Association between Fatty Liver Disease and Hyperplastic Colonic Polyp

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ABSTRACT: Background: Hyperplastic polyps (HPs) of the colon are the most common colorectal polyps. Metabolic syndrome components such as obesity and hyperlipidemia are considered the most common etiological factors for HPs as well contributing to the pathogenesis of fatty liver disease.

Objectives: To determine the possible association between biopsy-proven steatohepatitis and hyperplastic colonic polyps.

Methods: This retrospective cohort observational study conducted at the Holy Family Hospital in Nazareth, Israel, included subjects who underwent screening colonoscopy over a 2 year period. Data were extracted from the patient charts and included demographics, anthropometric measurements, vital signs, underlying diseases, medical therapy, laboratory data, and results of the liver biopsy. The colonoscopy report and pathological report of each extracted polyp were also evaluated.

Results: A total of 223 patients were included in the study: 123 patients with biopsy-proven non-alcoholic steatohepatitis (NASH) and 100 patients without NASH who served as the control. Fourteen colonic adenomas (11% of patients) were found in the NASH group vs. 16 (16%) in the control group (P = 0.9); 28 HPs were found in the NASH group (22.7%) vs. 8 in the control group (8%) (P < 0.05). The multivariate analysis, after adjusting for gender, age, C-reactive protein and smoking, showed that the presence of NASH (OR 1.69, 95%CI 1.36–1.98, P < 0.01) was associated with increased risk for HP.

Conclusions: Our study found an association between biopsy-proven steatohepatitis and the burden of hyperplastic polyp.

KEY WORDS: hyperplastic polyp (HP), fatty liver, metabolic syndrome, non-alcoholic steatohepatitis (NASH)

Patients and Methods

Despite being the most common type of polyp detected in the human colon and rectum, relatively little is known about the etiology and natural history of hyperplastic polyps (HPs) [1,2]. HPs are considered benign lesions that have little or no malignant potential. However, recent studies have suggested that HP may lie in the classic adenoma-carcinoma pathway [3,4]. Unhealthy lifestyle and diet are the most common risk factors for the development of HP according to epidemiological studies; other risk factors include alcohol consumption, cigarette smoking, obesity, and high fiber intake [5].

Non-alcoholic fatty liver disease (NAFLD) is an emerging condition and constitutes an important public health problem across the globe. Fatty liver disease can present as simple hepatic steatosis that may progress to non-alcoholic steatohepatitis (NASH), fibrosis, cirrhosis, and hepatocellular carcinoma (HCC) [8].

NAFLD is the most common cause of incidental elevated liver enzymes in the developed world. The prevalence of NASH in Europe and the United States ranges from 14% to 20%; this increase in prevalence is related directly to the epidemic of obesity seen in these populations [7].

Diabetes mellitus (DM), obesity and hyperlipidemia are common components of the metabolic syndrome, which is frequently associated with NAFLD. Therefore, NAFLD is the hepatic manifestation of metabolic syndrome [8]. The pathogenesis of NAFLD is not clearly elucidated, but accumulating data suggest that insulin resistance (IR), oxidative stress, lipotoxicity, intestinal endotoxins and bacterial translocation – all related to the metabolic syndrome – play a crucial role in the pathogenesis of steatosis, steatohepatitis and fibrosis [9]. Moreover, metabolic syndrome, which is associated with NASH, was also reported to be associated with several malignancies as well as benign and malignant gastrointestinal tract lesions [10]. Against this background, we conducted a retrospective study to assess whether a relationship of HP to NAFLD could be determined.

We conducted a retrospective cohort observational study in the Division of Internal Medicine at the Holy Family Hospital, Nazareth, Israel, of adult patients with biopsy-proven NASH who were sent for screening colonoscopy between April 2013 and April 2015.
Patients were included only if they had undergone a screening colonoscopy at our facility within the previous 2 years and a liver biopsy in the past 5 years. The control group consisted of non-NASH patients matched for age and gender who had undergone screening colonoscopy within the previous 2 years. Exclusion criteria included NASH patients without biopsy performed to confirm the diagnosis, patients with other liver disease, patients with known colonic disease including inflammatory bowel disease and polyposis syndrome, patients with a history of total or segmental colectomy, or a family or personal history of colonic cancer or colonic polyps.

Data were obtained from the medical charts of all enrolled patients and from the family physician in the case of missing data. The following information was extracted from the patients’ charts: demographics, anthropometric measurements, vital signs, underlying diseases, medical treatments, laboratory data, results of the liver biopsy, the colonoscopy report, and the pathological report on the extracted polyp.

Body mass index (BMI) for all patients was calculated as kg/m². A single expert hepatopathologist reviewed all liver biopsies and utilized the scoring system established by Brunt and colleagues [11].

Every patient underwent colonoscopy after completing bowel preparation with 4 L polyethylene glycol lavage solution. Colonoscopies were performed by one of the gastroenterologists at Holy Family Hospital. Each colonoscopy report was examined for the present of polyps, polyp location, polyp size, number of polyps, and histology; the location of the polyp was classified as cecum, ascending, hepatic flexure, transverse, splenic flexure, descending, sigmoid, or rectal.

The study was approved by the local ethics committee. The data were coded to keep patient anonymity. Informed consent was waived because of the non-interventional design of the study.

**STATISTICAL ANALYSIS**

Data were analyzed using SPSS version 19 (IBM SPSS, Chicago, IL, USA). Continuous variables are expressed as the mean ± standard deviation. The chi-square test was used to test differences in categorical variables between the cases and controls, and analysis of variance (ANOVA) or the Student’s t-test was used for comparisons of continuous variables. Spearman’s rank correlation and univariate regression analysis were used to determine the strength of the relationship between NAFLD and hyperplastic polyps after adjusting for independent variables previously known to be associated with HP, namely age, gender, BMI, current smoking, and C-reactive protein (CRP). A multiple logistic regression analysis was done to determine the association between the different risk factors for HP. A significance level of P < 0.05 was used in this test.

### RESULTS

A total of 223 patients who underwent screening colonoscopy comprised the study population: 123 patients with biopsy-proven NASH and 100 patients without NASH who served as the control group. Table 1 summarizes the clinical features of the two groups: those with and without NASH. In the NASH group 72 patients (86%) were males; the mean age was 41 ± 13 years, the mean body mass index was 25.3 ± 4.7, and the mean serum CRP level was 1.1 ± 0.7.

Regarding the prevalence of polyps, 14 adenomas were found in the NASH group (11% of patients) versus 16 in the control group (16% of patients) (P = 0.9). The location, size, number, morphology, and degree of dysplasia of the adenomas were similar between the two groups. The prevalence of HP was statistically significantly higher in the NASH group: 28 HPs (22.7%) versus 8 in the control group (8%) (P < 0.05). The size and morphology of the polyps were similar but the location differed between the groups: all HPs in the NASH group were located in the left colon, and 2 of 8 HPs in the control group were located in the right colon (25%).

The multivariate analysis is shown in Table 2. From the logistic regression analysis, older age (> 50 years), male gender, current smoking, high CRP levels, and the presence of NASH were associated with increased risk for HP [Table 2].

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender</td>
<td>1.80 (1.02–1.66)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Age &gt; 50</td>
<td>2.24 (1.91–2.13)</td>
<td>0.003</td>
</tr>
<tr>
<td>CRP &gt; 2 mg/L</td>
<td>1.47 (1.14–2.18)</td>
<td>0.027</td>
</tr>
<tr>
<td>Current smoking</td>
<td>1.35 (1.05–1.67)</td>
<td>0.022</td>
</tr>
<tr>
<td>Presence of NASH</td>
<td>1.69 (1.36–1.99)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
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OR = odds ratio, CI = confidence interval, CRP = C-reactive protein, NASH = non-alcoholic steatohepatitis
DISCUSSION

To the best of our knowledge this is the first study to evaluate the relationship between biopsy-proven steatohepatitis and colonic hyperplastic polyps. The findings demonstrate that NASH was significantly associated with an increased frequency of colonic hyperplastic polyps. Previous studies reported an association between metabolic syndrome and colorectal cancer and/or colorectal adenomatous polyps [12,13]. Moreover, a large population-based study from Korea comparing the relationship between ultrasound-diagnosed NAFLD and colorectal adenomas found a direct association with NAFLD and colorectal adenomas [14]. Another study from the USA found a similar association between biopsy-confirmed NAFLD and the prevalence of colonic adenomas [15]. Currently, patients with more than three colonic adenomas or any adenoma > 10 mm are subject to colonoscopic screening every 3 years [16]. Thus, patients with NAFLD may require more stringent endoscopic follow-up, and the previously presented data may have implications for future screening guidelines. However, despite being the most common type of polyp detected by colonoscopy, relatively little is known of the etiology, natural history, associations or growth of HPs.

Our study demonstrated an interesting association between the prevalence of HPs and biopsy-proven NASH. NASH/NAFLD is commonly referred to as the hepatic manifestation of metabolic syndrome; patients with metabolic syndrome have been shown to be at higher risk for colorectal HPs, as illustrated by several studies [17,18]. The mechanism that joins the two entities is most likely linked to insulin resistance, and the mechanism that leads to metabolic syndrome also plays a distinct role in the development of HPs [19,20].

Adiponectin is an adipokine found in decreased concentrations in individuals who are obese, or who have NASH or diabetes. Decreased adiponectin leads to increased insulin levels due to IR and increased insulin growth factor-1 (IGF-1) [21,22]. Adiponectin also directly inhibits tumor necrosis factor-alpha (TNFα), which plays a role in tumor cell proliferation and angiogenesis. Recent studies have shown that HPs may lie in the classic adenoma-carcinoma sequence and have demonstrated special molecular changes and genetic mutations that correlated with hyperplastic polyps and/or serrated colonic polyps representing mixed features of colonic adenomas and HPs [23-25].

Low adiponectin levels are inversely related to colonic tumor stage and predict cancer recurrence [21,24]. Insulin binds to IGF-1 receptors and plays an important role in cell proliferation, apoptosis and increased production of vascular endothelial growth factor, an angiogenic factor that supports tumor growth and may play role in the development and growth of HPs [25].

Plasma inflammatory biomarkers in NASH patients are increasing leading to a chronic and systemic low grade inflammatory state. Some of the mediators from the liver, including reactive oxygen species (ROS), TNFa, IL-6, PAI-1, and other pro-inflammatory cytokines were positively associated with the prevalence of colon rectal cancer, colorectal adenomas and most probably HPs [23-25]. According to our findings it seems that NASH increases the frequency of HPs due to the involvement of all the previously suggested factors.

Our study had several limitations. The retrospective design of the study makes it difficult to infer causality between NASH and risk for HPs. Second, there may have been a selection bias as the study subjects were recruited from patients who visit the hospital for a health examination and thus were more concerned about their health status. Third, the population size was too small to accurately reflect some risk factors known to be associated with HP such as ethnicity and family history.

In conclusion, we believe this study is the first to show an association between biopsy-proven steatohepatitis and the burden of hyperplastic polyp. Further prospective studies are required to confirm the hypothesis that NASH may cause colorectal hyperplastic polyp and may play a crucial role in its growth and natural history. Further studies are needed to assess whether the severity of hepatic injury or other factors could be involved in the natural history of HPs.

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Lehmann and team examined these cells in tumors growing between the thymic epithelial areas and circulation and may promote tumors. These cells inhabit the thymic perivascular space and thymus produce antibodies that are reactive to common viral proteins. These cells may help fine-tune therapeutic strategies to target only cells that promote tumors.

Tumor-associated macrophages (TAMs) and neutrophils (TANs), which have been implicated in both promoting and inhibiting tumor growth, express abundant Fcγ receptors. Lehmann and team examined these cells in tumors growing in different sites (skin and lung). The organ environment determined which TAM and TAN subpopulations contributed to antibody-dependent tumor immunotherapy. These data may help fine-tune therapeutic strategies to target only cells that promote tumors.

Robotic sleeve uses compressed air to power artificial silicone muscles that compress and twist, mimicking the movements of the normal human heart. The device increased cardiac ejection volume in vitro and when implanted in adult pigs during drug-induced cardiac arrest.

In-house thymus protection squad

Circulating antibodies from bone marrow-resident plasma cells help to protect the thymus from infection. Nuñez and fellow-workers found that plasma cells that reside in the human thymus produce antibodies that are reactive to common viral proteins. These cells inhabit the thymic perivascular space between the thymic epithelial areas and circulation and may fortify the thymus against pathogen invasion. The plasma cells are maintained in aging individuals, presumably contributing to lifelong thymic protection.