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Gluten, Grains, and Risk for Type 1 Diabetes in At-Risk Children

Consumption of oats, wheat, rye, gluten-containing cereals, gluten, and dietary fiber appear to confer an increased risk for islet autoimmunity.

Dietary factors have been implicated for many years as potential pathophysiologic triggers in the development of type 1 diabetes (T1D). High intake of cereals and other gluten-containing products may lead to an increased risk for islet autoimmunity (IA).

In a prospective birth cohort study in Finland, researchers examined dietary intake of cereals, fiber, and gluten and risk for IA and T1D in over 5500 children with human leukocyte antigen–conferred susceptibility to T1D. Islet autoantibodies and other markers of autoimmunity were obtained every 3 to 12 months for up to 15 years, and dietary assessments (with attention to wheat, barley, rye, rice, and oats intake) were completed at 3, 6, and 12 months and at 2-, 3-, 4-, and 6-year visits.

Incidence of IA and T1D were 4.4% and 1.6%, respectively, during the 6-year follow-up period. A high intake of oats, wheat, rye, gluten-containing cereals, gluten, and dietary fiber was associated with increased risk for IA. After adjusting for energy intake, consumption of oats and gluten-containing cereals showed statistically significant associations with T1D risk, but significance was lost after multiple testing correction.

COMMENT: This is the first study to report associations between intake of specific cereals and IA in children genetically predisposed to T1D. Of concern is that some of the dietary components implicated, such as fiber, are promoted for their health benefits. Until more is understood, encouraging moderate intake, not exceeding standard recommended amounts, of gluten, fiber, and selected grains might be reasonable, especially in the child who has a known strong family history of autoimmune disease.

CITATION(S): Hakola L et al. Association of cereal, gluten, and dietary fiber intake with islet autoimmunity and type 1 diabetes. *JAMA Pediatr* 2019 Aug 12; [e-pub]. (<https://doi.org/10.1001/jamapediatrics.2019.2564>)

JAMA Psychiatry 2019 Jul 31

Estrogen for Schizophrenia?

Transdermal estradiol appeared to improve antipsychotic efficacy, but only in women older than 38.

Endogenous estradiol may affect the natural course of schizophrenia, suggesting a therapeutic role for this hormone. To replicate a previous study, investigators conducted an 8-week, placebo-controlled trial of a 200- μ g estradiol patch in 200 nonmenopausal women in Moldova (median age, 38) already taking antipsychotic drugs for schizophrenia.

Across the entire study group, estradiol was significantly more effective than placebo for improving positive symptoms (the primary outcome) although the effect size was small. Estradiol was also significantly more effective for secondary outcome measures (e.g., total schizophrenia symptom score, clinical impression of severity). Further analysis revealed that estrogen appeared to be effective only in patients older than 38, in whom the effect size was large, whereas improvement among younger women was not significant.

COMMENT: One likely explanation for the apparent benefit of estradiol in older study participants is that the hormone sensitizes postsynaptic dopamine receptors to blockade, thereby augmenting the action of antipsychotic drugs. This phenomenon may also explain why lower doses of antipsychotics are effective in younger but not older women with schizophrenia. Since weekly estrogen levels were not measured here, whether estradiol might have raised antipsychotic levels remains unknown. Given that it's generally unwise for women with a uterus to take estrogen without a progestin, considerably more research is necessary before estrogen supplementation could be considered for women with schizophrenia.

CITATION(S): Weiser M et al. Effect of adjunctive estradiol on schizophrenia among women of childbearing age: A randomized clinical trial. *JAMA Psychiatry* 2019 Jul 31; [e-pub]. (<https://doi.org/10.1001/jamapsychiatry.2019.1842>)

JAMA 2019 Aug 27; 322:736

Vitamin D Supplementation: Is More Better?

In a randomized trial, higher doses unexpectedly were associated with greater declines in bone-mineral density.

The “if some is good, more is better” approach to supplementation has led to as many as 3% of U.S. adults taking high-dose vitamin D supplements (≥ 4000 IU daily). To address uncertainty about incremental benefit of vitamin D doses higher than 400 to 1000 IU daily, Canadian investigators randomized 311 adults (mean age, 62); without osteoporosis and with normal hydroxyvitamin D (25[OH]D) and serum calcium levels to one of three levels of supplementation (400 IU, 4000 IU or 10,000 IU) daily. At baseline, mean serum 25(OH)D was 32 ng/mL (79 nmol/L). Patients with prior high-dose vitamin D use, disorders of vitamin D metabolism, or high 10-year risk for osteoporotic fractures were excluded. Dietary

calcium intake was supplemented to recommended levels. Participants were assessed serially through 36 months. Bone-mineral density (BMD) and bone strength were assessed at the distal radius and tibia by high-resolution computed tomography (a method used in clinical research).

Serum 25(OH)D levels increased significantly for participants who received 4000 IU or 10,000 IU daily but not for participants who received 400 IU daily. At 3 years, declines in BMD at the radius were significantly steeper in the 4000 IU and 10,000 IU groups (−2.4% and −3.5%, respectively) than in the 400 IU group (−1.2%). A similar pattern was noted in the tibia. Bone-strength estimates declined in all three groups, with nonsignificant trends toward lower strength in the high-dose vitamin D groups than in the 400 IU group.

COMMENT: The authors speculate that this somewhat unexpected finding might be due to increased bone resorption secondary to parathyroid hormone suppression. In any case, the findings point to no benefit for bone integrity — and even potential harm — with high-dose vitamin D supplementation in patients whose vitamin D levels are adequate.

CITATION(S): Burt LA et al. Effect of high-dose vitamin D supplementation on volumetric bone density and bone strength: A randomized clinical trial. *JAMA* 2019 Aug 27; 322:736. (<https://doi.org/10.1001/jama.2019.11889>)

Diabetes Care 2019 Aug; 42:1481

Vitamin E Alone Is Ineffective for NASH in Patients with Type 2 Diabetes

Data do not support routine use of vitamin E in this population.

Vitamin E has shown some benefit for treating nonalcoholic steatohepatitis (NASH) in patients without type 2 diabetes mellitus (T2DM), but there are few data from patients with T2DM. Also, there is growing evidence that T2DM confers an added risk for cirrhosis and hepatocellular carcinoma in patients with NASH (*NEJM JW Gastroenterol Jul 2019* and *Clin Gastroenterol Hepatol* 2019 Apr 19 [e-pub]).

In an investigator-initiated, double-blind study, researchers evaluated the safety and efficacy of vitamin E alone or in combination with pioglitazone in 105 patients with NASH and T2DM recruited at two Veterans Affairs medical centers. Patients were randomized in a 1:1:1 fashion to receive vitamin E 400 IU twice daily, vitamin E plus pioglitazone (starting at 30 mg daily and titrated to 45 mg daily), or placebo for 18 months. The primary endpoint was reduction in the nonalcoholic fatty liver disease activity score of ≥ 2 points without worsening of fibrosis.

Baseline characteristics were similar between groups. Several patients discontinued treatment in each group. The primary endpoint was achieved at a significantly higher rate with combination therapy compared with placebo (54% vs. 19%) but not with vitamin E alone compared with placebo (31% vs. 19%; $P=0.26$). No significant improvement in fibrosis was seen in either treatment group.

COMMENT: In this proof-of-concept study, vitamin E alone was not effective in improving NASH in patients with T2DM. Although the combination of pioglitazone plus vitamin E did demonstrate significant improvement in NASH, the authors point out that it was similar to a previously reported finding of pioglitazone monotherapy in this population, further suggesting the ineffectiveness of vitamin E. Based on these data, together with some safety concerns, vitamin E should not be routinely used in this population.

CITATION(S): Bril F et al. Role of vitamin E for nonalcoholic steatohepatitis in patients with type 2 diabetes: A randomized controlled trial. *Diabetes Care* 2019 Aug; 42:1481. (<https://doi.org/10.2337/dc19-0167>)

Prenatal Fluoride Exposure Linked to Lower IQ in Preschoolers

Higher maternal urinary fluoride and self-reported intake during pregnancy were associated with lower IQ in children aged 3 to 4 years.

Community-wide fluoridation of drinking water is a longstanding strategy to reduce dental caries. Studies suggest that fluoride exposure during brain development might negatively affect neurocognitive outcomes in children.

Researchers evaluated data from 512 mother-child pairs recruited for a birth cohort study between 2008 and 2011 in six Canadian cities. They measured fluoride exposure during pregnancy (via both maternal urinary fluoride [MUF] concentration and self-reported beverage intake) and children's IQ scores at age 3 to 4 years. Analyses included multiple covariates, such as maternal education, household income, parity, and exposure to other chemicals, as well as child gestational age, birth weight, and sex.

In adjusted analyses, an increase of 1 mg/L in MUF was associated with a 4.5-point decrease in full-scale IQ (FSIQ) in boys but was not associated with FSIQ in girls. The same pattern was observed for children's performance IQ, whereas no association was found for verbal IQ. For each 1-mg increase in self-reported maternal fluoride intake during pregnancy, there was a 3.7-point decrease in FSIQ for boys and girls.

COMMENT: These data add to the controversy around community-level fluoridation of drinking water. As noted in an accompanying editorial and an editor's statement, one epidemiologic study is not enough to decide a debate. But methodologies are improving in this area, making these findings potentially concerning, particularly at the population level. Clinicians should be prepared to discuss the possible positive and negative effects of fluoride exposure, since parents may ask whether they should avoid giving fluoridated water to their young children or drinking it during pregnancy. Because prenatal fluoride is not believed to benefit the fetus, it is reasonable to recommend that women reduce fluoride intake during pregnancy.

CITATION(S): Green R et al. Association between maternal fluoride exposure during pregnancy and IQ scores in offspring in Canada. *JAMA Pediatr* 2019 Aug 19; [e-pub]. (<https://doi.org/10.1001/jamapediatrics.2019.1729>)

Bellinger DC. Is fluoride potentially neurotoxic? *JAMA Pediatr* 2019 Aug 19; [e-pub]. (<https://doi.org/10.1001/jamapediatrics.2019.1728>)

Christakis DA. Decision to publish study on maternal fluoride exposure during pregnancy. *JAMA Pediatr* 2019 Aug 19; [e-pub]. (<https://doi.org/10.1001/jamapediatrics.2019.3120>)

Treating Varicose Veins — Long-Term Results from a Randomized Trial

Laser ablation appeared to be the winner in a comparison of three types of treatment.

In a previously published, three-way randomized trial that involved 798 patients with symptomatic varicose veins of one or both legs, disease-specific quality of life at 6 months improved slightly more with laser ablation or with surgical ligation/stripping than with foam sclerotherapy (*NEJM JW Gen Med* Nov 1 2014 and *N Engl J Med* 2014; 371:1218). Now, the researchers report 5-year follow-up data.

At 5 years, disease-specific quality of life (as recorded on questionnaires that documented pain, swelling, skin changes, and interference with activity) improved significantly more with laser ablation or with surgery than with foam sclerotherapy. Improvement was similar in the laser ablation and surgery groups. Laser ablation was more cost-effective than surgery.

COMMENT: Considering both treatment efficacy and cost-effectiveness, laser ablation appears to be the winner in this comparison of treatments for patients with varicose veins.

CITATION(S): Brittenden J et al. Five-year outcomes of a randomized trial of treatments for varicose veins. *N Engl J Med* 2019 Sep 5; 381:912. (<https://doi.org/10.1056/NEJMoa1805186>)

N Engl J Med 2019 Sep 2

Clarity on Antithrombotic Therapy for Atrial Fibrillation plus Chronic CAD

Finally, we can be sure that anticoagulation without an antiplatelet agent is best for patients with atrial fibrillation and chronic coronary artery disease.

Several randomized, controlled trials (e.g., RE-DUAL; *NEJM JW Cardiol* Aug 27 2017; [e-pub] and *N Engl J Med* 2017; 377:1513) have shown that for most patients with atrial fibrillation (AF), the standard of care for the first year after percutaneous coronary intervention (PCI) is anticoagulation plus a single antiplatelet agent. However, pertinent data more than 1 year after PCI have been limited. AFIRE, a randomized trial from Japan ([NCT02642419](https://clinicaltrials.gov/ct2/show/study/NCT02642419)), provides clarity on optimal antithrombotic therapy in this population.

Researchers randomized 2236 patients with AF who had undergone PCI or coronary artery bypass grafting at least 1 year earlier, or who had a history of angiographically confirmed coronary artery disease (CAD; stenosis $\geq 50\%$) not requiring revascularization, to receive either rivaroxaban alone or rivaroxaban plus aspirin or a P2Y₁₂ inhibitor. The trial was stopped early because of increased mortality in the combination-therapy arm.

Incidence of the primary efficacy endpoint — stroke, systemic embolism, myocardial infarction, unstable angina requiring revascularization, or death from any cause — was noninferior with rivaroxaban, compared with combination therapy (4.14% vs. 5.75% per patient-year, respectively). Death from any cause, a prespecified secondary endpoint, was significantly less common with rivaroxaban alone than with combination therapy (1.85% vs. 3.37% per patient-year) — as was major bleeding (1.62% vs. 2.76% per patient-year, respectively).

COMMENT: We finally have clarity: Patients with AF and *chronic* CAD should receive only anticoagulation, not antiplatelet agents. Although existing guidelines had made this recommendation, the evidence base was slim, and many patients were nevertheless kept on anticoagulation plus an antiplatelet agent. These new data from AFIRE should help to end that practice. Notably, AFIRE used a 15-mg rivaroxaban dose for patients with normal renal function, but that dose in typical Japanese patients yields a serum level equivalent to 20-mg rivaroxaban in typical white patients — a fact to bear in mind when individualizing treatment.

CITATION(S): Yasuda S et al. Antithrombotic therapy for atrial fibrillation with stable coronary disease. *N Engl J Med* 2019 Sep 2; [e-pub]. (<https://doi.org/10.1056/NEJMoa1904143>)

Should Patients with Diabetes and Coronary Artery Disease Take Dual Antiplatelet Therapy?

A slight efficacy advantage with ticagrelor plus aspirin over aspirin alone is offset by a slightly increased risk for adverse events.

The secondary prevention of cardiovascular disease remains an area of intense interest. In THEMIS, an industry-sponsored, multicenter, randomized, double-blind study (NCT01991795), investigators examined the efficacy of ticagrelor versus placebo added to aspirin in 19,271 patients aged 50 or older who had stable coronary artery disease and type 2 diabetes.

Patients had no previous histories of myocardial infarction or stroke. The median follow-up was 39.9 months. Discontinuation was more common in the ticagrelor group (34.5% vs. 25.4%). The primary composite outcome (cardiovascular death, myocardial infarction, or stroke) occurred in 7.7% of the ticagrelor group versus 8.5% of the placebo group; at 36 months, Kaplan-Meier rates were 6.9% and 7.6% (hazard ratio, 0.90; 95% confidence interval, 0.81–0.99). The superiority of ticagrelor was primarily due to fewer myocardial infarctions and strokes. Rates of all-cause death were similar in the two groups (ticagrelor, 6.0%; placebo, 6.2%). Major bleeding was more common in the ticagrelor group (2.2% vs. 1.0%; HR, 2.32; 95% CI, 1.82–2.94). Intracranial hemorrhage was rare but significantly more common with ticagrelor (0.7% vs. 0.5%). Dyspnea was also more common with ticagrelor (21.4% vs. 7.3%).

COMMENT: The authors conclude that “ticagrelor therapy does not have a favorable risk–benefit ratio in this trial population.” I think that says it all. The razor-thin benefit was just across the conventional level of significance, and the risks (particularly, bleeding) were just a bit larger in the opposite direction. The results disappointingly fail to support a new strategy to reduce risk.

CITATION(S): Steg PG et al. Ticagrelor in patients with stable coronary disease and diabetes. *N Engl J Med* 2019 Sep 1; [e-pub]. (<https://doi.org/10.1056/NEJMoa1908077>)

Gynecol 2019 Sep; 134:527

Does Endometriosis Increase Risk for Certain Adverse Pregnancy Outcomes?

A large prospective cohort study suggests endometriosis is associated with adverse outcomes, including early pregnancy loss.

Although endometriosis is associated with infertility, most women with this disorder do eventually achieve pregnancy. But is endometriosis also associated with adverse pregnancy outcomes? To address this question, investigators utilized data from women participating in the prospective cohort Nurses' Health Study II from 1989 through 2009 (age range at study entry, 25–42).

A total of 8875 pregnancies in women with laparoscopically confirmed self-reported endometriosis were included. In analysis accounting for multiple pregnancies per woman, pregnancies in women with a history of endometriosis had higher relative risk for spontaneous abortion (RR, 1.40) and ectopic pregnancy (RR, 1.46) compared with 187,847 pregnancies without any history of endometriosis. This disorder was also associated with higher risks for gestational diabetes mellitus (RR, 1.35) and hypertensive disorders of pregnancy (RR, 1.30).

COMMENT: Despite this study's large size, its conclusions should be viewed with caution as they represent associations only (and not exceedingly strong ones at that) without providing insight into causality. Still, these observations indicate

the need for further investigation and for increased surveillance by clinicians caring for pregnant women with a history of endometriosis.

CITATION(S): Farland LV et al. Endometriosis and risk of adverse pregnancy outcomes. *Obstet Gynecol* 2019 Sep; 134:527. (<https://doi.org/10.1097/AOG.0000000000003410>)

JAMA Netw Open 2019 Jul 26; 2:e197700

Artificial Intelligence to Assess Hormonal Status of Breast Cancer Patients

A machine learning technique was noninferior to traditional immunohistochemistry in predicting molecular biomarker expression.

The pathological review of tumor samples, even for common molecular biomarkers such as estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2), is time consuming. Moreover, there is not always concordance between pathologists on the interpretation of samples. For example, it has been estimated that there is a discrepancy of up to 19% for ER estimation between central laboratories and local pathology laboratories.

Artificial intelligence (AI) and machine learning technologies are being applied to address this variation as well as to improve reliability and add efficiency. Currently, such technology can differentiate between cancerous and noncancerous tissue as well as determine presence of metastases in lymph nodes and perform tumor grading.

Now, investigators have conducted a retrospective, single-institution study to test the ability of a machine learning technique — referred to as morphological-based molecular profiling — to assess hormonal status of more than 20,000 digitized hematoxylin-eosin (H&E) pathology specimens from a microarray library of more than 5000 breast cancer patients.

Histology and biomarkers were found to be significantly correlated with all 19 assessed biomarkers, including most clinically relevant ER, PR, and HER2. For approximately half of the patients, the machine learning technique was able to predict biomarker expression with noninferiority to immunohistochemistry (IHC) in two validation cohorts with positive predictive values of 97% and 98%. Also, for patients with ER-negative/PR-positive tumors assessed by conventional IHC, machine learning techniques revealed resemblance to patients with ER-positive tumors, suggesting that the IHC result was falsely negative and that a fraction of ER-negative/PR-positive patients might benefit from endocrine therapy.

COMMENT: AI and machine learning are emerging technologies that are finding a role in many aspects of modern life, including medicine. These data represent a first effort to utilize a training set to gauge utility for pathological review of samples. It is not yet ready for prime-time use but with additional experience and data, machine learning may be a partner to clinicians in the care of patients.

CITATION(S): Shamaï G et al. Artificial intelligence algorithms to assess hormonal status from tissue microarrays in patients with breast cancer. *JAMA Netw Open* 2019 Jul 26; 2:e197700. (<https://doi.org/10.1001/jamanetworkopen.2019.7700>)

Comparing Colorectal Cancer Screening Modalities

Programmatic, multiple-round FIT detected more neoplasia than one-time sigmoidoscopy or colonoscopy in the intention-to-screen analysis, but there is more to the story.

Fecal immunochemical tests (FIT), sigmoidoscopy, and colonoscopy are the most commonly used modalities for colorectal cancer (CRC) screening worldwide. However, there is a lack of comparative data, particularly regarding multiple-round FIT versus endoscopic screening strategies.

Now, investigators have combined the findings of three population trials in which more than 30,000 average-risk, screening-naïve individuals in the Netherlands (median age, 59 years) received invitations for FIT, sigmoidoscopy, or colonoscopy screening. Persons in the FIT group were invited to use a FIT kit every other year, and those in the sigmoidoscopy and colonoscopy groups were invited to undergo the procedure once. Those with a positive FIT ($\geq 10 \mu\text{g}$ Hb/g feces) or sigmoidoscopy result underwent colonoscopy. After four rounds of FIT screening, results were as follows:

- The participation rate was higher with FIT (77%) than with sigmoidoscopy (31%) or colonoscopy (24%).
- The follow-up time was longer with FIT and sigmoidoscopy (8 years) than with colonoscopy (6 years).
- In the intention-to-screen analysis, the cumulative diagnostic yield of advanced neoplasia (advanced adenoma or CRC) was higher with FIT (4.5%) than with sigmoidoscopy (2.3%) or colonoscopy (2.2%).
- In the as-screened analysis, the cumulative diagnostic yield of advanced neoplasia was higher with colonoscopy (9.1%) than with sigmoidoscopy (7.4%) or FIT (6.1%).
- Colonoscopy detected more nonadvanced adenomas in both analyses.
- The rate of interval CRC (detected between a negative screening test and the next test) was lower with colonoscopy (0.01%) than with sigmoidoscopy (0.09%) or FIT (0.13%).

COMMENT: Despite the lack of randomization, this population-based study provides valuable information regarding the relative participation rates and diagnostic yield of the major CRC screening modalities. It is important to note that FIT participants received more attention than their sigmoidoscopy and colonoscopy counterparts, which likely led to lower participation rates for the endoscopic modalities. This difference, in addition to shorter follow-up, could explain why colonoscopy and sigmoidoscopy were associated with lower detection rates in the intention-to-treat analyses. Currently, there are four large, ongoing randomized controlled trials (3 European, 1 U.S.) comparing CRC mortality with colonoscopy versus FIT that should eventually provide more-definitive comparative efficacy data.

Note to readers: At the time we reviewed this paper, its publisher noted that it was not in final form and that subsequent changes might be made.

CITATION(S): Grobbee EJ et al. Diagnostic yield of one-time colonoscopy vs one-time flexible sigmoidoscopy vs multiple rounds of mailed fecal immunohistochemical tests in colorectal cancer screening. *Clin Gastroenterol Hepatol* 2019 Aug 13; [e-pub]. (<https://doi.org/10.1016/j.cgh.2019.08.015>)
