Albumin metabolism in rheumatoid arthritis

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It is now established that in rheumatoid arthritis changes are not confined only to the joints and the term ‘rheumatoid disease’ is employed to implicate the involvement of other organs and tissues. It would be helpful to have an index of the severity of the nonarticular involvement and several factors have been investigated from this point of view including the erythrocyte sedimentation rate, the serum iron level, and the serum albumin concentration. Each of these measurements has its protagonists, but the erythrocyte sedimentation rate is most commonly employed in routine clinical practice. One disadvantage of this measurement is its dependence on the gamma globulin concentration, which itself is directly involved in the disease process. The serum albumin concentration does not vary with immunological disturbances and is frequently found to be reduced in rheumatoid disease. However, the serum albumin concentration may be influenced by a wide variety of unrelated factors and, accordingly, in the present study we have measured the albumin catabolic rate in addition to the intravascular and extravascular albumin pool contents in normal subjects and in patients with rheumatoid arthritis. The aim of the study was to determine whether the degree of hypoalbuminaemia in rheumatoid arthritis was directly related to changes in albumin metabolism and the severity of the disease.

Subjects
Nine patients with ‘classical’ rheumatoid arthritis (Ropes, Bennett, Cobb, Jacox, and Jessar, 1959) aged between 34 and 60 years were carefully selected; eight were female. All had widespread articular involvement and at the beginning of the study the mean articular index (Ritchie, Boyle, McInnes, Jasani, Dalakos, Grieveson, and Buchanan, 1968) was 40 score units, serological tests for rheumatoid factor were positive in high titre (mean 1/128), and the mean erythrocyte sedimentation rate was 38 mm. 1st hr (Westergren), indicating the severity of the disease process in this group of patients. None had at any time received corticosteroid therapy, which can influence albumin metabolism (Rothschild, Schreiber, Oratz, and McGee, 1958). The doses of the conventional nonsteroidal anti-inflammatory compounds, which each was receiving, remained unchanged throughout the study.

Two male and one female patient with both clinical and radiological evidence of osteoarthritis of the knee joints were also studied. Their ages were 34, 60, and 65 years respectively, and there was neither clinical nor radiological evidence of past or present involvement of the other joints in any disease process. Serological tests for rheumatoid factor were negative and the erythrocyte sedimentation rates were less than 10 mm. 1st hr (Westergren). Serum albumin concentration was normal in all three patients.

Three female and two male members of the laboratory staff aged between 21 and 25 years also participated. None had either past or present clinical evidence of any disease process and in all the serum concentration was normal.

Clinical assessment
The patients with rheumatoid arthritis and with osteoarthritis were admitted to the Centre for Rheumatic Diseases, Glasgow. In the 5 days before starting the albumin studies abnormal faecal or urinary albumin loss was excluded. Frequent axillary temperature readings were within normal limits and concurrent disease was excluded by clinical examination; in particular malabsorption, peptic ulceration, and thyrotoxicosis were excluded by appropriate laboratory tests. A standard ward diet was instituted and continued throughout the study.

On the day before and the day after the period of albumin study each patient was assessed clinically by the same observer in a standard manner.

After a full clinical examination, the articular index (Ritchie and others, 1968) was assessed as a measure of total articular tenderness. The maximum possible value for any individual patient is +78 and the method possesses an acceptable degree of intraobserver error. The body weight was measured and the absence of recent weight loss confirmed. A peripheral venous blood sample was removed for the determination of erythrocyte sedimentation rate (Westergren) and of rheumatoid factor titre.

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Approximately 40 μCi of $^{99m}$technetium (Radiochemical Centre, Amersham) standardized by count rate was injected intravenously and the count rate over the knee joint was monitored for 15 minutes. A thallium-activated sodium iodide crystal and ancillary equipment (Ekco Electronics, Southend-on-Sea) were used for measuring $^{99m}$technetium. The geometries employed for counting both the administered dose and the activity over the knee joint were standardized and knee activity was expressed as a percentage of the dose. Using this method knee activity has been shown to be related to the severity of joint involvement and to alter with anti-inflammatory therapy in proportion to clinical indices of disease activity (Dick, Neufeld, Prentice, Woodburn, Whaley, Nuki, and Buchanan, 1970; St. Onge and Dick, 1970).

There were no significant differences in the results of any of the above factors at the beginning and end of the albumin study. The mean values for each of the clinical parameters (articular index: 40 score units; $^{99m}$technetium: 0.08 per cent.; ESR: 38 mm./1st hr) were employed in assessing correlation with the parameters of albumin metabolism.

### Table I  Normal albumin metabolism

<table>
<thead>
<tr>
<th>Normal subjects</th>
<th>Sex</th>
<th>Weight (kg.)</th>
<th>LBM (kg.)</th>
<th>Plasma volume (l.)</th>
<th>Plasma albumin (g./l.)</th>
<th>$t_d$</th>
<th>Albumin Intravascular</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(g.) (g./kg. BWt) (g./kg. LBM)</td>
</tr>
<tr>
<td>LS 1</td>
<td>F</td>
<td>50-5</td>
<td>38-5</td>
<td>2.117</td>
<td>45</td>
<td>15</td>
<td>95</td>
</tr>
<tr>
<td>LS 2</td>
<td>F</td>
<td>59-1</td>
<td>44-3</td>
<td>2.792</td>
<td>44</td>
<td>19</td>
<td>123</td>
</tr>
<tr>
<td>LS 3</td>
<td>F</td>
<td>65-0</td>
<td>47-6</td>
<td>2.347</td>
<td>42</td>
<td>18</td>
<td>99</td>
</tr>
<tr>
<td>OA 1</td>
<td>F</td>
<td>82-0</td>
<td>49-5</td>
<td>2.661</td>
<td>39</td>
<td>22</td>
<td>104</td>
</tr>
<tr>
<td>OA 2</td>
<td>F</td>
<td>71-9</td>
<td>44-5</td>
<td>3.220</td>
<td>40</td>
<td>20</td>
<td>129</td>
</tr>
<tr>
<td>LS 4</td>
<td>M</td>
<td>54-5</td>
<td>46-5</td>
<td>2.493</td>
<td>44</td>
<td>15</td>
<td>110</td>
</tr>
<tr>
<td>LS 5</td>
<td>M</td>
<td>70-0</td>
<td>55-5</td>
<td>3.280</td>
<td>43</td>
<td>19</td>
<td>141</td>
</tr>
<tr>
<td>OA 3</td>
<td>M</td>
<td>50-8</td>
<td>45-3</td>
<td>2.274</td>
<td>43</td>
<td>20</td>
<td>98</td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td>63-0</td>
<td>46-1</td>
<td>2.648</td>
<td>42-5</td>
<td>18-5</td>
<td>112</td>
</tr>
<tr>
<td>S.E.M.</td>
<td></td>
<td>4-0</td>
<td>1-7</td>
<td>0-151</td>
<td>0-73</td>
<td>0-9</td>
<td>6</td>
</tr>
</tbody>
</table>

### Table II  Albumin metabolism in rheumatoid arthritis

<table>
<thead>
<tr>
<th>Rheumatoid subjects</th>
<th>Sex</th>
<th>Weight (kg.)</th>
<th>LBM (kg.)</th>
<th>Plasma volume (l.)</th>
<th>Plasma albumin (g./l.)</th>
<th>$t_d$ (d-1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>58-0</td>
<td>47-7</td>
<td>2.781</td>
<td>34</td>
<td>12</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>67-5</td>
<td>46-3</td>
<td>2.493</td>
<td>31</td>
<td>11</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>47-3</td>
<td>40-3</td>
<td>2.114</td>
<td>38</td>
<td>14</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>43-3</td>
<td>34-8</td>
<td>2.273</td>
<td>24</td>
<td>13</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>74-8</td>
<td>46-0</td>
<td>3.320</td>
<td>32</td>
<td>17</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>55-4</td>
<td>41-1</td>
<td>2.741</td>
<td>34</td>
<td>20</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>57-4</td>
<td>39-8</td>
<td>2.173</td>
<td>33</td>
<td>15</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>72-5</td>
<td>46-6</td>
<td>2.332</td>
<td>37</td>
<td>13</td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>72-5</td>
<td>50-8</td>
<td>2.624</td>
<td>32-7</td>
<td>14-6</td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td>60-4</td>
<td>43-7</td>
<td>0-155</td>
<td>1-4</td>
<td>0-9</td>
</tr>
<tr>
<td>S.E.M.</td>
<td></td>
<td>3-7</td>
<td>1-7</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Parameters of albumin catabolism were calculated by the method of Matthews (1957) using either the 2- or the 3-compartment model as required. Appropriate programmes were constructed for use with a Wang 370 electronic calculator (Wang Europe Ltd., Tavistock Square, London).

Values for albumin metabolism were determined with reference both to body weight and to lean body mass, which was calculated from height and weight (Hume, 1966).

Serum albumin concentration was determined after cellulose acetate electrophoresis by an elution method (Webster, 1965). The coefficient of variation was 2 per cent.

Results

All subjects excreted less than 5 per cent. of the dose of $^{125}$iodine in the first 24 hrs after injection. In all cases values for fractional catabolic rate calculated from the ratio of urine to serum radioactivity (Campbell, Cuthbertson, Matthews, and McFarlane, 1956) remained constant within the limits of experimental error throughout the period of study.

Values for albumin contents and catabolic rates of the normal subjects and the osteoarthrotic patients are shown in Table I. Results are expressed relative to body weight (BWt) as well as lean body mass (LBM) to allow comparison with published series.

Results obtained from rheumatoid arthritic patients are shown on Table II. The intravascular, extravascular, and total body albumin contents were significantly lower than normal ($0.005 > P > 0.001$, $0.025 > P > 0.01$, and $0.005 > P > 0.001$ respectively). The fractional catabolic rate was increased ($0.025 > P > 0.01$), but there was no significant difference in absolute catabolic rate.

The values for fractional catabolic rate in the rheumatoid group did not correlate with body

<table>
<thead>
<tr>
<th>Extravascular</th>
<th>Total</th>
<th>Catabolic rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>(g.)</td>
<td>(g./kg. BWt)</td>
<td>(g./kg. LBM)</td>
</tr>
<tr>
<td>108</td>
<td>2.14</td>
<td>2.81</td>
</tr>
<tr>
<td>157</td>
<td>2.66</td>
<td>3.54</td>
</tr>
<tr>
<td>142</td>
<td>2.18</td>
<td>2.98</td>
</tr>
<tr>
<td>176</td>
<td>2.15</td>
<td>3.56</td>
</tr>
<tr>
<td>159</td>
<td>2.21</td>
<td>3.64</td>
</tr>
<tr>
<td>136</td>
<td>2.50</td>
<td>2.92</td>
</tr>
<tr>
<td>160</td>
<td>2.29</td>
<td>2.88</td>
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<tr>
<td>173</td>
<td>3.41</td>
<td>3.82</td>
</tr>
<tr>
<td>151</td>
<td>2.44</td>
<td>3.26</td>
</tr>
<tr>
<td>8</td>
<td>0.15</td>
<td>0.14</td>
</tr>
</tbody>
</table>

LS = Laboratory staff
OA = Cases of osteoarthrosis

<table>
<thead>
<tr>
<th>Albumin</th>
<th>Extravascular</th>
<th>Total</th>
<th>Catabolic rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>(g./kg. LBM)</td>
<td>(g./kg. LBM)</td>
<td>(g./kg. LBM)</td>
<td>Fractional</td>
</tr>
<tr>
<td>1.97</td>
<td>1.87</td>
<td>3.84</td>
<td>0.104</td>
</tr>
<tr>
<td>1.68</td>
<td>1.96</td>
<td>3.64</td>
<td>0.150</td>
</tr>
<tr>
<td>1.69</td>
<td>2.98</td>
<td>4.97</td>
<td>0.105</td>
</tr>
<tr>
<td>1.67</td>
<td>2.81</td>
<td>4.48</td>
<td>0.148</td>
</tr>
<tr>
<td>2.34</td>
<td>2.64</td>
<td>4.98</td>
<td>0.086</td>
</tr>
<tr>
<td>2.23</td>
<td>3.42</td>
<td>5.65</td>
<td>0.092</td>
</tr>
<tr>
<td>1.79</td>
<td>2.33</td>
<td>4.12</td>
<td>0.114</td>
</tr>
<tr>
<td>1.87</td>
<td>1.99</td>
<td>3.86</td>
<td>0.121</td>
</tr>
<tr>
<td>2.08</td>
<td>3.15</td>
<td>5.23</td>
<td>0.128</td>
</tr>
<tr>
<td>1.96</td>
<td>2.57</td>
<td>4.53</td>
<td>0.116</td>
</tr>
<tr>
<td>0.08</td>
<td>0.19</td>
<td>0.24</td>
<td>0.116</td>
</tr>
</tbody>
</table>
weight, plasma albumin concentration, or erythrocyte sedimentation rate, but did correlate with $^{99m}$technetium uptake (Fig. 1) and with articular index (Fig. 2).

![Diagram](https://example.com/diagram1.png)

**Fig. 1** Correlation of fractional catabolic rate of albumin and $^{99m}$technetium uptake. $r = 0.752; 0.05 > P > 0.01.$

![Diagram](https://example.com/diagram2.png)

**Fig. 2** Correlation of fractional catabolic rate of albumin and articular index. $r = 0.759; 0.05 > P > 0.01.$

**Discussion**

In this investigation parameters of albumin metabolism are quoted relative to lean body mass (Hume, 1966). Most other studies use body weight as reference, but, since a group of patients inevitably has a wide range of body weights, lean body mass is preferred.

Results derived by the method of Matthews (1957) are valid only if the subjects studied are in a 'steady-state' with respect to albumin metabolism and if the labelled albumin used is not significantly denatured.

Although there was no evidence of severe protein depletion, it is possible that the rheumatoid arthritic patients had an inadequate diet before admission to hospital. A period of 5 days' ingestion of a standard ward diet before injection of ($^{125}$I)-albumin was therefore used to avoid any influence of a change in nutrition on albumin metabolism. During the period of investigation a constant body weight was maintained. Plasma albumin and total protein concentrations and the erythrocyte sedimentation rate remained constant. Urine nitrogen excretion was stable and within normal limits throughout the study. There was no change in clinical assessment and in particular the $^{99m}$technetium uptake by the joint knee and the articular index were not significantly different at the beginning and end of the investigation. It therefore seems justified to assume that the albumin metabolism of these patients was in a 'steady-state'.

Some of the early clinical series studied involving mainly ($^{131}$I) albumin may be suspect, because of the use of labelled preparations containing an unacceptable level of altered molecules. The problems involved in labelling proteins have been reviewed by McFarlane (1964, 1965). It is believed that the commercial ($^{125}$I)-human serum albumin used in this study is suitable for clinical use, where one is primarily interested in changes in albumin content and catabolic rate. This is supported by the findings of normal values similar to published series (Cohen, Freeman, and McFarlane, 1961; Takeda and Reeve, 1963). An acceptable excretion of $^{125}$iodide in the first day after injection was found and there was no significant decrease in the value of fractional catabolic rate calculated from the ratio of urine to plasma radioactivity over the period of study. These are two of the criteria which must be met for a preparation of radioiodinated albumin to be considered adequate (McFarlane, 1965). The preparation of $^{125}$I albumin may not be suitable for calculation of transfer rates, when several extravascular compartments are assumed to exist. Since neither the anatomical nor metabolic significance of these is known, they are at present considered to be of little clinical interest.

Serum albumin concentration, although it was low in most rheumatoid patients, did not correlate with any of the indices of disease activity. Similarly, intravascular and total body albumin concentrations showed no correlation with disease activity.

The rheumatoid arthritic group had a lower intravascular and body content of albumin than had normal subjects. Presumably, in those patients with a decreased extravascular albumin content, there had been transfer of albumin from the extravascular compartment in an attempt to maintain the intravascular pool, a phenomenon which has been demonstrated in protein depletion (Hoffenberg, Black, and Brock, 1966). In nutritional
inadequacy, additional compensation is provided by a decrease in the catabolic rate.

The fractional catabolic rate of albumin was increased in rheumatoid arthritis, but there was no change in the absolute catabolic rate. It is important to consider both the fractional catabolic rate, i.e. catabolism expressed as a fraction of the intravascular mass, and the actual amount of albumin catabolized, since in disease they may not necessarily show parallel changes; for example in the nephrotic syndrome an increased fractional catabolic rate can occur in the presence of a normal absolute degradation rate (Jensen, Rossing, Andersen, and Jarnum, 1967).

It could be that, in severe rheumatoid arthritis, there is a continuing decrease in the intravascular albumin content due to increased catabolism with an increased fractional catabolic rate throughout and with an increased absolute catabolic rate during exacerbations of the disease. It would be worthwhile to determine albumin metabolism during an acute phase to investigate this possibility. Such patients were specifically excluded from the present study because one could not then assume the existence of 'steady-state' conditions.

Fractional catabolic rate correlated with 99m technetium uptake by the knee joint and with articular index, both of which are accepted indices of rheumatoid activity. It did not correlate with erythrocyte sedimentation rate, which can be regarded as too nonspecific an index for accurate assessment of rheumatoid arthritis.

Although these patients were carefully selected and all had 'classical' rheumatoid arthritis, there was some overlap with the normal group.

Wilkinson, Jeremy, Brooks, and Hollander (1965), who studied a similar group of rheumatoid arthritic patients, gave higher values for catabolic rate than we have shown. It is possible that the preparation of (131I)-albumin, which they used, was more denatured than the (125I)-albumin preparation used in the present study. They did not establish normal values with their preparation, but accepted a published series (Steinfeld, 1960) which used a similar preparation of albumin, and which yields a normal range with higher values for catabolic rate than are currently accepted (Cohen and others, 1961; Takeda and Reeve, 1963). However, similar conclusions are reached.

The findings of changes in albumin metabolism in rheumatoid arthritis, which correlate with accepted indices of disease activity, is another demonstration of the systemic effects of this condition. However, the technique involved is time-consuming and would not be suitable for routine clinical use.

Summary

Human serum albumin labelled with 125iodine was used to study albumin catabolism in nine patients with rheumatoid arthritis. Results were compared with those from eight subjects with normal albumin metabolism.

The albumin content of both the intravascular and extravascular pools were decreased in rheumatoid disease. There was a corresponding increase in fractional but not of absolute catabolic rate. Values for albumin concentration and content did not correlate with indices of disease activity, but values for fractional catabolic rate did correlate with these factors.

This project was undertaken while A. Fleck was in receipt of a grant from the Medical Research Council.

References


ROTHSCHILD, M. A., SCHREIBER, S. S., ORATZ, M., AND Mcgee, H. L. (1958) J. clin. Invest., 37, 1229 (The effects of adrenocortical hormones on albumin metabolism studied with albumin-


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