Association between non-alcoholic fatty liver disease and endometrial cancer

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Abstract

Metabolic syndrome (MetS) increase the risk of endometrial cancer (EC). Non-alcoholic fatty liver disease (NAFLD) is related with MetS and share many risk factors with EC that may have significant roles in its development; however, the relationship between NAFLD and EC remains unclear. 207 patients who were operated for endometrial cancer in our hospital between 2011 and 2015, and 243 gynecological patients without a history of malignancy who were randomly selected as the control group. NAFLD was diagnosed based on abdominal ultrasonography findings. There was no significant difference presence of diabetes mellitus and ALT, AST levels between EC group and control group. In EC group, age, body mass index (BMI), hypertension and NAFLD were significantly higher than those in control group (P < 0.001). Logistic regression analysis showed that age and NAFLD are independent risk factors for presence of EC. Age and NAFLD were a possible independent risk factor for EC in the present study. Therefore, a multi-center and large-population study will be needed to prove our conclusions.

Keywords: endometrial cancer, non-alcoholic fatty liver disease, obesity, metabolic syndrome

1. Introduction

Endometrial carcinoma (EC) is one of the most common gynecological malignancies and as the worldwide burden of EC continues to increase, interest is growing in the development of early preventive strategies for women at increased risk (1). Especially endometrial adenocarcinoma (type 1) is related to a series of endocrine and metabolic disorders which may influence estrogen/progesterone levels, which may increase the risk of malignant endometrial changes (1-4). According to the World Cancer Research Fund, being overweight or obese is related to an increased incidence of EC (5). For these people, the risk of EC is associated with their lifestyle, dietary factors and physical inactivity (6-8). Non-alcoholic fatty liver disease (NAFLD), defined as excess lipit accumulation in the liver, which has become the most common cause of chronic liver disease in children and adolescents, and a major cause of liver disease in adults (9). The incidence of NAFLD is dramatically increasing in parallel with an increasing prevalence of obesity due to diet and lifestyle changes worldwide. EC and NAFLD share common risk factors such as obesity, diabetes and the presence of metabolic syndrome (MetS) and its component disorders (10).

There is large body of literature linking the risk of EC with individual conditions associated with MetS, however association with NAFLD has not been established (10-14).

Therefore, the aim of the present study was to evaluate the relationship between NAFLD and clinicopathological features of patients with endometrial adenocarcinoma.

2. Participants and Methods

After Institutional Review Board approvals, patients with endometrioid EC who underwent primary surgical treatment between January 2011 and December 2015 at the Department of Gynecologic Oncology, Zekai Tahir Burak Education and Research Hospital were retrospectively reviewed. All patients provided informed consent for the surgical procedure and research use of their medical information at admission. Type 1 endometrial cancer patients with distant metastasis, type 2 endometrial cancer patients or additional malignancies were excluded from the study. A total of 207 EC patients met the criteria and were included in the study. A history of medical conditions, including type 2 diabetes, clinical obesity, drug treated hypertension, and drug-treated or clinical diagnosis of hyperlipidemia, was self-reported and included age at first diagnosis. Anthropometric data were collected, and biochemical analyses were performed in routine health examinations. We calculated body mass index (BMI) as weight/height² (kg/m²). Serum biochemical test results taken from the patients and control group were recorded from the digital archives. Diabetes mellitus (DM) was defined by any or all of the following: exposure to any antidiabetic agents, hemoglobin A1c ≥6.5%, fasting plasma glucose ≥7.0 mmol/L (≥126 mg/dL) in two measurements 1 month apart. Blood pressure was measured in rest state with a standard mercury

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sphygmomanometer and hypertension was identified by a resting blood pressure of ≥140/90 mm Hg. All the participants routinely underwent hepatic ultrasonography (US) scanning (Siemens; Munich, Germany) by experienced radiologists. Exception of viral hepatitis, cirrhosis, liver cancer or other liver disease, and excess alcohol consumption, participants meeting specific ultrasonographic features including hepatomegaly, diffusely increased echogenicity of liver parenchyma, and blurring of vasculature were diagnosed as NAFLD (15). The values of CA125 were pre-surgery values. The control group comprised 243 individuals with no oncological or systemic disease and no history of diabetes mellitus, obesity or MetS. The statistical analysis was performed with the SPSS 19.0 (SPSS, Chicago, IL). The statistical results are presented as the mean± standard deviation or percentages. Independent sample Student t test was used for continuous variables and Chi-squared for categorical variables. In addition, logistic regression analysis was also performed to estimate the probability of the presence of hypertension, hepatosteatosis, BMI and age and the 95% CI for each risk factor adjusting for EC.

3. Results
In our study, 207 patients who were operated for endometrial cancer in our hospital between 2011 and 2015, and 243 gynecological patients without a history of malignancy who were randomly selected as the control group. Baseline characteristics of the study participants with patient and control group were summarized in Table 1.

Table 1. Differences between patient and control group

<table>
<thead>
<tr>
<th></th>
<th>Control group (n=243)</th>
<th>Patient (n=207)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year, std)</td>
<td>49.9±10.3</td>
<td>58.1±10.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension (n, %)</td>
<td>8 (25.8 %)</td>
<td>23 (%74.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes mellitus (n, %)</td>
<td>51 (49.5 %)</td>
<td>52 (50.5 %)</td>
<td>0.313</td>
</tr>
<tr>
<td>AST (IU/L, std)</td>
<td>20.2±9.98</td>
<td>21.9±9.90</td>
<td>0.066</td>
</tr>
<tr>
<td>ALT (IU/L)</td>
<td>20.2±16.9</td>
<td>22.4±13.4</td>
<td>0.122</td>
</tr>
<tr>
<td>NAFLD (n, %)</td>
<td>100 (40 %)</td>
<td>150 (60 %)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.8±3.49</td>
<td>25.96±3.32</td>
<td>0.035</td>
</tr>
</tbody>
</table>

Mean age of the patients was higher than control group (58.1±10.7 year vs 49.9±10.3 year p=0.001). Hypertension and NAFLD were observed more frequently in individuals with EC than in the control group (23 (74.2%) vs 8 (25.8 %) p<0.001 and 150 (60%) vs 100 (40%) p<0.001). Compared with normal subjects, the endometrial cancer group subjects had higher BMI (23.82±3.49 kg/m² vs 25.96±3.32 kg/m² p<0.001). There were no differences of AST, ALT levels and prevalence of diabetes mellitus in both group (Fig. 1).

Table 2. Logistic regression analysis

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>RR (95% OR)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>0.5 (0.2-1.2)</td>
<td>0.143</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>0.4 (0.32-1.05)</td>
<td>0.06</td>
</tr>
<tr>
<td>NAFLD</td>
<td>0.3 (0.19-0.45)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age</td>
<td>1.08 (1.06-1.1)</td>
<td>&lt;0.001</td>
</tr>
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When logistic regression analysis was performed for age, hypertension, BMI and the presence of NAFLD, it was determined that age and the presence of NAFLD were independent risk factors for endometrial cancer (Table 2).

4. Discussion
In this retrospective study, we demonstrated that patients with EC had a higher incidence of NAFLD than the general population. To our best knowledge, this is the first cohort study investigating the presence of NAFLD in EC patients.

Recently, many risk factors have been linked to the occurrence of EC, such as obesity, diabetes and hyperinsulinemia. In addition, a sedentary lifestyle, Lynch syndrome, nulliparity, early menarche, and anovulatory conditions were also found to be potential risk factors for EC.

NAFLD is usually an outcome of ectopic fat storage due to chronic positive energy balance leading to obesity. It is characterized by excess deposition of triglycerides (TG) in the hepatocyte followed by development of inflammatory NAFLD and fibrogenic responses. Although there are some noninvasive diagnostic techniques to evaluate NAFLD, liver biopsy is the gold standard for diagnosis. Conventional US is often the first imaging modality used to evaluate fatty liver clinically, especially for screening of suspected NAFLD, due to its lack of invasiveness, wide availability, and relatively low cost (15,16).

NAFLD is the most common chronic liver disease worldwide and associated with visceral obesity, insulin resistance, type 2 diabetes (T2D) and has been often considered as the hepatic expression of the MetS. There are some potential biological mechanisms by which MetS modulates cancer risk. First, adipose tissue is an important source of estrogen and estrogen induces proliferation of endometrial cancer cells (1, 17, 18). Also, MetS is represented by insulin resistance and hyperinsulinemia, and hyperinsulinemia leads to decreased hepatic synthesis of insulin-like growth factor (IGF)-binding protein 1 (IGFBP-1) and protein 2 (IGFBP-2) and may result in increased bioactivity of IGF-1 (19). IGF-1 promotes proliferation and is anti-apoptotic. In addition, some authors
believe that NAFLD directly leads to insulin resistance and hyperinsulinemia (20, 21). There are many studies continually confirming that NAFLD is closely related to the increased risk of various cancers, including oesophagus, stomach, pancreas, colorectal, breast and urinary system cancers (22, 23). But its relationship in endometrial cancer has not been investigated before.

Age is an important risk factor for EC. EC incidence and mortality are dramatically increased in people aged 50 years or older (24). In our study age of the patient group was significantly higher than the control group.

Some limitations exist in the present study. First of all, this is a single-center retrospective analysis and the number of the patients is relatively small. As in other observational studies, it is possible that confounding due to unmeasured confounders might have somewhat distorted the results obtained. Also, it was not practical to control for all possible risk factors, such as dietary factors and lifestyle.

In conclusion, this retrospective cohort study demonstrated that patients with EC had a higher incidence of NAFLD. These data suggest that further investigation of potential interactions between endogenous and exogenous factors involved in endometrial carcinogenesis may help to clarify the magnitude and extent of EC risk experienced by persons with NAFLD. Our findings will provide insights to health care providers about the risk for EC those women diagnosed with NAFLD and underscore the need for interventions to treat and prevent EC. Therefore, a multi-center and large-population study will be needed to prove our conclusions.

Conflict of interest
The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References
Topfedaizsi Ozkan et al. / J Exp Clin Med

