HIGH MOLECULAR WEIGHT KININOGENS (HMWK) AND COAGULATION FACTOR VII AS PROGNOSTIC LANDMARKS IN THE PREDICTION OF HEPATIC DECOMPENSATION

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ABSTRACT
Owing to their delicate nature, coagulation proteins could be strongly considered as sensitive parameters in assessment of the hepatic functions, Vierling (1984). Plasma coagulation factors are very sensitive to liver failure yielding a good indication of terminal liver protein insufficiency. Many investigators studied various coagulation parameters aiming at evaluation of their prognostic value in chronic liver diseases. They reported that no single parameter is by itself a definitive indication for a terminal hepatopathy, Biland et al. (1978). This problem is still controversial. Vierling (1984) suggested that a prothrombin time eight seconds longer than the control values represent an adverse prognostic index hepatic insufficiency. In fact prothrombin time assay does not seem to differentiate between survivors and non survivors when cirrhotic cases were followed. Therefore, a great deal of attention has been given to identify blood coagulation factors that are more sensitive to liver failure to evaluate their prognostic importance. Initial studies suggested that factor VII - a protein of prothrombin complex with a short half life - and HMWK are sensitive indexes of liver damage, Orlando et al. (1982) and Cordova et al. (1984). Therefore, the objective of the present study is to further investigate this clinical problem. Therefore, coagulation factor VII and
HMWK have been assayed simultaneously in liver cirrhosis and chronic hepatitis in compensated as well as decompensated stages.

MATERIALS AND METHODS
A. Materials:
This study was performed on 38 subjects. Twelve of them were normal representing a reference group, they were clinically and laboratory free particularly from liver diseases as hepatitis, schistosomiasis, jaundice or drugs that might influence the results all had been confirmed. Their liver function profile as well their haemostatic profile were within normal. Their age ranged from 19 to 52 years (M : 38.9y) and they were all males. The patients group comprized 26 male cases, of them 14 were suffering from bilharzial hepatic fibrosis diagnosed by history of exposition, rectal snip and liver biopsy. They were further subclassified into compensated group (8 cases), their mean age was 29.6 years (23-58 ys) and decompensated group (6 cases) with a mean age of 44.2 years (32-63 ys). Hepatic decompensation was considered in the presence of either ascitis, hepatic encephalopathy, prothrombin activity <49%, serum albumin <3 g/dl or serum bilirubin >5.9 mg/dl. The other group included patients who were diagnosed as chronic hepatitis as proved by and liver biopsy viral markers for hepatitis B&C viruses besides the drained hepatic functions particularly the enzymatic parameters. This group included 12 male patients who ertr again subgrouped into compensated (7 cases) with a mean age of 24.6 years (17-42 ys) and 5 decompensated cases with a mean age of 30.6 years (22-59 ys).

B. Methods:
In addition to the routine haematological, serum biochemical and immunological investigations necessary for diagnosis and follow up of the cases the following tests had been carried out for all subjects:
* Prothrombin time (PT) which explores vitamin k dependent factors (II, VII and X), was assayed by the Quick method, Dacie & Lewis (1991).
* High molecular weight kininogens (HMWK) plasma activity was assayed by chromogenic S-222, kabi-Diagnostics, Mariani et al. (1982).

* Coagulation factor VII plasma activity was assayed by chromogenic S-222, kabi-Diagnostics, Mariani et al. (1982).

**RESULTS**

The specific laboratory findings obtained in this study had been tabulated as follows:

<table>
<thead>
<tr>
<th></th>
<th>Bil. Fibrosis (n: 14)</th>
<th>Ch. Hepatitis (n: 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Compen. n: 8</td>
<td>Decomp. n: 6</td>
</tr>
<tr>
<td>Prothrombin Time</td>
<td>12 ± 0.7</td>
<td>14.6 ± 1.1</td>
</tr>
<tr>
<td>(sec)</td>
<td>29 ± 6.0</td>
<td>38.4 ± 3.6</td>
</tr>
<tr>
<td>APTT (sec)</td>
<td>92 ± 12.0</td>
<td>62.0 ± 14.0</td>
</tr>
<tr>
<td>Factor VII (%)</td>
<td>34 ± 4.0</td>
<td>43.8 ± 2.5</td>
</tr>
<tr>
<td>HMWK (sec)</td>
<td>7 ± 0.5</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>P&lt;sub&gt;1&lt;/sub&gt;</td>
<td></td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>P&lt;sub&gt;2&lt;/sub&gt;</td>
<td></td>
<td>-</td>
</tr>
</tbody>
</table>

n = number of cases,
compen. = compensated,
decomp. = decompensated,
Bil. = Bilharzial,
P<sub>1</sub> = compensated or decompensated versus control,
P<sub>2</sub> = compensated versus decompensated.
A significantly prolonged PT, HMWK and low factor VII activity were noticed in both cirrhotic as well as chronic hepatitis groups as compared to the reference values. The magnitude of such change was clearly proportionate to the severity of liver damage as evidenced by the significantly low values in the decompensated subgroups. This reduction in factor VII activity and HMWK was mostly significant in decompensated chronic hepatitis subgroup.

DISCUSSION

Diagnostic and prognostic aspects of chronic Liver diseases might be verified via the assessment of blood coagulation profile. Since all the coagulation factors - except factor VII - are solely synthesized by the hepatocytes, they possess both diagnostic as well as prognostic significancies in acute as well as chronic liver cell failure, cordova et al. (1986). As reported by Biland (1978) and Martine et al. (1982), vitamin k dependent factors factor V, XIII, plasminogen and antithrombin III are very sensitive to hepatic insults particularly protein synthesis failure. Meanwhile, Biland et al. (1978) reported that prothrombin time did not differentiate survivors from liver cirrhosis from non survivors, while plasminogen level and factor VIII activity may be informative. Owing to its short half life, factor VII has been considered the most sensitive index of liver protein synthesis failure, Green et al. (1976). Therefore, it exhibits an informative prognostic significance in hepatic insults particularly the acute ones.

This work, has clarified that plasma activity of factor VII was reduced in both patient groups namely hepatitis and bilharzial fibrosis, being more significantly lower in cirrhotic group than in hepatitis. Moreover, this reduction was related to the type and duration of hepatic damage as proved by the progressive significant reduction in decompensated when compared to the compensated cases. This could be referred to the chronic ischaemia of the hepatocytes resulting from the consequent periportal fibrosis in such cases besides the early affection of factor VII due to its short half life.
The low plasma activity of HMWK revealed in cirrhotic patients further support the previous findings that was more manifest in decompensated cases. Similarly a more significant reduction could be detected in chronic hepatitis cases. Such reduction was more pronounced in decompensated hepatitis patients. The relationship between HMWK and perkalikrin had been investigated in chronic liver diseases by many researchers, et al. (1977) and Liu et al. (1977). The strong correlation between HMWK and factor VII emphasize that both coagulation parameters could have a similar sensitivity in the prediction of liver protein failure. This could be attributed to the fact that the half life of HMWK is very short as that of factor VII. Moreover, non significant differences had been detected on comparing the cirrhotic versus the hepatitis group despite their different histopathological features. This could be attributed to a similar functional cell injury. These findings had been found to be in agreement with these reported by cordova et al. (1986). Accordingly, we can come to a conclusion that factor VII assay and HMWK could be considered a sensitive prognostic indices in the prediction of hepatic cell failure.

SUMMARY

Plasma coagulation factors are very sensitive to liver failure so that it may yield a good indication for terminal protein insufficiency. Because of their half life and hence their early affection factor VII as well as HMWK were selected for assay in this study looking for a more definitive prognostic value in chronic liver insults. Accordingly, twenty six hepatic patients were investigated besides 12 healthy controls. Patients were grouped into bilharzial hepatic fibrosis and chronic viral hepatitis group, each category comprised a compensated as well as decompensated varieties. From this study it is clear that plasma coagulation factor VII and HMWK were significantly reduced in both diseases. Moreover, this reduction was much more evident in decompensated subgroups, being very low in decompensated chronic hepatitis patients. Accordingly, factor VII and HMWK could be considered a sensitive prognostic indices in the prediction of hepatic cell failure.
REFERENCES


الكينينوجينات عالية الوزن الجزيئي وعامل التجلط السابع في البلازما ومعدلاتها في توقع الهبوط الكبدى

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المتوصيات والاستنتاجات:
نظراً للحساسية المفرطة للهبوط الكبدى، فإن عوامل التجلط في البلازما يمكن أن تعطي مؤشراً لعدم كفاءة الكبد في تخليق البروتينات. ونظراً لقصر فترة بقائها ومن ثم تأثيرها المبكر - فقد أظهر عامل التجلط السابع والكينينوجينات تكثيفاً للوزن الجزيئي للمعايرة في هذه الدراسة، حيث يدل ذلك على نقص في الكبد، وقد تقدم في أعراض الكبد المزمنة. وعلى ذلك فقد نقص 25 مريضاً كيبيداً إلى جانب 12 شخساً من الأصحاء كمجموعة ضابطة. وقد ضمت مجموعة المرضى تشمل احدهما مرضى تليف الكبد البهلاري والآخر مرضى الالتهاب الفيروسي الكبدى المزمن، وتعتبر كل مجموعة من حيث حالة الكبد إلى فحص أحدثهما متكافئاً، وتبين أن هذه الدراسة أن هناك انخفاضاً ملحوظاً في مستوى عامل التجلط السابع والكينينوجينات في مجموعة المرضى بالمقارنة بالمجموعة الضابطة. و بناءً على هذا الانخفاض كان أكثر وضوحاً في مرضى الهبوط الكبدى. خاصاً في مجموعة الالتهاب الكبدى الفيروسي المزمن الغير متخلف، وفي ضوء ذلك يمكن اتخاذ مستوى عامل التجلط السابع والكينينوجينات عالية الوزن الجزيئي كمؤشرات دقيقة في متابعة مرضى الكبد واتجاه حدوث الهبوط الكبدى.

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