INTERNET NEWS

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Low-Dose Aspirin Reduces Liver Fat, Inflammation Markers

Neil Osterweil
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BOSTON — Patients with metabolic-associated steatotic liver disease (MASLD, formerly NAFLD) without cirrhosis who took daily low-dose aspirin in a double-blind randomized trial demonstated significant reductions in liver fat content over 6 months compared with similar patients who took a placebo, study results show.

"In MASLD without cirrhosis, low-dose aspirin, 81 milligrams daily, led to decreases in liver fat and improved markers of hepatic inflammation and fibrosis," reported Robert M. Wilechansky, MD, a transplant hepatology fellow at Massachusetts General Hospital in Boston.

In preclinical studies, aspirin has been shown to have both anti-inflammatory and antitumor effects in the liver through inhibition of cycloxygenase-2 and platelet-derived growth factor signaling, as well as through modulation of bioactive lipids, Wilechansky said.

In observational studies, use of aspirin was associated with a reduction in the prevalence of hepatic steatosis and fibrosis progression in patients with MASLD, and there was a decrease in the incidence of hepatocellular carcinoma and liver-related mortality among patients with viral hepatitis, he noted.

As for the potential mechanism of action of aspirin for patients with MASLD, Wilechansky noted that there may be some reduction in steatosis, and "if there is a reduction in inflammation, we may see some reduction in steatohepatitis."

Study Details

To see whether the so-called "wonder drug" could work wonders for patients with MASLD without cirrhosis, the researchers recruited 80 adults with MASLD and randomly assigned them to receive either aspirin 81 mg once daily or placebo for 6 months.

Patients with baseline cirrhosis or other liver disease, heavy drinkers, those who had used aspirin within 6 months, or those who used other antiplatelet or anticoagulant agents were excluded, as were patients with severe renal or cardiovascular disease, active cancer, pregnancy, were breastfeeding, had thrombocytopenia, or had undergone bariatric surgery within the past 2 years.

At baseline, 36.3% of all patients had F2-F3 fibrosis, as determined by vibration-controlled transient elastography (VCTE), and of 44 patients who had previously undergone liver biopsy, 37 (84.1%) were confirmed to have steatohepatitis.

At 6 months, the absolute change in hepatic fat fraction (HFF) from baseline, the primary endpoint, was a decline of 6.1% for patients taking aspirin compared with a 4.2% increase for patients taking placebo, which translates into a 10.3% difference in favor of aspirin ($P = .009$).

The relative change in HFF, a secondary endpoint, for aspirin vs placebo was -59.2% ($P = .003$).

In addition, the use of aspirin was associated with a relative reduction in HFF of at least 30% among 16 of the 40 patients who received it.

Aspirin was significantly better than placebo for the secondary endpoints of absolute change in hepatic fat by MRI proton-density fat fraction (MRI-PDFF), with -2.9% vs placebo ($P = .018$), and the relative change in hepatic fat by MRI-PDFF, with a difference of -24.8% vs placebo ($P = .009$).

Aspirin was also associated with significantly greater reductions in liver transaminase levels and liver stiffness by VCTE.

People With Diabetes Have a Higher Risk of Colon Cancer: Study

Written by Lisa O'Mary

2 min read

Nov. 14, 2023 – People with diabetes had a 47% increased risk of getting colorectal cancer, compared to people without diabetes, according to results of a large new study. Getting a colonoscopy dramatically reduced the risk, the results showed.

The findings, published today in *JAMA Network Open*, suggest that colonoscopies are particularly important for people with diabetes. People diagnosed with diabetes within the past 5 years have the greatest colorectal cancer risk, the study found, suggesting screening should be part of a person's

Researchers analyzed data for 54,597 people who contributed at least 2 years of health data as part of a study that recruited people from 12 southeastern states between 2002 and 2009. The people self-reported their diabetes status, and although researchers tried to only include people with type 2 diabetes, it's possible that some people in the study had type 1 diabetes. The average age of those in the study was 51 years old; 64% were women; more than half of them had an income of less than $15,000 per year; and 66% of them were African American.

Among the people in the study who had diabetes, the risk of having colorectal cancer was not strongly impacted by their race or ethnicity, gender, weight, or income level, the study showed.

While race didn't predict whether people with diabetes would get colorectal cancer, the findings are particularly important because most of the people in the study were African American. Diabetes and colorectal cancer disproportionately affect African American people, the authors noted. Medical research studies often struggle to recruit people of color, resulting in a lack of data to help guide health care priorities and decision-making.

The study also provided important guidance for people newly diagnosed with diabetes. People who were diagnosed with diabetes within the past 5 years were at a particularly increased risk of getting colorectal cancer, compared to people who had been diagnosed for 5 to 10 years.

The authors concluded that increased referrals for colonoscopies among people with diabetes, particularly among those newly diagnosed, could greatly reduce the impact of colorectal cancer. Current guidelines suggest most people should begin colorectal cancer screenings at age 45, according to the CDC.

Methotrexate improves pain, stiffness with osteoarthritis

Study author Professor Flavia Cicuttini, the head of the musculoskeletal unit at Monash University and the head of rheumatology at Alfred Hospital, explained the difficulty surrounding treatment options for hand osteoarthritis.

"Hand osteoarthritis is a disabling condition that causes pain and affects function, impeding daily activities such as dressing and eating. It can significantly reduce quality of life," she told *MNT*.

- **Data from a recent study found that methotrexate—a common treatment for other arthritis types—may help treat hand osteoarthritis and inflammation of the synovial membrane.**

People use their hands daily to accomplish tasks and go about their lives. When the joints in the hand become stiff and rigid to move, it can be debilitating and hard to function. This can be the case for people who have hand osteoarthritis. Researchers are interested in understanding the most effective treatment options for people with hand osteoarthritis.

A recent study published in *The Lancet* examined how well the drug methotrexate may help treat hand osteoarthritis.

The study found that participants who received methotrexate over six months had moderate pain improvement.

The results indicate that methotrexate, which is helpful in treating other types of arthritis such as psoriatic or rheumatoid arthritis, may benefit people with hand osteoarthritis and inflammation.

To look at the effectiveness of methotrexate in improving pain in people with hand osteoarthritis with synovitis, researchers conducted the current study.

The study was a double-blind, randomized, placebo-controlled trial. The researchers included 97 participants in their analysis. Of this number, 50 participants received methotrexate, and 47 received the placebo. Participants took either the placebo or methotrexate weekly for six months.

All participants had hand osteoarthritis and synovitis in at least one joint, as confirmed by MRI. They excluded participants who had other types of arthritis and certain conditions like cancer and hepatitis B.

In addition to their study participation, participants also got their typical care from their health practitioners. They took folic acid on any other day of the week that they weren't taking methotrexate, as this can help with methotrexate side effects.

The methotrexate group had a slightly higher body mass index than the placebo group. Other than this, the groups were very similar.

Researchers found that the methotrexate group had a higher level of pain and stiffness reduction than the placebo group.

There were some reported adverse events in both groups, which could have been related to study medications. However, overall, methotrexate was well-tolerated.

Chronic Diarrhea Management: Be Wary of False Diarrhea

Vincent Richeux
November 13, 2023

PARIS — Most diarrhea that leads patients to seek medical advice is actually a false alarm, said gastroenterologist Nassim Hammoudi, MD, PhD, of the Lariboisière Hospital in Paris, during France's annual general medicine conference (JNMG 2023). He said that doctors need to understand the characteristics of chronic diarrhea and adapt its management accordingly. In his presentation, Hammoudi highlighted the clinical signs that should be considered.

Mechanisms of Chronic Diarrhea

Chronic diarrhea can result from different mechanisms, such as motility disorders related to accelerated intestinal transit, malabsorption, osmotic diarrhea, and secretory diarrhea, which are often interlinked. When an endoscopy is performed, it is recommended to conduct multi-level biopsies to detect microscopic colitis, which Hammoudi believes is "probably underdiagnosed."

Diarrhea is defined as the passage of frequent stools (more than three a day), soft to liquid in consistency, and a daily weight exceeding 300 g. It is considered chronic when it persists for more than a month.

Identifying False Diarrhea

Practitioners must first distinguish between genuine and false diarrhea, with the latter presenting in most consultations. "Thorough questioning is fundamental," Hammoudi emphasized. It is essential to determine the daily stool count, the presence of nocturnal stools, and stool consistency. "A soft stool passed once a day is not diarrhea," he said.

The most challenging form of false diarrhea to identify is what he called "constipated person's diarrhea." These patients, who are typically elderly, reside in care homes, and are bed-bound and taking morphine, have daily liquid stools but are actually constipated. "Taking anti-diarrheal medications makes the situation worse," said Hammoudi.

Another type of false diarrhea is tenesmus, in which patients feel like they have a full rectum, even though it is physiologically empty. The recurring urge to defecate results in mucus discharges that resemble diarrhea. Inflammatory rectal involvement could be the cause, necessitating a gastroenterology consultation.

Anal incontinence can also cause false diarrhea. It is more common in elderly people residing in care homes and in women in the postpartum period. This condition is difficult to manage and requires referral to a gastroenterologist.

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Metformin Cessation and Dementia Incidence

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Key Points

Question Is cessation of metformin therapy associated with dementia incidence, and is the association mediated by hemoglobin A_{1c} (HbA_{1c}) level or insulin use?

Findings This cohort study of 12 220 early terminators and 29 126 routine users of metformin found that cessation of metformin therapy without abnormal kidney function markers was associated with 1.21 times the hazard of dementia diagnosis compared with continuation of therapy or cessation with abnormal kidney function markers. This association was minimally mediated by increases in HbA_{1c} level and not mediated by insulin use 1 or 5 years after metformin cessation.

Meaning The findings of this study suggest that metformin cessation is associated with increased dementia incidence and that mechanisms other than glucose control or insulin use may mediate this association.

Abstract

Importance Prior studies suggested that metformin may be associated with reduced dementia incidence, but associations may be confounded by disease severity and prescribing trends. Cessation of metformin therapy in people with diabetes typically occurs due to signs of kidney dysfunction but sometimes is due to less serious adverse effects associated with metformin.

Objective To investigate the association of terminating metformin treatment for reasons unrelated to kidney dysfunction with dementia incidence.

Design, Setting, and Participants This cohort study was conducted at Kaiser Permanente Northern California, a large integrated health care delivery system, among a cohort of metformin users born prior to 1955 without history of diagnosed kidney disease at metformin initiation. Dementia follow-up began with the implementation of electronic health records in 1996 and continued to 2020. Data were analyzed from November 2021 through September 2023.

Exposures A total of 12 220 early terminators, individuals who stopped metformin with normal estimated glomerular filtration rate (eGFR), were compared with routine metformin users, who had not yet terminated metformin treatment or had terminated (with or without restarting) after their first abnormal eGFR measurement. Early terminators were matched with routine users of the same age and gender who had diabetes for the same duration.

Results The final analytic sample consisted of 12 220 early terminators (5640 women [46.2%]; mean [SD] age at start of first metformin prescription, 59.4 [9.0] years) and 29 126 routine users (13 582 women [46.6%]; mean [SD] age at start of first metformin prescription, 61.1 [8.9] years). Early terminators had 1.21 times the hazard of dementia diagnosis compared with routine users (hazard ratio, 1.21; 95% CI, 1.12 to 1.30). In mediation analysis, contributions to this association by changes in HbA_{1c} level or insulin use ranged from no contribution (0.00 years; 95% CI, −0.02 to 0.02 years) for insulin use at 5 years after termination to 0.07 years (95% CI, 0.02 to 0.13 years) for HbA_{1c} level at 1 year after termination, suggesting that the association was largely independent of changes in HbA_{1c} level and insulin usage.

Conclusions and Relevance In this study, terminating metformin treatment was associated with increased dementia incidence. This finding may have important implications for clinical treatment of adults with diabetes and provides additional evidence that metformin is associated with reduced dementia risk.

Introduction

Type 2 diabetes occurs among an increasing fraction of people aged older than 65 years in the US, and diabetes is associated with increased dementia risk.[1,2] Approved in 1995 in the US,[3] metformin (dimethylbiguanide) has been the preferred first-line agent for type 2 diabetes since 2006.[4-6]

Metformin treatment reduces incidence of diabetes complications and diabetes-related and all-cause mortality.[7] Metformin may also reduce dementia risk by improved glucose control or by mechanisms unrelated to diabetes, including activation of adenosine monophosphate–activated protein kinase, which may mimic starvation,[7] or by inhibition of aromatase, which may be associated with lower blood pressure.[8,9]

Previous randomized clinical trials found that metformin treatment improved cognition and lowered dementia risk in people with type 2 diabetes, but this may reflect cognitive benefits of glucose lowering independent of the agent used.[10] In contrast, the Action to Control Cardiovascular Risk in Diabetes-Memory in Diabetes (ACCORD-MIND) randomized clinical trial[11,12] found no evidence of cognitive benefit for an intensive glucose-control strategy (glycated hemoglobin A_{1c} [HbA_{1c}] target level: <6.0%), which increased exposure to antidiabetes drugs, including metformin, compared with an HbA_{1c} target level of 7.0% to 7.9%. Prior observational studies found that initiating metformin treatment was associated with a benefit in dementia risk, including a benefit compared with other antidiabetes drugs.[10,13] However, confounding by diabetes severity and duration may bias associations.[10] Additionally, increasing metformin use[14,15] and decreasing age-specific dementia incidence in the US[16] complicate observational comparisons between metformin and other agents.[10] Furthermore, some prior studies compared prevalent users with nonusers, which can lead to immortal person-time and confounding biases.[17]

FDA Green-Lights Tirzepatide, Marketed as Zepbound, for Chronic Weight Management

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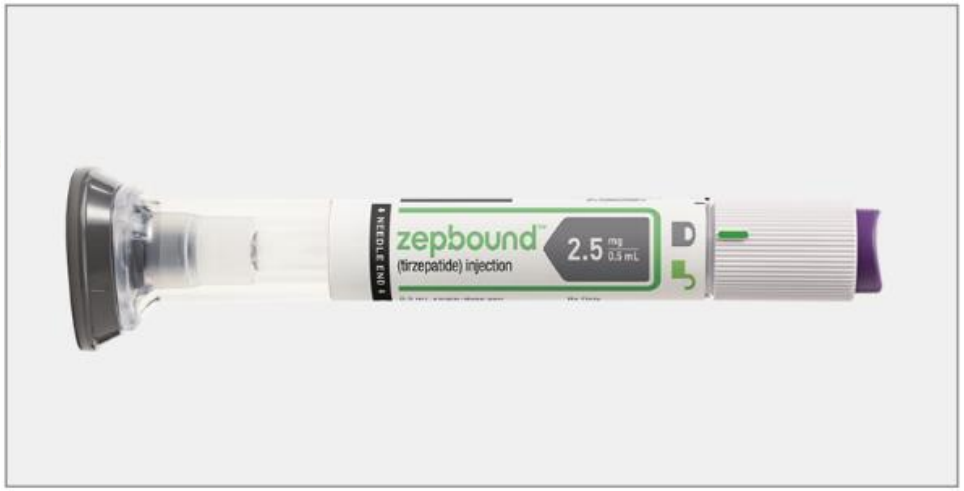

The options for obesity treatment continue to grow with the November 8 US Food and Drug Administration (FDA) approval of tirzepatide for chronic weight management. Marketed by Eli Lilly as Zepbound, the drug will be available as a once-a-week injection. It's approved for people with obesity, defined as a body mass index (BMI) of 30 or greater, or people who are overweight with at least 1 weight-related condition like high blood pressure, high cholesterol levels, type 2 diabetes, obstructive sleep apnea, or cardiovascular disease.

Tirzepatide has been approved for type 2 diabetes treatment under the name Mounjaro since May of 2022. For both the diabetes and weight-management indications, the drug should be prescribed alongside diet and exercise changes, the FDA said.

People who received the maximum dose of tirzepatide lost an average of 21% of their body weight, compared with about 3% average weight loss in the placebo group, according to the results of the 72-week SURMOUNT-1 phase 3 randomized clinical trial, which did not include participants with diabetes. Zepbound's dose can be increased to once-weekly target doses of 5 mg, 10 mg, or a maximum of 15 mg over 4 to 20 weeks.

"Those of us in obesity medicine are very excited about today's approval of Zepbound or tirzepatide for obesity with BMI over 30," Caroline Apovian, MD, codirector of the Center for Weight Management and Wellness at Brigham and Women's Hospital and Harvard Medical School, told *JAMA* in an email. "This adds to the medications we currently have available for this chronic disease which affects 42% of the US population."

In June 2021, the FDA approved Novo Nordisk's semaglutide, marketed as Wegovy, for weight management. Wegovy is associated with 15% weight loss in people with obesity or overweight without diabetes.

Semaglutide and tirzepatide both mimic gut hormones, delaying gastric emptying and curbing appetite. Both are glucagon-like peptide-1 (GLP-1) agonists, but tirzepatide is also a glucose-dependent insulinotropic polypeptide (GIP) receptor agonist.

Like semaglutide, tirzepatide's common adverse effects are mainly gastrointestinal, including nausea, diarrhea, vomiting, and constipation. As for more serious issues, Zepbound has been shown to cause thyroid C-cell tumors in rats and, like Wegovy, is contraindicated for people with a personal or family history of medullary thyroid cancer or multiple endocrine neoplasia syndrome type 2.

The FDA announcement also notes that Zepbound should not be used alongside other GLP-1 receptor agonists because its safety and effectiveness when combined with similar drugs has not been studied. In a press release announcing the approval, Lilly cautioned that the drug also hasn't been studied in people with a history of pancreatitis or with severe gastrointestinal disease, such as severe gastroparesis.

According to Lilly, 6 different Zepbound doses ranging from 2.5 mg to 15 mg should be available in the US by the end of the year at a list price of about $1060 per month.

Apovian emphasized the importance of access to the growing crop of pricey hormone-based antiobesity medications: "Hopefully this addition will herald a move to decrease the costs of these nutrient-stimulated hormonal therapies such as Wegovy and Saxenda and prompt the Centers for Medicare & Medicaid Services and private payors to cover these blockbuster agents."

W. Scott Butsch, MD, director of obesity medicine at the Bariatric and Metabolic Institute at the Cleveland Clinic, echoed the message. "We now have the most effective antiobesity medication ever," he said in an email. "However, until we have more thoughtful and forward-thinking conversations about the costs of these new drugs and coverage of obesity treatments, the full extent of this highly effective medication will not be known."

THANK YOU !