

Mayo Clinic Proceedings' September 2018 Issue Summary

Greetings, I am Dr Karl Nath, the Editor-in-Chief of *Mayo Clinic Proceedings*, and I am pleased to welcome you to the multimedia summary for the journal's September 2018 issue. There are 4 articles this month that have been selected as our Editor's Choice or Highlight articles.

Our Editor's Choice is an Original Article that examined the basis for the increasing incidence of diverticulitis. It is authored by Dr Tae Hee Lee and colleagues from Mayo Clinic in Rochester, Minnesota. Prior studies published by this group indicated that, using the data base of the Rochester Epidemiology Project, the incidence of diverticulitis has significantly increased in Olmsted County, Minnesota. This increased incidence was most pronounced in subjects younger than 50 years, a surprising finding as age, along with obesity, is conventionally considered a risk factor for diverticulitis.

The present studies examined temporal changes in age, body mass index (BMI), abdominal visceral and subcutaneous fat content, and diverticulitis in a population from Olmsted County, Minnesota, again using the data base of Rochester Epidemiology Project.

The authors identified individuals who were diagnosed as having diverticulitis from 1980 through 2007. Because BMI is only a surrogate index for adipose tissue, computed tomographic estimations of abdominal fat content were determined in a case-controlled study; this case-controlled study compared 381 subjects with diverticulitis and 381 age- and sex-matched controls who had abdominal CT scans, but no lifetime history of diverticulitis.

Compared with the decade before 2000, the incidence of diverticulitis increased by 50% in the 7 years after 2000. Concomitantly, the prevalence of obesity in Olmsted County increased from 12% to 49% in the overall adult population, and from 19% to 40% in patients with diverticulitis. At the same time, the Olmsted County population aged, with the proportion of individuals aged 45 to 64 years, and 65 years and older, significantly increased in 2010 as compared with 1990.

Temporal trends in age, BMI, and the increased incidence of diverticulitis in people with normal-weight BMI accounted for approximately 48%, 47%, and 20%, respectively, of corresponding trends in diverticulitis. In the case control study, BMI was greater in the subjects with diverticulitis as compared with controls. However, visceral and subcutaneous fat was independently associated with an increased risk for diverticulitis. Indeed, after incorporating abdominal

and visceral fat content in these analyses, it was found that BMI was associated with a lower risk of diverticulitis.

The authors conclude that aging, increased obesity, and increased incidence of diverticulitis in subjects with normal BMI, account for the temporal increase in diverticulitis. Rather than BMI per se, it is increased visceral and subcutaneous adipose tissue that is independently associated with diverticulitis. The authors speculate that the finding that higher BMI is associated with a decreased risk of diverticulitis, after adjusting for visceral and subcutaneous tissue, may reflect that increased muscle and bone mass may prove protective, in some way as yet undefined, against the development of diverticulitis.

Our first Highlight is an Original Article that examined the basis for the increased risk of cancer in solid organ transplant recipients by analyzing immunosuppression regimens, demographic characteristics, and donor features. It is authored by Dr Mamatha Bhat from the University Health Network and University of Toronto, Ontario, Canada, and colleagues from Mayo Clinic in Rochester, Minnesota.

Previous studies indicate more than 2-fold higher risk of de novo malignancies, depending on the duration of follow-up and era of transplantation. Several factors may contribute to the development of malignancies, including sun exposure, smoking, and concomitant viral infection. However, it is the level and duration of immunosuppression that is most closely associated with this heightened risk. Using the Scientific Registry of Transplant Recipients database, the authors compared malignancy across solid organ transplant groups such as kidney, liver, lung, heart, and pancreas, focusing on the role of immunosuppression in cancer incidence. Data were systematically tracked and collected at 6 months, 1 year after transplant, and annually thereafter.

The study included adult recipients 18 years old or older who underwent kidney, liver, pancreas, heart, or lung transplant from October 1987, through March 2015. Demographic characteristics such as age, sex, body mass index, race, etiology of underlying disease, history of malignancy, diabetes, renal function at time of transplantation, and donor characteristics were all extracted. Smoking history was not available. Immunosuppression medications that were documented at baseline included sirolimus, everolimus, tacrolimus, cyclosporine, azathioprine, and mycophenolate mofetil. The primary end point

Mayo Clinic Proceedings' September 2018 Issue Summary

of the analysis was incidence of any malignancy, including non-melanoma skin cancers. More than 500,000 solid organ transplant recipients were included in this study, and breakdown of malignancies included 49% skin cancers, 11% hematologic malignancies, and 40% solid organ malignancies.

The authors concluded that transplant recipients are at increased risk for malignancy compared with the general population, with heart and lung transplant recipients having the highest risk. Increasing donor age and white race are predictors of heightened cancer risk across all solid organ transplant patients. The presence of multiple immunosuppressants with different mechanisms of action increases the malignancy risk, as seen in the higher risk in heart and lung transplant recipients compared with the liver and kidney patients who receive lesser immunosuppression. A mild protective effect seen with mTOR inhibitor use may suggest a role in preventing skin cancer in solid organ transplant recipients.

Overall, these findings suggest that tailored immunosuppression regimens limiting exposure, to the extent possible, is advisable. Whenever possible and prudent, clinicians should minimize the number of immunosuppressant agents and the degree of immunosuppression used so as to prevent cancer incidence, especially in at-risk older, white, male patients with a history of malignancy. In addition, internists caring for transplant recipients with such risk factors should screen them more carefully for malignancies to optimize post-transplant survival.

The second Highlight is an Original Article that utilized the electronic health record at a pediatric primary care center to assess lifestyle behaviors and the risk for obesity. It is authored by Dr Robin Shook from Children's Mercy in Kansas City, Missouri, and colleagues from the University of Kansas Medical Center.

With increasing use of electronic health records, opportunities are emerging for improved surveillance of health outcomes, such as childhood obesity, both at a local and a population level. Childhood obesity is a major health concern in the US and is one that is potentially preventable. The current study presents the results of a lifestyle assessment occurring in a large, ethnically diverse pediatric primary care clinic to quantify physical activity level, screen time as a measure of sedentary behavior, and consumption of dairy, water, fruits and vegetables, in children and adolescents. This assessment involved questions administered by the nursing staff to the parent/caregiver

during the check-in process for the yearly preventive examination; this examination involved children 2 years and older, with close to 25,000 patients included in the final analysis. The sample approximated an even mix of boys and girls, and was diverse in race/ethnicity. Approximately 34% of the children were overweight or obese, and 63% were normal weight.

For most behaviors (the exception being water consumption), adherence was highest in young children and progressively declined with age. Notable differences between boys and girls were demonstrated across most lifestyle behaviors and age groups, except for screen time in 12 to 18 year-olds, water consumption in 2 to 5 year-olds, and fruit/vegetable consumption in 2 to 5 year-olds and 12 to 18 year-olds, which were not statistically significant.

Adherence to recommendations for physical activity, in particular, was much more prevalent in boys compared with girls, regardless of race. Across all age groups, African-American boys and girls showed lower adherence to screen time recommendations compared with those that were white or Hispanic. Overall, children not meeting any recommendations were more likely to be obese than children meeting recommendations for all 5 behaviors. Obesity risk was statistically lower if 1 recommendation was met, and the risk of obesity was eliminated entirely if a child met 2 or more recommendations. The authors conclude that these findings support the assessment of lifestyle behaviors in pediatric primary care as a component of multilevel initiatives to prevent childhood obesity.

The third Highlight is a Review article that explored the pathophysiology of heart failure with preserved ejection fraction, or HFpEF, a condition where no treatment has been found to have clinical benefit. It is authored by Drs Melissa Lyle and Frank Brozovich from Mayo Clinic in Rochester, Minnesota.

Heart failure affects approximately 5 million Americans. Heart failure with preserved ejection fraction is currently defined as an ejection fraction of greater than 50%, with normal left ventricular size and evidence of reduced diastolic left ventricular function. It is often associated with other comorbidities including hypertension, corrected valvular disorders, atrial fibrillation, diabetes mellitus, obesity, sleep disordered breathing, lung disease, and renal disease. The proportion of patients with heart failure with preserved ejection fraction is estimated to be 50%. However, its prevalence is increasing: in 1987, it was 38% of all documented heart failure cases in Olmsted County, whereas in 2001 it increased to 54%.

Diastolic dysfunction is a central consideration in the pathophysiology of heart failure with preserved ejection fraction. The components of diastolic dysfunction include left ventricular hypertrophy, impaired relaxation, and left ventricular stiffening. In their review, the authors discuss the pathophysiology and cardiac abnormalities in depth, including diastolic dysfunction, cardiac hypertrophy, the role of NO-cGMP-protein kinase G signaling, and arterial stiffness.

From a mechanistic perspective, emphasis is conventionally placed on these central cardiac abnormalities. However, as underscored by Drs. Lyle and Brozovich, in heart failure with preserved ejection fraction, there are peripheral abnormalities that exist in the vasculature and these include, notably, arterial stiffness, resting vasoconstriction and a decreased sensitivity to nitric oxide. Vasoconstriction and decreased nitric oxide sensitivity may be both explained by changes in expression of vascular smooth muscle contractile proteins, and thus represent intrinsic vascular abnormalities contributing to heart failure with preserved ejection fraction. Similarly, systolic hypertension and aging both predispose to arterial stiffness, the latter representing another pathophysiologic mechanism in the vasculature itself underlying the development of this type of diastolic heart failure.

In summary, future studies are needed to develop treatments to improve symptoms and survival in patients with heart failure with preserved ejection fraction. In this regard, there are two pathophysiologic components to consider: ones residing in the heart such as cardiac muscle hypertrophy/diastolic dysfunction, and those residing in the vasculature such as increased vascular tone and a decrease in the sensitivity of the vasculature to nitric oxide. Drs Lyle and Brozovich conclude that novel therapies that improve morbidity and mortality in patients with this disease may be facilitated in two main ways: First, the study of this disease at an earlier time-point in its evolution such that causal pathophysiologic mechanisms may be more readily delineated. Second, the recognition that heart failure with preserved ejection fraction originates, not only from central cardiac abnormalities, but also from peripheral intrinsic abnormalities in the vasculature.

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Mayo Clinic Proceedings' September 2018 Issue Summary

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