

### Hemochromatosis and Hepatic Malignancy

The predominant cause of hereditary hemochromatosis is HFE p.C282Y homozygous pathogenic variant. Liver carcinoma and mortality risks are increased in individuals with clinically diagnosed hereditary hemochromatosis, but risks are unclear in mostly diagnosed HFE p.C282Y homozygous-identified community genotyping.

To estimate the incidence of primary hepatic carcinoma and death by HFE variant status, a cohort study of 451,186 UK Biobank participants of European ancestry aged 40 to 70 years old, followed up from baseline assessment (2006-2010), until January 2018 was carried out.

Men and women with HFE p.C282Y and p.H63D genotypes was compared with those with neither HFE variants. Two linked co-primary outcomes (incident primary liver carcinoma and death from any cause), were ascertained from followup by way of inpatient hospital records, national cancer registry, and death certificate records, and from primary care data among a subset of participants for whom data was available. Associations between genotype and outcomes were tested using Cox regression adjusted for age, assessment center, genotyping array, and population genetic substructure.

Kaplan-Meier lifetable probabilities of incident diagnoses were estimated from age 40 to 75 years by HFE genotype and sex. A total of 451,186 participants had a mean age of 56.8 years; 54.3% women, and were followed up for a median of 8.9 years. Among the 1294 male p.C282Y homozygotes, there were 21 incident hepatic malignancies, 10 of which were in participants without a diagnosis of hemochromatosis in baseline and pC2827 homozygous men had a higher risk of hepatic malignancies (HR 10.5), and all cause of mortality (N = 88; HR 1.2) compared with men with neither HFE variant.

In lifetable projections for male p.C282Y homozygotes to 75 years, the risk of primary hepatic malignancy was 7.2% compared with 0.6% for men with neither variant and the risk of death was 19.5%, compared with 15.1% among

men with neither variant.

Among female p.C282Y homozygotes (N = 1596), there were 3 incident hepatic malignancies and 60 deaths, but the associations between homozygosity and hepatic malignancy and death were not statistically significant (HR 2.1 and 1.2, respectively).

It is concluded that among men with HFE p.C282Y homozygosity, there was a significant increased risk of incident primary hepatic malignancy and death. Compared with men without p.C282Y or p.H63D variant, there was not a significant association for women. The effects of early diagnosis and treatment require further research.

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Atkins, J., Pilling, L., Masoli, J., et al. "Association of Hemochromatosis HFE pC282Y Homozygosity With Hepatic Malignancy." JAMA 2020; Vol. 324, pp. 20, 2048-2057.

### Response to Bariatric Surgery in Non-Alcoholic Steatohepatitis

To determine the long-term effects of bariatric surgery for patients with non-alcoholic steatohepatitis (NASH), sequential liver samples were evaluated that were collected at the time of bariatric surgery and 1 and 5 years later to assess the long-term effects of that surgery in patients with NASH.

A prospective study of 180 severely obese patients with biopsy-proven NASH defined by the NASH clinical research network histologic scores was performed. Patients underwent bariatric surgery at a single center in France and were followed for 5 years. Liver samples were obtained from 125 of 169 patients (76%), having reached 1 year in 64 of 94 patients (68%), having reached 5 years after surgery. The primary endpoint was resolution of NASH without worsening of fibrosis at 5 years. Secondary endpoints were improvement in fibrosis (reduction of 1 or greater stage at 5 years and regression of fibrosis and NASH at 1 and 5 years).

At 5 years after bariatric surgery, NASH

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was resolved without worsening fibrosis in samples from 84% of patients (N=64). Fibrosis decreased compared with baselines, in samples from 70.2% of patients. Fibrosis disappeared from samples from 56% of all patients and from samples from 45.5% of patients with baseline bridging fibrosis. Persistence of NASH was associated with no decrease in fibrosis unless weight loss (reduction in BMI of 6.3 kg/m<sup>2</sup> in patients with persistent NASH vs. reduction of 13.4 kg/m<sup>2</sup> with resolution of NASH). Resolution of NASH was observed at 1 year after bariatric surgery in biopsies from 84% of patients with no significant recurrence between 1 and 5 years. Fibrosis began to decrease from year 1 after surgery and continued to decrease until 5 years.

It was concluded in a long-term followup study of patients with NASH who underwent bariatric surgery, observation revealed resolution of NASH in liver samples from 84% of patients 5 years later. The reduction of fibrosis is progressive, beginning the first year and continuing through 5 years.

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Lassailly, G., Caiazzo, R., Ntandja-Wandji, L. et al. "Bariatric Surgery Provides Long-Term Resolution of Nonalcoholic Steatohepatitis and Regression of Fibrosis." *Gastroenterology* 2020; Vol. 159, pp. 1290-1301.

### **Minimally Invasive Endoscopic Management of Gastroesophageal Reflux**

Endoscopic management of gastroesophageal reflux disease (GERD) is being employed increasingly. A scoping review was published, assessing the volume of available evidence on the benefits of endoscopic and minimally invasive surgical therapies for GERD.

Criteria were used to perform an extensive literature search of data regarding the reported benefits of endoscopic therapies and GERD randomized control studies were utilized when available. However, data from observed observational studies were also reviewed.

A formal review of evidence was performed in 22 studies. Inclusion and exclusion criteria and study duration were noted and tabulated. Assessment of outcomes was based on symptoms and objective criteria reported by investigators reported outcomes for the interventions tabulated under the heading of subjective (symptom scores), quality of life metrics, and change in proton pump inhibitor use, objective metrics (pH parameters, endoscopic signs and lower esophageal sphincter pressure changes).

Adverse events were noted and tabulated. The majority of studies showed symptomatic and objective improvement of GERD with device therapies. Adverse events were minimal. However, normalization of acid exposure occurred in about 50% of patients and for some modalities, long-term durability is uncertain.

It was concluded that this scoping review revealed that the endoluminal and minimally-invasive surgical devices for GERD therapy are a promising alternative to proton pump inhibitor therapy. Their place in the treatment algorithm for GERD will be better defined when important clinical parameters, especially durability of effect, are better understood.

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Vaezi, M., Shaheen, N., Muthusamy, V. "State of Evidence in Minimally-Invasive Management of Gastroesophageal Reflux: Findings of a Scoping Review." *Gastroenterology* 2020; Vol. 159, pp. 1504-1525.

### **Famotidine Use in COVID-19**

To compare outcomes in patients hospitalized with Coronavirus (COVID-19), receiving famotidine therapy with those not receiving famotidine, a retrospective, propensity-matched observational study of consecutive COVID-19 positive patients was carried out between 2/24/2020 and 5/13/2020.

Of 878 patients in the analysis, 83 (9.5%), received famotidine. In comparison to patients not treated with famotidine, the patients treated with famotidine were younger (63.5 vs. 67.5 years), but did not differ with respect to baseline

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demographics or preexisting comorbidities. Use of famotidine was associated with a decreased risk of in-hospital mortality (OR 0.37), and combined death or intubation (OR 0.47). Propensity score matching to adjust for age difference between groups did not alter the effect on either outcome. In addition, patients receiving famotidine despite lower levels of serum markers for severe disease, including lower median peak CRP levels (9.4 vs. 12.7 mg/dL), lower median procalcitonin levels (0.16 vs. 0.30 ng/mL), and a nonsignificant trend to lower median mean ferritin levels (797.5 vs. 964 ng/mL).

Logistic regression analysis demonstrated that famotidine was an independent predictor of both lower mortality and combined death/intubation, whereas older age, BMI greater than 30 kg, chronic kidney disease, national early warning score, and higher neutrophil/lymphocyte ratio were all predictors of adverse outcomes.

It was concluded that famotidine use in hospitalized patients with COVID-19 is associated with a lower risk of mortality, lower risk of combined outcome of mortality and intubation, and lower levels of serum markers for severe disease in hospitalized patients with COVID-19.

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Mather, J., Seip, R., McKay, R. "Impact of Famotidine Use on Clinical Outcomes of Hospitalized Patients With COVID-19." *American Journal of Gastroenterology* 2020; Vol. 115, pp. 1617-1623.

### Family History of Colorectal Cancer and Prevalence of Advanced Colorectal Neoplasia in Screening

To evaluate the clinical significance of family history (FH) of colorectal cancer (CRC) in first degree relatives (FDRs) in screening stratified by different age groups, investigation of the relationship between FH and the presence of advanced colorectal neoplasia (ACN), and screened individuals in different age groups

were evaluated.

Data from screened individuals aged 40 to 45 years (N = 2263), and 55 to 69 years (N = 2621), who underwent their first-ever screening colonoscopy, were analyzed. The relationship between FH and ACN was examined and a multivariate logistic regression analysis incorporating other baseline characteristics was performed.

Among individuals age 40 to 55 years, the prevalence of ACN was significantly higher in 249 individuals with affected FDRs than in those without (5.6% vs 1.6%), with an adjusted odds ratio of 3.7. The prevalence was particularly high in those having FDRs with CRC mortality (7.3%). Among individuals age 55 to 69 years, the prevalence of ACN was not significantly different between 291 individuals with affected FDRs and those without (5.8% vs 5.8%). However, individuals with two FDRs with CRC and mortality showed a high prevalence of ACN (17.4% and 42.9%, respectively).

It was concluded that an FH of CRC in FDRs was associated with a higher prevalence of ACN in younger individuals with a particularly high impact of FH on CRC mortality. In contrast, the impact of FH was weaker in older individuals, except those having two FDRs with CRC on mortality.

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Sekiguchi, M., Kakujawa, Y., Nakamura, K., et al. "Family History of Colorectal Cancer and Prevalence of Advanced Colorectal Neoplasia in Asymptomatic Screened Populations in Different Age Groups." *Gastrointestinal Endoscopy* 2020; Vol. 91, pp. 1361-1370.

### Cognitive Deficit and White Matter Changes in Celiac Disease

To validate previous reports over the presence and prevalence of brain injury in patients with celiac disease, neuropsychological dysfunction in patients with celiac disease included in the National UK Biobank was carried out, containing experimental medical data from 500,000 adults in the United Kingdom.

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## FROM THE LITERATURE

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Biobank participants with celiac disease (N = 104; mean age 63 years; 65% female) were matched with healthy individuals (N = 198; mean age 63 years; 67% female) for age, sex, level of education, body mass index and diagnosis of hypertension. All participants were otherwise healthy.

Scores were compared from five cognitive tests and multiple choice responses in 6 questions about mental health between groups using the t test and chi-squared analyses. Groupwise analyses of MRI brain data included a study of diffusion tensor imaging metrics (mean diffusivity, fractional anisotropy, radial diffusivity, axial diffusivity), voxel-based morphometry and Mann-Whitney U comparisons of Fazekas grades.

Compared with controlled individuals, participants with celiac disease had significant deficits in reaction time and significantly higher proportions had indications of anxiety, depression, thoughts of self-harm and health-related unhappiness. Tract-based spatial

statistics analysis showed significantly increased axial diffusivity in widespread locations, demonstrating white matter changes in brains of participants with celiac disease. Voxel-based morphometry and Fazekas grade analyses did not differ significantly between groups.

It was concluded in an analysis of data from the UK Biobank that participants were found with celiac disease to have cognitive deficit, indications of worsened mental health, and white matter changes, based on analyses of brain images. These findings support the concept that celiac disease is associated with neurological and psychological features.

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Croall, I., Sanders, D., Hadjivassiliou, M., Hoggard, N. "Cognitive Deficit and White Matter Changes in Persons With Celiac Disease: A Population-Based Study." *Gastroenterology* 2020; Vol. 158, pp. 2112-2122.

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Murray H. Cohen, DO, "From the Literature" Editor, is on the Editorial Board of *Practical Gastroenterology*.

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