrease in supply of endogenous as well as exogenous materials for lipogenesis was the possible cause for the lowered metabolism of lipid in the aged.

INTRODUCTION

The natural history of lipid metabolism in man is effected by three major factors; (i) heredity, (ii) environment, and (iii) aging. Each of them has been extensively studied by a large number of authors. The genetic aspect of lipid metabolism has been brought to light by recent studies on phenotyping familial disorders of lipid transport1 and on identification of congenital enzyme defects in the lipid storage diseases.2 The environmental factors have been described with particular emphasis on the relationship between lipid metabolism and atherosclerosis.3-4. We, too, have reported on some epidemiological evidence for the close association of environmental factors with hyperlipidemias and atherosclerosis.5

Of the effects of aging upon the lipid metabolism, we have conducted so far several experiments designed to demonstrate the temporal alterations in the following aspects of lipid metabolism; (i) the mean concentrations of lipids in
population, amount of dietary intake, metabolic responses of glucose, free fatty acids (FFA) and immuno-reactive insulin (IRI) to oral glucose tolerance test, post-heparin lipolytic activity (PHLA), and release of FFA from adipose tissues. In the present paper we will give a brief review on the effects of aging upon lipid metabolism on the basis of facts made clear by these experiments, and will consider a possible mechanism for the lipid metabolism being characteristic of the aged.

SUBJECTS AND METHODS

(i) The mean lipid concentrations and the dietary intake in population: One hundred ninety nine subjects, 96 males and 103 females, were randomly chosen from the habitants of a middle sized town called Maisaka (pop. 10,672) on the Pacific coast of Aichi prefecture in Japan. They were of varying ages, and their blood samples were taken after overnight fasting of 12 to 16 hours. The serum lipid concentrations were determined for cholesterol and triglycerides. Their dietary intake was analysed by dieticians using an interview method. The total calorie, the amount of protein, carbohydrates and fat taken on the day before blood examinations were assessed by using the Standard Table for Nutritional Contents in Japanese Foods.

(ii) Responses of glucose, FFA and IRI to oral glucose tolerance test: 50 g of oral glucose tolerance test was performed on 63 subjects (19 males and 44 females). Four blood samples were taken every hour, each blood sample being measured for glucose, FFA and IRI.

(iii) Post-heparin lipolytic activity (PHLA): PHLA was determined on 57 subjects at Musashino Hospital in Tokyo, of which 30 (26 males and 4 females) were under 40, and 27 (16 males and 11 females) were over 55 years of age. Both groups were matched with obesity index.

(iv) Release of FFA from adipose tissues: Adipose tissue pads were gained from the abdominal wall of 23 surgical patients at Saitama State Hospital in the vicinity of Tokyo, of whom 16 were under 55 years, and 7 were over 60 years. The tissue pad obtained was washed with saline solution and weighed, then incubated with 10 ml Krebs-Ringer phosphate buffer solution added with 5% bovine albumin at 37°C for 4 hours. The FFA released were measured five times with the intervals of one hour before and after addition of 0.011 µ/ml epinephrin to the incubating medium.
RESULTS

(i) The mean lipid concentrations and the dietary intake: The temporal alterations of the mean cholesterol and triglycerides were shown in Fig. 1. The means were obtained from 199 subjects being divided into two groups according to sex, and calculated for the subgroup of every 5 years of age. The mean serum cholesterol level of male increased with age until 50 years, then gradually fell as the age advanced. The mean cholesterol level in female, on the other hand, continued to increase with age even after 50 years. The mean triglyceride concentrations also increased with age until 50 years in male and 60 years in female, after which they both fell gradually in the mean concentrations.

Fig. 2 is the temporal changes in triglyceride level in the four groups formed according to their response to glucose tolerance test and by their obesity index. The upper part of the Fig. 2 is the mean triglyceride level of non-diabetic subjects, the lower part the diabetic group. The obese subjects either diabetic or non-diabetic had higher mean triglyceride concentrations than the non-obese. In all the groups the triglycerides increased with age, but fell after 45 or 55 years.

![Fig. 1 Temporal alterations of serum cholesterol and triglycerides in a Japanese population.](image1)

![Fig. 2 Temporal alterations in plasma triglycerides in four groups subjects according to their obesity index values and glucose tolerance patterns.](image2)
Table 1 is the results of dietary analyses of 166 subjects (85 males and 81 females) who gave satisfactory answers to questionnaire. They were divided into four groups according to their serum triglyceride level and their age. The groups of over 60 years of age had lower caloric intake than those of under 50 years. This difference in total calorie was chiefly due to the diminished intake of carbohydrates in the group of the aged.

Table 1
Comparison of dietary intake between the subjects under 50 and above 60 years of age. The two age groups were further divided according to the serum triglyceride concentrations. CHO in the table means dietary carbohydrates, TG serum triglycerides.

<table>
<thead>
<tr>
<th></th>
<th>Under 50 years</th>
<th>Over 60 years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Non-elevated TG</td>
<td>Elevated TG</td>
</tr>
<tr>
<td>n</td>
<td>48 ± 22, 916</td>
<td>41 ± 22, 919</td>
</tr>
<tr>
<td>TG (mg/dl)</td>
<td>81 ± 25</td>
<td>190 ± 51</td>
</tr>
<tr>
<td>T. Cal.</td>
<td>2,409 ± 71</td>
<td>2,336 ± 79</td>
</tr>
<tr>
<td>CHO</td>
<td>1,687 ± 61</td>
<td>1,704 ± 73</td>
</tr>
<tr>
<td>protein</td>
<td>364 ± 13</td>
<td>323 ± 16</td>
</tr>
<tr>
<td>fat</td>
<td>358 ± 13</td>
<td>309 ± 18</td>
</tr>
</tbody>
</table>

(ii) Responses of glucose, FFA and IRI to glucose tolerance test: The changes in plasma glucose and FFA during 50 g oral glucose tolerance test in the group of less than 50 years of age were shown in Fig. 3, while those of the group of more than 60 years of age in the Fig. 4. Although both glucose and FFA levels were higher in the obese subjects than in the non-obese group, there were no significant differences in the glucose and FFA response patterns between the two groups of under 50 and over 60 years.

Fig. 5 demonstrates the IRI response to glucose tolerance test. The group of obesity with hypertriglyceridemia had the greatest response to the test, but no significant difference was seen between the two age groups of over 60 and under 50 years.

(iii) Post-heparin lipolytic activity (PHLA): Table 2 shows the comparison of PHLA between the two age groups under 49 and above 54 years. They were further divided into two subgroups according to their serum triglyceride concentrations. Among the four groups thus made, no significant difference was observed in PHLA.

(iv) Release of FFA from adipose tissue: Fig. 6 shows the in vitro release of FFA from adipose tissue pad. The rate of FFA release from the tissue
Fig. 3 Response of glucose and FFA to 50g oral glucose tolerance test in 74 non-diabetic but obese subjects (48 males and 26 females) under 50 years of age.

Fig. 4 Response of glucose and FFA to 50g oral glucose tolerance test in 145 non-diabetic but obese subjects (65 males and 80 females) of over 60 years of age.

Fig. 5 Changes in plasma IRI levels during 50g glucose tolerance test in 145 subjects above 60 years. They were subgrouped according to their obesity index and triglyceride concentrations.
Table 2
Comparison of PHLA between the two groups under 49 and over 54 years of age. The two age groups were subdivided according to their plasma triglyceride levels.

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Under 49 years of age</th>
<th>Over 45 years of age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal TG</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>μEqFFA/mℓ plasma/h</td>
<td>16</td>
<td>112±4 p&gt;0.05</td>
<td>105±3%</td>
</tr>
<tr>
<td></td>
<td>16</td>
<td>96±6</td>
<td>97±5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.46±0.30 p&gt;0.05</td>
<td>2.04±0.28</td>
</tr>
<tr>
<td>High TG</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>μEqFFA/mℓ plasma/h</td>
<td>14</td>
<td>115±5 p&gt;0.05</td>
<td>110±4%</td>
</tr>
<tr>
<td></td>
<td>11</td>
<td>242±40</td>
<td>207±18</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.96±0.18 p&gt;0.05</td>
<td>2.20±0.26 (M±SE)</td>
</tr>
</tbody>
</table>

Fig. 6 Comparison of FFA release from abdominal adipose tissue between the subjects under 55 and above 60 years of age.

of the subjects under 49 was greater than that of those above 60. This indicated that FFA were less readily released from the adipose tissue in the older subjects.

DISCUSSIONS

The effects of aging have been investigated by epidemiological and experi-
mental studies. First, it was observed that the mean concentrations of serum cholesterol and triglycerides increased with age until around 55 years of age, and gradually decreased thereafter to the level of thirties. This observation confirmed the findings made by Schaefer\textsuperscript{18} and Schilling et al.\textsuperscript{19} who reported that the mean lipid concentrations rose up with age as far as 55 years, and then followed by gradual fall as age advanced. These suggested that the functional niveau of lipid metabolism was lowered in the aged for some reasons.

As a possible explanation for this lowered lipid metabolism of the aged, we consider the data as shown in Fig. 3, 4, 5, and Table 3 important, that is, neither the response of glucose, FFA and insulin to glucose loading nor the PHLA changed with age. This indicate that lipid synthesis in terms of insulin activity or the removal of triglycerides represented by PHLA does not alter with age. So it is unlikely that these two factors of decreased lipogenesis and/or increased lipolysis are the cause for the lowered lipid levels of the aged.

But as shown in Table 1 and Fig. 6, low caloric intake due to the diminished take of carbohyderates as well as the slower release of FFA from adipose tissue seems to be the probable cause for low level of lipids in the aged. Dietary carbohydrates are known to be converted to triglycerides by way of triose to α-glycerophosphate,\textsuperscript{20} and the released FFA's are also used for triglyceride synthesis through esterification with glyceroles in the liver.\textsuperscript{21} The facts that neither exogenous carbohydrates nor endogenous FFA is high in their concentrations leads us to conject that the body is relatively short of exogenous as well as endogenous materials for lipogenesis of triglycerides. This very limitation of materials for production of lipids is most likely to be responsible for the low lipid levels among the aged. We also assume that the reduction in intake of dietary cholesterol is also the cause of low blood cholesterol concentration in the aged, since a large number of epidemiological and experimental studies have shown a close relationship between the two.\textsuperscript{22}

However, the fact that the mean cholesterol level in the female group in Fig. 1 did not lower even after 50 years in contrast to the lipids in male after 50 years suggests that the decreased supply of materials for lipogenesis cannot be the only cause for low lipid levels in the aged. Some other metabolic changes that are not examined in our present experiments, such as influence of sex hormones, may be playing an important role. With this in mind we would like to further our future studies.

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REFERENCES

10. Technicon Autoanalyser Method File N-24a