Role of Vitamin K2 in the Development of Hepatocellular Carcinoma in Women With Viral Cirrhosis of the Liver

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WE PREVIOUSLY REPORTED a 2-year study showing that vitamin K2 (menaquinone) helps to prevent bone loss in women with viral cirrhosis of the liver.1 Most of the women agreed to participate in a longer study to clarify the long-term effects of vitamin K2 on bone loss associated with cirrhosis. The incidence of hepatocellular carcinoma was found to differ between women who received vitamin K2 and those who did not.

METHODS
The participants in this study were 50 women with viral liver cirrhosis who were admitted to a university hospital between 1996 and 1998. When the results of abdominal dynamic computed tomography and abdominal ultrasonography suggested the presence of hepatocellular carcinoma, abdominal angiography or needle biopsy was performed to confirm the diagnosis. The diagnosis of cirrhosis was based on histological examination of liver specimens obtained by laparoscopy or needle biopsy performed under ultrasonic guidance.

Hepatocellular carcinoma was confirmed in 3 women in the treatment group and 4 in the control group. These 7 women were excluded from further study. The remaining 43 women were randomly assigned using sealed envelopes to a treatment or control group.

Context Previous findings indicate that vitamin K2 (menaquinone) may play a role in controlling cell growth.

Objective To determine whether vitamin K2 has preventive effects on the development of hepatocellular carcinoma in women with viral cirrhosis of the liver.

Design, Setting, and Participants Forty women diagnosed as having viral liver cirrhosis were admitted to a university hospital between 1996 and 1998 and were randomly assigned to the treatment or control group. The original goal of the trial was to assess the long-term effects of vitamin K2 on bone loss in women with viral liver cirrhosis. However, study participants also satisfied criteria required for examination of the effects of such treatment on the development of hepatocellular carcinoma.

Interventions The treatment group received 45 mg/d of vitamin K2 (n=21). Participants in the treatment and control groups received symptomatic therapy to treat ascites, if necessary, and dietary advice.

Main Outcome Measure Cumulative proportion of patients with hepatocellular carcinoma.

Results Hepatocellular carcinoma was detected in 2 of the 21 women given vitamin K2 and 9 of the 19 women in the control group. The cumulative proportion of patients with hepatocellular carcinoma was smaller in the treatment group (log-rank test, P=.02). On univariate analysis, the risk ratio for the development of hepatocellular carcinoma in the treatment group compared with the control group was 0.20 (95% confidence interval [CI], 0.04-0.91; P=.04). On multivariate analysis with adjustment for age, alanine aminotransferase activity, serum albumin, total bilirubin, platelet count, \alpha\,-fetoprotein, and history of treatment with interferon alfa, the risk ratio for the development of hepatocellular carcinoma in patients given vitamin K2 was 0.13 (95% CI, 0.02-0.99; P=.05).

Conclusion There is a possible role for vitamin K2 in the prevention of hepatocellular carcinoma in women with viral cirrhosis.

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VITAMIN K2 AND LIVER CANCER AMONG WOMEN

Table 1. Baseline Characteristics

<table>
<thead>
<tr>
<th>Treatment Group (n = 21)</th>
<th>Control Group (n = 19)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>59.8 (8.7)</td>
<td>61.4 (7.1)</td>
</tr>
<tr>
<td>Hepatitis virus, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>1 (4)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>C</td>
<td>20 (95)</td>
<td>18 (95)</td>
</tr>
<tr>
<td>Albumin, g/dL</td>
<td>3.9 (0.3)</td>
<td>3.9 (0.3)</td>
</tr>
<tr>
<td>Platelets, ×10^9/mL</td>
<td>147 (54)</td>
<td>121 (52)</td>
</tr>
<tr>
<td>Total bilirubin, mg/dL</td>
<td>0.8 (0.2)</td>
<td>0.9 (0.4)</td>
</tr>
<tr>
<td>Alanine aminotransferase, U/L</td>
<td>81.7 (42.7)</td>
<td>70.4 (33.4)</td>
</tr>
<tr>
<td>α-Fetoprotein, mg/mL</td>
<td>13.4 (17.7)</td>
<td>13.3 (8.7)</td>
</tr>
<tr>
<td>Interferon, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior to enrollment§</td>
<td>4 (19)</td>
<td>3 (16)</td>
</tr>
<tr>
<td>At enrollment</td>
<td>17 (81)</td>
<td>16 (84)</td>
</tr>
</tbody>
</table>

SI conversion units: To convert bilirubin to µmol/L, multiply by 17.1.
*Values expressed as mean (SD) unless otherwise indicated.
†Values calculated using the Mann-Whitney U test.
‡Values calculated using the χ² test.
§Hepatocellular carcinoma developed in 1 of 4 patients in the treatment group and 1 of 3 patients in the control group who received interferon prior to enrollment.

Figure 1. Flow of Participants Through Trial

Figure 2. Cumulative Incidence of Hepatocellular Carcinoma Diagnosed in Women Treated With Vitamin K2

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VITAMIN K₂ AND LIVER CANCER AMONG WOMEN

Table 2. Profiles of Women With Hepatocellular Carcinoma

<table>
<thead>
<tr>
<th>Case No./Age, y</th>
<th>Group</th>
<th>Type of Hepatitis</th>
<th>Virus</th>
<th>No. of Days After Diagnosis Occurred</th>
<th>No. of Tumors</th>
<th>Diameter of Largest Tumor, mm</th>
<th>UICC Stage</th>
<th>Method of Therapy</th>
<th>Histological Grade</th>
<th>Type of Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/70 Control</td>
<td>C</td>
<td></td>
<td></td>
<td>200</td>
<td>1</td>
<td>15</td>
<td>1</td>
<td>Biopsy</td>
<td>1*</td>
<td>PEIT</td>
</tr>
<tr>
<td>5/62 Control</td>
<td>C</td>
<td></td>
<td></td>
<td>2333</td>
<td>2</td>
<td>20</td>
<td>2</td>
<td>AAG</td>
<td>Unknown</td>
<td>TAE</td>
</tr>
<tr>
<td>6/59 Control</td>
<td>C</td>
<td></td>
<td></td>
<td>282</td>
<td>1</td>
<td>9</td>
<td>1</td>
<td>Biopsy</td>
<td>1*</td>
<td>PEIT</td>
</tr>
<tr>
<td>9/70 Control</td>
<td>C</td>
<td></td>
<td></td>
<td>91</td>
<td>1</td>
<td>13</td>
<td>1</td>
<td>Biopsy</td>
<td>1*</td>
<td>PEIT</td>
</tr>
<tr>
<td>21/43 Control</td>
<td>C</td>
<td></td>
<td></td>
<td>1516</td>
<td>1</td>
<td>30</td>
<td>2</td>
<td>Biopsy</td>
<td>2*</td>
<td>MCT</td>
</tr>
<tr>
<td>25/59 Control</td>
<td>C</td>
<td></td>
<td></td>
<td>1569</td>
<td>2</td>
<td>18</td>
<td>2</td>
<td>AAG</td>
<td>Unknown</td>
<td>TAE</td>
</tr>
<tr>
<td>28/67 Control</td>
<td>B</td>
<td></td>
<td></td>
<td>949</td>
<td>1</td>
<td>32</td>
<td>2</td>
<td>AAG</td>
<td>Unknown</td>
<td>TAE</td>
</tr>
<tr>
<td>33/57 Control</td>
<td>C</td>
<td></td>
<td></td>
<td>2600</td>
<td>1</td>
<td>30</td>
<td>2</td>
<td>AAG</td>
<td>Unknown</td>
<td>TAE</td>
</tr>
<tr>
<td>40/68 Control</td>
<td>C</td>
<td></td>
<td></td>
<td>1002</td>
<td>1</td>
<td>21</td>
<td>2</td>
<td>Biopsy</td>
<td>3*</td>
<td>Operation</td>
</tr>
<tr>
<td>4/64 Vitamin K₂</td>
<td>C</td>
<td></td>
<td></td>
<td>907</td>
<td>1</td>
<td>30</td>
<td>2</td>
<td>AAG</td>
<td>Unknown</td>
<td>TAE</td>
</tr>
<tr>
<td>27/68 Vitamin K₂</td>
<td>C</td>
<td></td>
<td></td>
<td>1054</td>
<td>1</td>
<td>11</td>
<td>1</td>
<td>Biopsy</td>
<td>1*</td>
<td>PEIT</td>
</tr>
</tbody>
</table>

Abbreviations: AAG, abdominal angiography; MCT, microwave coagulation therapy; PEIT, percutaneous ethanol injection therapy; TAE, transcatheter hepatic arterial embolization; UICC, International Union Against Cancer.

*Vitamin K₂ group compared with control group.

COMMENT

Vitamin K is a cofactor for the enzyme γ-glutamyl-carboxylase, which converts glutamate residues into γ-carboxyglutamate. Vitamin K–dependent proteins include prothrombin II and the coagulation factors VII, IX, X, proteins C and S, osteocalcin, surfactant-associated proteins, and bone matrix protein. The vitamin K family of molecules comprises the natural forms vitamin K₁ (phylloquinone) and vitamin K₂ (menaquinones) and the synthetic form of vitamin K₁ (menadione). These naphthoquinone-containing molecules inhibit tumor cell growth in culture, with vitamin K₁ being more potent than either vitamin K₁ or K₂. Vitamin K₂ inhibits growth of human cancer cell lines and induction of differentiation in various human myeloid leukemia cell lines. Vitamin K₁ has successfully treated myelodysplastic syndrome.

A number of findings indicate that vitamin K may play a role in controlling cell growth. Underlying mechanisms possibly involve (1) cycling of oxidation and reduction (as known for vitamin K₁), (2) proteins with growth-inhibitory properties induced by vitamin K, such as prothrombin,10 (3) previously unidentified pathways involving arylation,11 (4) or growth arrest genes such as gas 6.12 Geranylgeraniol, which is a side chain of vitamin K₂, strongly induces apoptosis of tumor cells, suggesting that geranylgeraniol might play an important role in inhibiting cell growth.13 The mechanisms responsible for the inhibition of cell growth mediated by vitamin K₂ remain unexplained. These or other hypothetical mechanisms may have contributed to the reduced hepatocellular carcinoma incidence among patients receiving vitamin K₂. Indeed, the annual incidence of hepatocellular carcinoma in the control group was 8.8%, which is similar to the incidence of hepatocellular carcinoma (7.9%; 32/107) in cirrhotic patients in Japan compared with 1.6% in the treatment group.

As shown in Table 4, the albumin level showed the highest odds ratio for the development of hepatocellular carcinoma. The serum albumin level is considered an important prognostic factor in liver cirrhosis.14-17 Low serum albumin levels in patients with liver cirrhosis are associated with disease progression, poor nutritional status, and compromised immunity, which increases the risk of carcinogenesis. The importance of low serum albumin levels as a risk factor for hepatocellular carcinoma should be confirmed in larger studies.

The original goal of our trial was to assess the long-term effects of vitamin K₂ on bone loss in women with viral liver cirrhosis. Our trial had several important limitations when the data were used to assess the value of vitamin K₂ for the primary prevention of hepatocellular carcinoma in patients with liver cirrhosis, resulting from the small study group,
the inclusion of only women, and the participation of only 1 center. However, similar to previously reported randomized controlled studies of cirrhosis in which the primary end point was the development of hepatocellular carcinoma, patients with evidence of hepatocellular carcinoma on highly sensitive imaging studies were excluded, and the 2 study groups were similar with respect to risk factors for hepatocellular carcinoma, such as age, severity of cirrhosis, history of interferon therapy, and type of hepatitis virus infection. The procedures used for the surveillance and diagnosis of hepatocellular carcinoma were also similar to those used in our study. The sensitivity of these procedures for the detection of hepatocellular carcinoma was underscored by the fact that all of the detected cases of hepatocellular carcinoma were stage I or stage II. Our results must also be tempered by the fact that 3 cases of hepatocellular carcinoma were diagnosed in the control group within a year of enrollment. These patients may have harbored occult disease at the time of enrollment. Nonetheless, despite its small size, our study indicates that vitamin K₂ decreases the risk of hepatocellular carcinoma to about 20% compared with the control group, suggesting that vitamin K₂ may delay the onset of hepatocarcinogenesis. Moreover, the safety, relatively low cost, and ease of use of vitamin K₂ led to good compliance with treatment. The results of this preliminary trial are intriguing and suggest that a potential role for vitamin K₂ to prevent hepatocarcinogenesis in patients with liver cirrhosis. These results must be confirmed by multicenter randomized controlled studies with the prevention of hepatocellular carcinoma by vitamin K₂ as the primary end point.

Author Contributions: Dr Shiomi had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Habu, Shiomi, Kubo, Nishiguchi.

Acquisition of data: Habu, Shiomi, Tamori, Takeda, Nishiguchi.

Analysis and interpretation of data: Habu, Shiomi, Tamaki, Kubo, Nishiguchi.

Drafting of the manuscript: Habu, Shiomi, Tamori, Takeda, Kubo, Nishiguchi.

Critical revision of the manuscript for important intellectual content: Habu, Shiomi, Tamaki, Nishiguchi.


Obtained funding: Habu, Shiomi, Tamori, Takeda, Nishiguchi.

Administrative, technical, or material support: Habu, Shiomi, Tamori, Nishiguchi, Kubo.

Supervision: Shiomi, Nishiguchi, Kubo.

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REFERENCES


