**Summary:** The β2-microglobulin plasma level is often high in patients suffering from cirrhosis. Many authors believe this to be due to an increased production, provided that the creatinine level is in the normal range. In the present study, alterations in the plasma level and production of β2-microglobulin were investigated in patients with liver cirrhosis without overt renal failure.

62 patients, 48 men and 14 women, suffering from liver cirrhosis were examined. The glomerular filtration rate (GFR) and plasma β2-microglobulin were measured in all patients and in 16 controls. As β2-microglobulin is freely filtered by glomeruli and its extrarenal catabolism is negligible, the β2-microglobulin filtration rate was calculated as the product of the β2-microglobulin plasma level times the GFR. In steady state conditions, the β2-microglobulin filtration rate may be used as an indirect index of β2-microglobulin production.

The β2-microglobulin plasma level was high in 26 patients; however, only 12 of them showed a definite rise in β2-microglobulin production, as shown by an increased β2-microglobulin filtration rate. The 14 patients with high β2-microglobulin plasma levels without high β2-microglobulin filtration rates obviously showed a decreased GFR; however, creatinine was not increased because of its small sensitivity as an index of renal function.

A linear correlation was found between IgG and the β2-microglobulin filtration rate \( r = 0.52; p < 0.02 \), not between IgG and the β2-microglobulin plasma level. The other indices of liver damage were not related to the β2-microglobulin filtration rate or plasma level.

In conclusion:

1) About half of the patients with high β2-microglobulin plasma levels and normal creatinine actually showed an increased β2-microglobulin production evaluated by the β2-microglobulin filtration rate. In the others the high β2-microglobulin plasma level was due to a subtle renal impairment which occurred before an increase in serum creatinine. Therefore, the β2-microglobulin plasma level was not a reliable index of β2-microglobulin production.

2) The use of the β2-microglobulin filtration rate as an index of β2-microglobulin production allowed us to detect a relationship between β2-microglobulin production and immunological alterations (IgG level) in cirrhosis.


Eine lineare Korrelation bestand zwischen IgG und Filtrationsrate von β2-Mikroglobulin (r = 0,52; p < 0,02), nicht zwischen IgG und Konzentration von β2-Mikroglobulin im Plasma. Andere Indikatoren für Leberschäden zeigten keine Beziehung zur Filtrationsrate von β2-Mikroglobulin oder seiner Konzentration im Plasma.

Schlußfolgerungen:


2. Die Verwendung der Filtrationsrate von β2-Mikroglobulin als Hinweis auf eine β2-Mikroglobulinbildung erlaubte uns, eine Beziehung zwischen β2-Mikroglobulinbildung und immunologischen Veränderungen (IgG-Konzentration) bei Lebercirrhose nachzuweisen.

Introduction

β2-Mikroglobulin is a low molecular weight plasma-protein (M_r = 11800) isolated from the urine of patients with tubular proteinuria by Berggärd (1). It is a single chain polypeptide synthesized by lymphocytes, mesenchymal and epithelial cells (2, 3). β2-Mikroglobulin is eliminated from the blood via glomerular filtration followed by catabolism in the kidneys after tubular reabsorption. Only a small amount of β2-mikroglobulin is excreted in the urine. As β2-mikroglobulin is freely filtered by glomeruli (4), the product of the β2-mikroglobulin plasma level times the glomerular filtration rate (GFR) shows with sufficient accuracy the extent of the filtration rate of β2-mikroglobulin.

In the steady state, the filtration rate of β2-mikroglobulin can be considered as an indirect index of β2-mikroglobulin production, because the extrarenal catabolism of β2-mikroglobulin is negligible (5).

Renal function is frequently impaired in liver cirrhosis (6, 7). This can account for an increased β2-mikroglobulin plasma level. However, plasma β2-mikroglobulin is also often high in cirrhotics without an increased creatinine level (8—11). The pathogenesis of such an increase is not yet clarified. Many authors suppose that it could be consequent on an increased production (8—11). However the creatinine plasma level is not so sensitive an index of the GFR as β2-mikroglobulin (12), therefore an increased β2-mikroglobulin level in plasma could be due to decreased filtration, even before any of the clinical or biochemical signs of renal failure used in ordinary practice are evident.

The aim of this research was:

a) to study β2-mikroglobulin production by means of β2-mikroglobulin filtration rate;
b) to compare the β2-mikroglobulin plasma level with the β2-mikroglobulin production;
c) to investigate the relationships between β2-mikroglobulin production and main indices of liver disease; in patients with liver cirrhosis without overt renal failure.
Materials and Methods

The study comprised sixtytwo consecutive in-patients, fortyeight
men and fourteen women, suffering from liver cirrhosis, who had
not suffered from organic nephropathy and had a creatinine level
lower than 13 mg/l. Twentyfour had alcoholic cirrhosis, twenty
posthepatitic cirrhosis and eighteen cryptogenic cirrhosis. The mean
age of the patients was fortynine years, and the standard
deviation was twelve. The diagnosis was made by case history,
clinical and laboratory findings and confirmed by histology in
thirty cases. In all patients and in sixteen controls (eleven men and
two women, mean age forty-five, standard deviation seven) the
glomerular filtration rate was measured by means of theulin
clearance. At the same time plasma samples were assayed for as-
partate aminotransferase, alanine aminotransferase, total bili-
rubin, prothrombin time, plasma protein electrophoresis and
creatinine. The creatinine level was determined by a colorimetric
method (Creatinine Test Combination. Cat. No. 124192. Boehr-
gerin Mannheim West Germany). Immunoglobulins, measured
by a nephelometer, were determined only in the last twentyfour
patients studied, because of a planning fault. Ten of them had
alcoholic cirrhosis, seven posthepatitic cirrhosis and seven crypto-
egenic cirrhosis. Immunoglobulin levels in cirrhotics are shown in
tab. 1.

| Tab. 1. Immunoglobulins in the three groups of cirrhotics. |
|----------------|----------------|----------------|
|                | (g/l)           | (g/l)          | (g/l)          |
| Alcoholic cirrhosis | 16.58 ± 3.45   | 5.60 ± 1.06    | 2.04 ± 1.08    |
| Cryptogenic cirrhosis | 20.60 ± 5.64   | 4.68 ± 2.18    | 3.16 ± 1.52    |
| Posthepatitic cirrhosis | 16.20 ± 4.80   | 4.36 ± 1.67    | 2.74 ± 1.59    |

Range of reference:
IgG 8–18 g/l, IgA 0.6–4.0 g/l, IgM 0.5–2.5 g/l

β2-Microglobulin was measured in plasma samples obtained dur-
ing inulin clearance by means of a radioimmunoassay technique
(Phadebas Beta-2-micro-test. Pharmacia Diagnostics. Uppsala,
Sweden).

Statistics

The normal range for β2-microglobulin plasma level and β2-
microglobulin filtration rate was considered to be the mean in the
controls ±2 s.d. The comparison between the values of the indices
of liver damage in patients with normal and high β2-microglobulin
plasma level or β2-microglobulin filtration rate was carried out
with Student's "t" unpaired test; 2 P values in "Table Scienti-
fiques", Geigy 1963, were used to ascertain statistical signifi-
cance. The significance in the frequency distribution of cirrhotics
with high β2-microglobulin plasma level or β2-microglobulin fil-
tration rate was not related to the aetiology of cirrhosis (respectively χ² = 0.32 and χ² = 1.1, not significant). In patients in whom both β2-
microglobulin plasma level and β2-microglobulin fil-

Results

The mean β2-microglobulin plasma level and mean
β2-microglobulin filtration rate were respectively 1.5
± 0.6 mg/l and 186 ± 73 μg/min in controls. They
were respectively 2.6 ± 1.1 mg/l and 251 ± 122 μg/
min in cirrhotic patients. β2-Microglobulin plasma
levels were high in twentysix patients. The β2-micro-
globulin filtration rate was high in fourteen; in
twelve cases both β2-microglobulin plasma level and
β2-microglobulin filtration rate were high (fig. 1).
The increase in β2-microglobulin plasma level or β2-
microglobulin filtration rate was not related to the
aetiology of cirrhosis (respectively χ² = 0.32 and χ² = 1.1, not significant). In patients in whom both β2-
microglobulin plasma level and β2-microglobulin fil-

Fig. 1. Concentrations of β2-microglobulin in plasma in the three
groups of cirrhotics (cirrhotics with β2-microglobulin fil-
tration rate O within, D above the normal range; --- upper limit of the normal range for β2-microglobulin plas-
ma level).

Tab. 2. Indices of liver disease in patients with or without high β₂-microglobulin plasma level.

<table>
<thead>
<tr>
<th>Index</th>
<th>High β₂-microglobulin plasma level</th>
<th>Low β₂-microglobulin plasma level</th>
<th>t</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspartate aminotransferase</td>
<td>60 ± 44 U/l</td>
<td>72 ± 58 U/l</td>
<td>0.877</td>
<td>n.s.</td>
</tr>
<tr>
<td>Alanine aminotransferase</td>
<td>53 ± 41 U/l</td>
<td>59 ± 71 U/l</td>
<td>0.383</td>
<td>n.s.</td>
</tr>
<tr>
<td>Prothrombin time</td>
<td>36 ± 18 %</td>
<td>69 ± 18 %</td>
<td>1.467</td>
<td>n.s.</td>
</tr>
<tr>
<td>Total bilirubin</td>
<td>19 ± 13 mg/l</td>
<td>23 ± 25 mg/l</td>
<td>0.770</td>
<td>n.s.</td>
</tr>
<tr>
<td>Albumin</td>
<td>33 ± 5 g/l</td>
<td>32 ± 6 g/l</td>
<td>0.696</td>
<td>n.s.</td>
</tr>
<tr>
<td>γ-Globulins</td>
<td>21 ± 7 g/l</td>
<td>21 ± 6 g/l</td>
<td>0.000</td>
<td>n.s.</td>
</tr>
<tr>
<td>IgG</td>
<td>17.57 ± 5.18 g/l</td>
<td>17.72 ± 6.41 g/l</td>
<td>0.067</td>
<td>n.s.</td>
</tr>
<tr>
<td>IgA</td>
<td>4.67 ± 1.98 g/l</td>
<td>5.09 ± 1.54 g/l</td>
<td>0.567</td>
<td>n.s.</td>
</tr>
<tr>
<td>IgM</td>
<td>2.09 ± 1.12 g/l</td>
<td>2.67 ± 1.41 g/l</td>
<td>0.881</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

Tab. 3. Indices of liver disease in patients with or without high β₂-microglobulin filtration rate.

<table>
<thead>
<tr>
<th>Index</th>
<th>High β₂-microglobulin filtration rate</th>
<th>Low β₂-microglobulin filtration rate</th>
<th>t</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspartate aminotransferase</td>
<td>46 ± 39 U/l</td>
<td>71 ± 53 U/l</td>
<td>1.582</td>
<td>n.s.</td>
</tr>
<tr>
<td>Alanine aminotransferase</td>
<td>50 ± 63 U/l</td>
<td>59 ± 63 U/l</td>
<td>0.478</td>
<td>n.s.</td>
</tr>
<tr>
<td>Prothrombin time</td>
<td>71 ± 17 %</td>
<td>72 ± 19 %</td>
<td>0.165</td>
<td>n.s.</td>
</tr>
<tr>
<td>Total bilirubin</td>
<td>21 ± 15 mg/l</td>
<td>22 ± 23 mg/l</td>
<td>0.153</td>
<td>n.s.</td>
</tr>
<tr>
<td>Albumin</td>
<td>35 ± 4 g/l</td>
<td>32 ± 6 g/l</td>
<td>1.700</td>
<td>n.s.</td>
</tr>
<tr>
<td>γ-Globulins</td>
<td>22 ± 6 g/l</td>
<td>21 ± 7 g/l</td>
<td>0.702</td>
<td>n.s.</td>
</tr>
<tr>
<td>IgG</td>
<td>23.30 ± 3.34 g/l</td>
<td>16.75 ± 3.77 g/l</td>
<td>2.818</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>IgA</td>
<td>6.01 ± 1.31 g/l</td>
<td>4.80 ± 1.70 g/l</td>
<td>1.173</td>
<td>n.s.</td>
</tr>
<tr>
<td>IgM</td>
<td>2.83 ± 1.07 g/l</td>
<td>2.59 ± 1.65 g/l</td>
<td>0.199</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

Fig. 2. Correlation between β₂-microglobulin filtration rate (index of β₂-microglobulin production) and IgG: \( y = 2.5x + 1173 \) (\( r = 0.52, p < 0.02 \)).

Discussion

β₂-Microglobulin plasma levels in controls corresponded to those found in the literature (4, 9). The β₂-microglobulin filtration rate corresponded to the production of β₂-microglobulin measured by the disappearance of \(^{125}\)I-labelled β₂-microglobulin from the vascular compartment (4). This is a confirmation of the renal catabolism of β₂-microglobulin and of the value of the β₂-microglobulin filtration rate as an indirect index of β₂-microglobulin production.

A definite rise in β₂-microglobulin production, as shown by an increased β₂-microglobulin filtration rate, was ascertained in 46% of the patients with high β₂-microglobulin plasma levels. In the patients with high β₂-microglobulin plasma levels without an increased β₂-microglobulin filtration rate, the GFR was decreased, but so slightly that on an average it did not affect the serum creatinine level. Possibly the reduction in muscle mass, commonly found in cirrhosis, could explain the low sensitivity of serum creatinine as an index of renal function. In fact, serum creatinine depends not only on the GFR, but also on the muscle production of creatinine. Therefore, even if serum creatinine is in the normal range, the high β₂-microglobulin plasma level can often be consequent on a reduction in glomerular filtration, especially in patients with liver cirrhosis, where a decreased renal function is very common (6, 7).
As far as the pathogenesis of the raised production of β2-microglobulin in liver cirrhosis is concerned, three mechanisms were hypothesized: one, an increased protein release due to hepatic tissue necrosis; two, an increased hepatic synthesis during reparative growth; three, an increased lymphocytic synthesis reflecting an elevated inflammatory activity (8).

In our series, neither the β2-microglobulin plasma level nor the β2-microglobulin filtration rate were found to be related to the plasma level of transaminases or to the main indices of liver damage, in agreement with the findings of Beorchia (9). Therefore it is unlikely that tissue necrosis and liver function could have any role in the increased production of β2-microglobulin. Our results do not allow us to express any opinion about an increase in β2-microglobulin hepatic synthesis (an hypothesis not yet completely elucidated by any author).

The immunological hypothesis is based on the fact that β2-microglobulin shares many structural features with the immunoglobulin polypeptide chains, particularly with the Cα3 domain of IgG (2, 14), and it is closely associated with the major human histocompatibility antigens (15, 16); moreover the β2-microglobulin plasma level in liver diseases decreases during immunosuppressive treatment (9). The linear correlation between the β2-microglobulin filtration rate and IgG that we found is good evidence in support of this hypothesis. It could be hypothesized that β2-microglobulin overproduction was an expression of B lymphocyte hyperreactivity due to endotoxin—a potent B cell mitogen—or of the cellular immunity depression found in many chronic liver diseases (17, 18).

A wide variability in the immunologic-phlogistic reactions in the three aetiologic groups of our series could explain why neither β2-microglobulin plasma level nor β2-microglobulin filtration rate appeared related to the aetiology of liver cirrhosis.

References