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The Risk of Colorectal Adenomas in Patients with Nonalcoholic Fatty Liver Disease (Nafld). A Case-Control, Prospective Study

KEYWORDS: colorectal adenomas, nonalcoholic fatty liver disease, nonalcoholic steatohepatitis, chromoendoscopy

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ABSTRACT *Few studies have evaluated the prevalence of colonic adenomas and carcinomas on patients with NAFLD. We included in the study 100 patients with or without NAFLD who underwent panchromoendoscopy. NAFLD with or without nonalcoholic steatohepatitis (NASH) was diagnosed by liver biopsy or by abdominal ultrasounds followed by laboratory tests to eliminate the other causes of steatosis. We detected 12 colonic advanced neoplasms and 52 adenomas. No difference in the detection rate of adenomas (32% vs. 22%; p=0.260), but there was difference in the prevalence of advanced colonic neoplasms (20% vs. 4%; p<0.014) between groups. Multivariate regression analysis demonstrated an independent risk of colorectal adenomas with NASH after adjustment, according to demographic and metabolic factors (OR= 9.52; p=0.010). The prevalence of adenomas and carcinomas is higher in patients with NAFLD than non-NAFLD patients. NASH is an independent factor that is associated with the presence of colorectal adenomas.*

INTRODUCTION

Colorectal carcinoma (CRC) is a serious health issue [1]. The early detection of colonic adenomas through colonoscopy has led to a lower mortality rate in left colorectal cancers, but not in right colorectal cancers [1,2]. The panchromoendoscopy with specific dyes improves the detection rate of colonic adenomas, especially the plane ones or those of the right colon.[2] Hyperinsulinemia and insulin resistance are two factors involved in the pathogenesis of colorectal cancer. Numerous studies have proven that obesity and diabetes mellitus are two diseases which are more frequently associated with colorectal adenomas and carcinomas [3,4,5]. The non-alcoholic fatty liver is associated with liver insulin resistance.

The association of colorectal adenomas and carcinomas with nonalcoholic fatty liver is currently being assessed. The most recent data shows that patients with fatty liver have a higher risk of colonic adenomas and carcinomas, especially on the right colon, than those without liver steatosis [6,7,8].

In this study we aimed at assessing the detection rate of colorectal adenomas and advanced neoplasms evaluated through chromoendoscopy, in patients with NAFLD compared to patients without NAFLD. Also, our objective was to evaluate if NAFLD is independent risk factor for colorectal adenomas or advanced neoplasms and this risk is not depending on the values of BMI (body mass index), basal glucose or triglycerides. Theoretically, carrying out a panchromoendoscopy in these patients we tried to detect more adenomas even small ones, especially on right colon.

MATERIALS AND METHODES

The study is a case-control, prospective study. The protocol of the study was approved by the Ethical Committee of the University of Medicine and Pharmacy "Iuliu Hatieganu" from Cluj-Napoca in December 2011.

Patients

Study participants were prospectively recruited from subjects who were planned to undergoing a colonoscopy for different symptoms (not screening, because in Romania screening program for colorectal cancer does not exist) at the 4th Medical Clinic Cluj-Napoca, from January 2012 to April 2013).

All patients aged between 35 and 75 years, which are included in the study, agreed with the study data and signed the informed consent. We have screened 230 consecutive patients.

An abdominal ultrasounds, medical history and laboratory tests were performed before colonoscopy.

Information on medical history, current use of medications, daily alcohol consumption was obtained from all participants using a standard questionnaire. Patients with alcohol intake over 20g/day, infectious hepatitis, acute or chronic liver disease, hereditary liver disease and immunological liver damage, family and personal history of colorectal adenoma or carcinomas, patients with inflammatory bowel disease were excluded from the study.

Were excluded from study 111 patients (43 patients intake over 25 g/day of alcohol, 2 were diagnosed with chronic hepatitis B, 5 with chronic hepatitis C, 2 patients with autoimmune hepatitis, 3 with hemocromatosis, 32 patients had personal history of adenomatous polyps, 8 patients had personal history of colorectal cancer and 16 were previously diagnosed with inflammatory bowel disease).

For the first group (NAFLD group) we enrolled either patients with steatosis on abdominal ultrasounds, negative medical history of liver disease or drug induced-hepatitis, negative

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blood tests for other causes of steatosis or patients with hepatic liver biopsy consisted of NAFLD with or without different staging of NASH.

Liver biopsy was proposed in patients with steatosis on abdominal ultrasounds, negative medical history of liver disease or drug induced-hepatitis, negative blood tests for other causes of steatosis but with abnormal liver biochemistry (abnormal level of aminotransferases). Sixteen patients were agreed with liver biopsy and 2 rejected the procedure. At the end, only 50 patients were included in NAFLD group (34 without liver biopsy and 16 patients with liver biopsy).

The second group (control group) consisted of patients without steatosis on abdominal ultrasounds and who was planned for a colonoscopy for different reasons and who agreed with our methodology of study. For statistically reason we limited this group at 50 consecutive patients, so we excluded the last consecutive 17 patients without steatosis on abdominal ultrasonpgraphy.

In all patients (case and control) demographic data (name, age, environmental status) and anthropometric measurements (weight, BMI, waist circumference) were recorded, blood pressure was measured, biochemical analysis were performed, as well as abdominal ultrasounds and panchromoendoscopy.

In patients with colorectal polyps and tumors on colonoscopy, a histological exam was made.

The body mass index (BMI) for all patients was calculated in kg/m². Increased waist circumference was defined as waist greater than 94 cm in men and greater than 80 in women. The blood pressure was measured in all patients. Patients with antihypertensive drugs and blood pression over than ≥140 mmcolHg and /or ≥90mmcolHg at consecutive two measurements were diagnosed with hypertension.

Also, the presence of components of metabolic syndrome such as: increased waist circumference, high blood pressure, type 2 diabetes mellitus/glucose intolerance, hypertriglyceridemia, low HDL-cholesterol were recorded in all patients included in the study.

The metabolic syndrome was diagnosed when there 3 criteria from 5 have met: increased waist circumference, high blood pressure, type 2 diabetes mellitus/glucose intolerance, hypertriglyceridemia or low HDL-cholesterol.

Abdominal ultrasound
Hepatic abdominal ultrasound was carried out for all screen patients, by one of five sonographers with more than 5 years experience. The hepatic abdominal ultrasounds were done before colonoscopy, in order to detect the presence of liver steatosis. This is defined by the presence of increased echogenicity of the liver accompanied by deep beam attenuation with impaired diaphragm visualization, contrast liver to kidney, bright vessels walls and impaired gallbladder walls visualization [9].

Laboratory exams
Fasting blood was taken from all category of patients for the following analysis: total blood count cell, transaminases, alkaline phosphatase, gamma glutamyl transferase, total bilirubin, serum electrophoresis, glucose, glucose tolerance test, HDL-cholesterol, LDL-cholesterol, triglycerides, Surface Hepatitis B Antigen, Hepatitis C Virus Antibodies, Antinuclear antibodies , Mitochondrial Antibodies, Liver Kidney Microsomal type 1 Antibodies, Soluble Liver Antigen , blood iron levels, ferritin, transferrin saturation coefficient, ceruloplasmin levels.

Ultrasound-guided liver biopsy
Using an ultrasonograph Aloka 7 (Hitachi Aloka Medical, Ltd.), an ultrasound-guided liver biopsy was made in patients with liver steatosis on abdominal ultrasounds and abnormal liver biochemistry who were included in study and were agree and signed an standard inform consent for liver biopsy (from 18 patients, 2 of patients were not agreed with liver biopsy and were excluded). An interventional ultrasonographist with more than 10 years experience made all liver biopsies. A single pass ultrasound-guided liver biopsy was made in each patient, after a local anesthesia with 10 ml of Lidocain sol. 2%. The liver biopsies were performed with a Bard Tru-Cut biopsy needle of 22 Ga in diameter. A tissue fragment larger than 5 mm was considered sufficient for histological exam. If the material was insufficient a second pass was made.

Colonoscopy-panchromoendoscopy
Following bowel preparation with 4 L polyethylene glycol lavage solution, all patients underwent total colonoscopy under sedation. Total chromoendoscopy with 0.4% indigo carmine dye was carried out only by one endoscopist with experience in chromoendoscopy. In the patient study chart the number of polypoid or non-polypoid colonic polyps, the size, location and type of endoscopic resection were recorded.

Histopathology exam
All liver specimens from liver biopsy were sent to histopathology exam. According to American Association for the Study of Liver Diseases, American College of Gastroenterology, and the American Gastroenterological Association Guideline, NAFL was defined as the presence of hepatic steatosis with no evidence of hepatocellular injury in the form of ballooning of the hepatocytes. NASH was defined as the presence of hepatic steatosis and inflammation with hepatocyte injury (ballooning) with or without fibrosis [10].

All biopsied or removed lesions from colonoscopy were sent to histopathology exam, to assess polyp or tumor histology. Non-adenomatous polyps were excluded from the study. Adenomatous polyps were evaluated according to histological type, presence of dysplasia, grade of dysplasia and presence of carcinoma. Advanced colorectal neoplasm was defined as cancer or adenomas with villous architecture or high grade dysplasia or adenoma larger than 10mm in diameter. Invasive colorectal cancer was defined by the presence of tumor cells in the submucosa.

Statistical analysis
The statistical analysis was performed with the IBM SPSS program version 19 (trial version). The statistical results are presented as the mean ±standard deviation or percentages. Statistical analyses included one-way analysis of variance (ANOVA), Student's t-test, Pearson Chi Square (Hi²), Fisher test, robust test of Brown-Forsythe and post-test analysis-Tukey HSD. The relationship of NAFLD with the presence of adenomatous polyps was assessed by multiple logistic regression analysis after adjustment for independent variables, including age, sex, BMI, waist circumference, diabetes and NASH. Each odds ratio (OR) is presented together with its 95% confidence interval (CI), $p<0.05$ was considered statistically significant.

RESULTS
From 230 patients who were screened, we excluded 113 patients from the study because they had one or more exclusion criteria. Furthermore, we limited at 50, patients in the control group for statistically reasons, so we also excluded the consecutive last 17 patients from control group. Finally, out of 100 patients were included in the study, 50 were with NAFLD and 50 were without NAFLD. Out of 50 patients, 34 patients were diagnosed with NAFLD based positive abdominal ultrasound for steatosis, negative history for alcohol intake, hereditary, chronic or drug-induced hepatitis and negative serological tests (infectious, alcoholic, immunological, and hereditary). In sixteen patients (steatosis on abdominal ultrasonography and abnormal liver

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biochemistry), the NAFLD was proven through liver biopsy (all patients were diagnosed with different grading of NASH).

Median age was 59,14 ±8,5 years in NAFLD group and 58,26 ±13,2 years in controls with no statistically difference. The women were predominant (31/50, 62%) then men (19/50, 38%) in both groups. Baseline characteristics, anthropometric measurements, clinical and biochemical data of the participants in this study can be seen in table nr.1.

Table 1, about baseline characteristics, anthropometric measurements, clinical and biochemical data of the study participants with NAFLD and control patients

Variables	NAFLD group N=50	Control group N=50	p-value
Age (years)	59,14 ±8,5	58,26 ±13,2	p>1,000
F M	31 (62%) 19 (38%)	31 (62%) 19(38%)	p>1,000
UA RA	30 (60%) 20(40%)	32 (64%) 18 (36%)	p>1,000
BMI (kg/m²)	32,17 ±5,4	25,42 ±4,5	p<0,001
IC	43 (86%)	7 (14%)	p<0,001
Hyper-Trigly	24 (48%)	26 (52%)	p>1,000
Low HDL-Chol	32 (64%)	18 (36%)	p>1,000
HTA	30 (60%)	20 (40%)	p>1,000
DM	13 (26%)	37 (74%)	p>1,000
MS	32 (64%)	16 (32%)	p>1,000

F, females; M, men; UA, urban aria; RA, rural aria; BMI, body mass index; IC- increased circumference; Hyper-Trigly, high level of triglycerides; HDL-Chol, lipoprotein with high density; HTA, arterial hypertension; DM, diabetes mellitus; MS, metabolic syndrome

Compared with control group, those with NAFLD had a significantly higher BMI (p<0.001) and higher waist circumference (p<0.001).

Out of the 100 patients included in the study, 27 had adenomatous polyps (27%) on colonoscopy. Out of these, 16 were in the NAFLD group and 11 were in the control group. The prevalence of adenomas was 32% (16/50) in the NAFLD group and 22% (11/50) in the control group. The p value between the two groups was not statistically significant (Hi² test X2=1.268, df=1, p=0.260>0.05). The total number of adenomatous polyps was 33 in the NAFLD group and 19 in the control group, with no statistical difference (p=0.197) (table nr. 2).

Table 2, about prevalence of colorectal adenomas and advanced neoplasms in patients with or without NAFLD

Endoscopic Findings	NAFLD N=50	Control N=50	p-value
Adenomas (no. pts.)	16	11	
Adenomas (prevalence)	32%	22%	p=0,260
Adenomas (total no).	33	19	p=0,197
Advanced neoplasm (no. pts.)	10	2	
Advanced neoplasm (prevalence)	20%	4%	p=0,014

No.pts., number of patients; total no., total number

Adenoma distribution can be seen in table nr. 3.

Table 3, about adenoma distribution in both groups.

	NAFLD	Control	p-value
Adenomas (total no.)	33	19	p=0,197
Proximal Adenomas	4 (12,1%)	9 (47,3%)	p=1,000
Distal Adenomas	29 (87,8%)	10 (52,6%)	p=1,000

We detected 29 adenoams on distal colon in NAFLD group and only 4 adenomas on proximal colon with no differences between groups. However, when the total number of polyps were counted (hyperplasic polyps included) a statistical difference between groups was detected (p=0.024). Patients with NAFLD had statistically more polyps (adenomas and hyperplasic) than controls.

In the NAFLD group, the risk of colorectal adenomas had statistically significant correlation with the presence of NASH (p=0.044, OR=3.48 (95% IC: 1.007-12.057), higher waist circumference ((p=0.027) and obesity (p=0.041). Multivariate regression analysis showed an independent association of colorectal adenomas only with NASH after adjustment for age, gender, body mass index, glucose intolerance and waist circumference (OR=9.52 (95%IC: 1.71-52.85; p=0.010).

Out of 100 patients included in the study, 12 had advanced colorectal neoplasms (12%). Out of these, 10 were in the NAFLD group and only two in the control group. The prevalence of advanced colorectal neoplasm was 20% in the NAFLD group and 4% in the control group. The p value was statistically significant between groups (Hi² test X2=6.601, df=1, p=0.014>0.05; OR=6,000 (95%IC: 1.24-28.98) (table nr.2).

In the NAFLD group, the risk of colorectal advanced neoplasms had no statistically significant correlation with the presence of NASH (p=1.00) . A multivariate regression analyses could not been done because of the small numbers of advanced neoplasms.

DISSCUTIONS

The definition of NAFLD requires that there is evidence of hepatic steatosis, either by imaging or by histology and there are no causes for secondary hepatic fat accumulation such as significant alcohol consumption, use of steatogenic medication or hereditary disorders, etc. [10].

In the majority of patients, NAFLD is associated with metabolic risk factors such as obesity, diabetes mellitus, and dyslipidemia. NAFLD is histologically further categorized into nonalcoholic fatty liver (NAFL) and nonalcoholic steatohepatitis (NASH) [10].

The association of liver steatosis and the high risk of colorectal adenomas and colorectal cancer is still under assessment. The exact mechanism is yet unknown, but probably insulin resistance, with or without hyperinsulinemia, and systemic inflammation are involved.

The present study is the first prospective case-control study, which comprised 50 patients with NAFLD (in 16 patients proven by liver biopsy) and 50 patients without NAFLD, in which panchromoendoscopy was carried out in order to detect more colorectal adenomas and carcinomas. We detected a 32% prevalence of adenomas in NAFLD vs. 22% in the control group (p=0.260) and a 20% prevalence of advanced neoplasms in the NAFLD group vs. 4% in the control group (p<0.014). Our findings are in agreement with previous studies. Recent investigations have demonstrated that NAFLD is an independent risk factor for colorectal adenomas and

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carcinomas [6,7,8]. In a study on 1211 colonoscopies, Stadlmayr et al observed that the risk of colorectal adenomas in patients with NAFLD is 1.47 higher, after adjustment for age, gender, BMI and impaired fasting glucose [8]. A positive association between the presence of NAFLD and colorectal adenomas was observed by Hwang et al. They evaluated the presence of colorectal adenomas in 2917 patients with or without NAFLD. Following a continuous logical statistical regression analysis, the authors found a 1.28 risk of developing colonic adenomas in patients with NAFLD [6]. But some authors failed to demonstrate an increased incidence of colorectal adenomas in patients with biopsy-proven NAFLD compared with those without NAFLD [11].

In our study, in the NAFLD group, patients with NASH had a higher prevalence of adenomas (p=0.044, OR 3. 48). After adjustment according to demographic and metabolic factors, NASH remained associated with adenomas (adjusted OR 9. 52). Wong et al showed similar results in a cross-sectional study. After adjustment according to demographic and metabolic factors, NASH remained associated with adenomas (adjusted OR 4. 89 (95%CI: 2.04-11.70; p=0.005) and advanced neoplasms (OR 5.34; 95% CI: 1.92-14.84). Just like in our investigation, in the study conducted by Wong et al, those with only liver steatosis had a similar risk of developing adenomas or advanced adenomas with that of the healthy population [7].

In the NAFLD group the left distribution of adenomas and advanced neoplasms was predominant, but without significant differences between groups. This is not in concordance with the literature, where an increased incident of right lesions was detected in patients with NAFLD [6,7]. We selected the chromoendoscopy, a priori, for a better detection of right colonic lesions. Panchromocolonoscopy failed to demonstrate a detection of more numbers of proximal adenomas than distal adenomas in NAFLD patients. However, in our regional area, an increased incidence and prevalence of left colorectal adenomas and carcinomas was previously reported [12].

The rank of adenomas was no different in NAFLD vs. the control groups, like in previous studies [6,11]. Anecdotally, we found a more significant burden of polyps in NAFLD than in the control group.

Our study had several limitations. The population was too small to accurately reflect the true association of adenomas and advanced neoplasms with NAFLD. Secondly, the small number of advanced neoplasms has made a multivariate regression analysis in this group rather difficult.

CONCLUSIONS

Patients with NAFLD have an high risk to develop advanced colorectal carcinomas than controls. In patients with NASH, the risk of colorectal adenomas is statistically and significantly higher than in patients with simple steatosis, after the adjustment according to demographic and metabolic factors. For an early colorectal cancer screening, we can select a group of high risk subjects.

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REFERENCE [1](American Cancer Society, Cancer facts and figures, 2009, Atlanta: American Cancer Society, 2009). | [2]Lau, P.C.& Sung, J.J. (2010). Flat adenoma in colon: two decades of debate. Journal of Digestive Diseases, 11(4), 201-7. | [3] Kang, H.W., Kim, D., Kim, H.J., Kim, C.H., Kim, Y.S., Park, M.J., Kim, J.S. et al (2010).Visceral obesity and insulin resistance as risk factors for colorectal adenoma: a cross-sectional, case-control study. American Journal of Gastroenterology, 105(1), 178-87. | [4]Yang, Y.X., Habel, L.A., Capra, A.M., Achacoso, N.S., Quesenberry, C.P. Jr, Ferrara, A., Levin, T.R. et al (2010). Serial glycosylated hemoglobin levels and risk of colorectal neoplasia among patients with type 2 diabetes mellitus. Cancer, 19(12), 3027-36. | [5]Burke, C.A. (2010). Colonic complications of obesity. Gastroenterology Clinical North American, 39(1), 47-55. | [6]Hwang, S.T., Cho, Y.K., Park, J.H., Kim, H.J., Park, D.I., Sohn, C.I., Jeon, W.K. et al (2010). Relationship of non-alcoholic fatty liver disease to colorectal adenomatous polyps. Journal of Gastroenterology and Hepatology, 25(3), 562-7. | [7]Wong, V.W., Wong, G.L., Tsang, S.W., Fan, T., Chu, W.C., Woo, J., Chan, A.W. et al (2011). High prevalence of colorectal neoplasm in patients with non-alcoholic steatohepatitis. Gut, 60(6), 829-36. | [8]Stadlmayr, A., Aigner, E., Steger, B., Scharinger, L., Lederer, D., Mayr, A., Strasser, M. et al.(2011). Nonalcoholic fatty liver disease: an independent risk factor for colorectal neoplasia. Journal of Internal Medicine, 270(1):41-9. | [9]Hamaguchi, M., Kojima, T., Itoh, Y. Harano, Y., Fujii, K., Nakajima, T., et al (2007). The severity of ultrasonographic findings in nonalcoholic fatty liver disease reflects the metabolic syndrome and visceral fat accumulation. American Journal of Gastroenterology, 102(12):2708-15. | | [10]Chalasani, N., Younossi, Z., Lavine, J.E., Diehl, A.M., Brunt, E.M., Cusi, K., | (2010). The Diagnosis and Management of Non-Alcoholic Fatty Liver Disease: Practice Guideline by the American Association for the Study of Liver Diseases, American College of Gastroenterology, and the American Gastroenterological Association. Hepatology, 55(6): 2005-2023). | | [11] Touzin, N.T., Bush, K.N.V., Williams, C.D., Harrison, S.A. (2011). Prevalence of colonic adenomas in patients with nonalcoholic fatty liver disease. Therapeutic Advanced Gastroenterology, 4(3):169-76. | [12] Tantau, A. & Tantau, M. (2012). Prevalence, proportion, clinic-morphological features and endoscopic diagnosis of superficial colorectal lesions. In A. Tantau & M. Tantau (Eds), The endoscopic diagnosis and treatment of early gastrointestinal neoplasia, (p68-82). Cluj Napoca, University of Medicine and Pharmacy "Iuliu Hatieganu".