News and Views

Impact of Gastroesophageal Reflux on Chronic Cough and Interstitial Lung Disease

Patients with interstitial lung disease (ILD) and chronic cough have high levels of pepsin in the bronchial lavage fluid suggesting acid reflux as an etiologic factor, according to a study from Turkey published in the November 2024 issue of the journal *Respiratory Medicine*[1].

The study included 52 patients with ILD and 81 patients with chronic cough who underwent bronchoscopy at a tertiary clinic between January 2021 and February 2022. Seventy-nine patients with a prediagnosis of lung cancer, served as the control group. In this study, researchers from Turkey explored the potential link between pepsin and ILD and chronic cough. They also evaluated pepsin levels in bronchial lavage in patients with ILD. The most common symptoms in all the three groups were shortness of breath and cough.

The pepsin levels were 16.71 ng/mL in patients with chronic cough, 15.6 ng/mL in those with ILD and 10.58 ng/mL in the control group. Pepsin levels in the ILD and chronic cough group were statistically significantly higher than in the lung cancer group. The increase in pepsin levels in the ILD and chronic cough groups versus the lung cancer (control) group was statistically significant.

However, the study found no statistical difference in pepsin levels between patients with ILD and chronic cough. Pepsin levels were found to be lower among patients who received anti-reflux treatment in all three groups. There was no difference in pepsin levels among ILD subgroups.

The elevated pepsin levels in bronchial lavage among patients with ILD and chronic cough suggest a potential role of reflux in the etiology of these conditions. The reduction in pepsin levels in patients who received anti-reflux therapy supports the occult reflux as a contributing factor. Hence, incorporating antacid therapy into treatment strategies could help patients with chronic cough and ILD by improving symptom control and disease outcomes.

Reference

1. Ala Çitlak FS, et al. Investigation of pepsin levels in bronchial lavage in patients with interstitial lung disease and chronic cough. Respir Med. 2024;233:107781.

Younger Age at Type 2 Diabetes Diagnosis Linked to Higher Mortality Rates

New research published in *The Lancet Diabetes & Endocrinology* suggests that patients who were newly diagnosed with type 2 diabetes under 40 years of age are at a higher mortality risk, including higher risk of incident diabetes-related complications and poorer glycemic control, compared to those who were diagnosed after 40 years[1].

This study focused on examining differences in complications and mortality rates between those with younger-onset diabetes and those with later-onset diabetes over a follow-up period of 30 years. The study analyzed data of 4,550 participants, aged 25 to 65 years, from the UKPDS trial collected between 1977 and 2007. All the participants tested negative for diabetes autoantibodies. Standardized mortality ratios (SMRs) were evaluated against UK general population data, and incidence rates of outcomes were analyzed by 10-year age intervals at time of diagnosis. The predefined outcomes were diabetes-related end points, diabetes-related death, any-cause death, myocardial infarction, peripheral vascular disease, stroke, and microvascular disease.

Out of the 4,550 participants who tested negative to all measured autoantibodies, nearly 10% (n = 429) had younger-onset type 2 diabetes at an average age of 35.1 years, while the remainder had later-onset type 2 diabetes at an average age of 53.8 years,. Nearly 60% of the participants were male and the mean glycated hemoglobin (HbA1c) was 76 mmol/mol.

At the time of diagnosis of type 2 diabetes, participants with younger-onset type 2 diabetes were more likely to be of Asian or Indian ethnicity. They also had a higher mean body mass index or BMI (30.6 kg/m^2 vs. 29.0 kg/m^2), higher proportion of participants with obesity (50.8% vs. 35.2%), lower mean HbA1c (8.7% vs. 9.2%), and higher median fasting triglycerides (1.85 vs. 1.69 mmol/L) versus those with later-onset type 2 diabetes.

Over a median follow-up of 17.5 years, the excess mortality associated with type 2 diabetes compared with the general population was higher in younger-onset type 2 diabetes; the SMRs for younger-onset diabetes was found to be significantly higher (3.72) than those for later-onset diabetes (1.54). Younger-onset diabetes showed higher incidence rates for microvascular disease

(14.5 vs. 12.1 per 1,000 person-years) and worse glycemic control (elevated annual mean HbA1c levels) compared to later-onset type 2 diabetes over the first 20 years.

For those with younger-onset diabetes, the 5-year incidence of diabetes-related outcomes, all-cause mortality including diabetes-related mortality, microvascular disease, and myocardial infarction was higher at any age compared to later-onset diabetes. In participants assigned to either intensive or conventional glycemic control, "no interactions by subgroup of younger-onset versus later-onset type 2 diabetes for any outcome" were observed.

This study demonstrates that the mortality risk is increased nearly fourfold in patients with younger age of onset of type 2 diabetes compared with people with later-onset disease. This heightened risk together with the higher incidence rates of complications and poorer glycemic control emphasizes the need for identification and effective management of these patients.

Reference

1. Lin B, et al. Younger-onset compared with later-onset type 2 diabetes: an analysis of the UK Prospective Diabetes Study (UKPDS) with up to 30 years of follow-up (UKPDS 92). Lancet Diabetes Endocrinol. 2024;12(12):904-14.

Predicting Gestational Diabetes Using Continuous Glucose Monitoring

The continuous glucose monitoring (CGM) parameters have superior predictive accuracy for incident gestational diabetes mellitus (GDM) in early pregnancy compared to the traditional risk model. Additionally, these CGM parameters effectively predicted the likelihood of cesarean deliveries and large-for-gestational-age infants at birth[1,2].

The objective of this study was to assess the potential role of CGM in predicting GDM and related outcomes in the first trimester of pregnancy. The study included pregnant Asian women of multiple ethnicity with overweight or obesity from a hospital-based, prospective cohort. All the study participants wore CGM devices in early pregnancy at 11 to 15 weeks (baseline). They were later screened for GDM at 24 to 28 weeks. Early pregnancy risk factors and CGM-derived parameters were used for models to evaluate and compare how well each could predict GDM and pregnancy outcomes.

Various CGM parameters analyzed included average glucose and glycemic variability parameters such as liability index, mean amplitude of glycemic excursions, mean of daily differences, J-index, % in coefficient variability (% CV)[2].

Results published in the journal *Diabetes Care* show that there were 18 cases of GDM out of a total of 103 participants. Women with GDM showed significantly higher levels in mean glucose, time-above-range duration, and other glycemic variability parameters compared to the non-GDM group[2]. CGM-derived parameters showed strong predictive performance for incident GDM in the early GDM prediction model compared to the traditional risk model (maternal age, baseline BMI and baseline systolic blood pressure) with area under the curve of 0.953 vs. 0.722. Additionally, CGM data was significantly effective in predicting primary cesarean sections and large-for-gestational-age infants.

This study shows that the use of CGM in early pregnancy could be useful for early prediction of incident GDM and adverse outcomes, particularly among pregnant women with overweight or obesity who are at high risk.

References

1. Lim BSY, et al. Utilizing continuous glucose monitoring for early detection of gestational diabetes mellitus and pregnancy outcomes in an Asian population. Diabetes Care. 2024;47(11):1916-21.
2. Lim B, et al. 1239-P: Utilizing continuous glucose monitoring for early detection of gestational diabetes mellitus in a multiethnic Asian population. Diabetes. 2024;73(Supplement_1):1239-P.

Risk of Pulmonary Embolism-Related Mortality in Patients with COPD

Patients, aged 65 to 85 years, with chronic obstructive pulmonary disease (COPD) are at a higher risk of developing fatal pulmonary embolism (PE) and may benefit from individualized, targeted thromboprophylaxis strategies, suggests a study published in the journal *Chest*. These findings were also presented at the CHEST 2024 Annual Meeting, which was held in Boston[1].

In this study, researchers analyzed data on deaths with PE due to any underlying cause. Data was sourced from the Centers for Disease Control and Prevention (CDC)'s WONDER database, covering the period from 1999 to 2020. Their aim was to assess the contribution of COPD to PE-related deaths across different age groups. The participants were categorized into two groups (with or without COPD) whose data were included in the multiple causes of death (MCOD) dataset in the age groups ranging from 35 years to over 100 years. The proportional mortality ratios in the non-COPD group were calculated and applied to the COPD-positive group among different age ranges to estimate

the observed versus expected number of deaths. The observed-to-expected mortality ratio was then derived for each age group.

A total of 10,434 individuals who died from PE with COPD listed as one of the causes of death were identified. Of these, 5,181 were females (F:M 1:1). The peak range of deaths occurred among those aged 75 to 84 years. Analysis showed a statistically significant rise in mortality due to PE among COPD patients aged 65 to 85 years. The ratios of observed-to-expected deaths among these patients were "substantially greater than 1". Patients in the age group 75 to 79 years had the highest risk for PE-related death, with an observed-to-expected ratio of 1.443.

Among patients aged 85 to 89 years, the observed number of deaths (1,189) was nearly identical to the expected number (1,170), with the 95% confidence interval for the observed-to-expected ratio including[1]. This suggests that COPD has a limited effect on PE-related mortality risk in persons aged 85 and older. The risk for death from PE among patients aged 35 to 64 years was not significantly higher for any of the 5-year age categories.

These findings therefore highlight the importance of proactive targeted thromboprophylaxis and tailored management strategies for patients with COPD, aged 65 to 85, due to increased PE mortality, particularly in those within the high-risk age group. The researchers further emphasize that "given the observed trend, individualized patient assessments are imperative to optimize preventable measures against PE in the aging COPD population". However, the contribution of confounding comorbid conditions in the heightened risk of PE-related mortality cannot be totally negated.

Reference

1. Zahergivar A, et al. Age-specific patterns of pulmonary embolism-associated mortality in patients with chronic obstructive pulmonary disease: insights from a retrospective database analysis. Chest. 2024;166(4 Suppl):A4989.

Cardiovascular Benefits of GLP-1 Receptor Agonists in High-Risk Type 2 Diabetes

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) significantly lower the risk of cardiovascular events in high-risk type 2 diabetes patients, especially with combination therapy and in those with chronic kidney disease, according to a systematic review and meta-analysis published online October 26, 2024 in the journal *Diabetology & Metabolic Syndrome*[1]. Although the beneficial effects were evident with monotherapy, their impact was stronger when used as combination therapy, which notably reduced all-cause mortality, cardiovascular death, and heart failure-related hospitalization.

A systematic review and meta-analysis of randomized controlled trials was conducted to evaluate the effect of GLP-1RAs on cardiovascular outcomes in patients with high-risk type 2 diabetes. Following a comprehensive search of PubMed, Embase, Web of Science, and The Cochrane Library databases, nine randomized controlled trials with 63,613 participants, focusing on cardiovascular protection accorded by GLP-1RAs were selected for the meta-analysis.

Analysis of cardiovascular outcomes showed that GLP-1RAs significantly reduced risks for major cardiovascular events. The hazard ratio (HR) for the primary composite outcome was 0.86. The HR was 0.85 for cardiovascular death, 0.87 for all-cause death, 0.90 for myocardial infarction, 0.85 for stroke, and 0.90 for hospitalization due to heart failure. However, the reduction in hospitalization for unstable angina was statistically nonsignificant with HR 1.04. The benefits were most pronounced in patients receiving combination therapy, especially among patients with chronic kidney disease. Based on the GRADE (Grading of Recommendations, Assessment, Development, and Evaluations) system, the evidence quality was rated as "high" for six outcomes, while for unstable angina hospitalization, it was rated as "moderate".

This study reaffirms the cardioprotective effects of GLP-1RAs, such as semaglutide, in general or low-to-moderate risk patients with type 2 diabetes. At the same time, it provides evidence for cardiovascular benefits and safety in high-risk type 2 diabetes patients, particularly those with a history of cardiovascular events or severe chronic kidney disease. Nonetheless, the authors advocate additional research to confirm the long-term effects of GLP-1RAs.

Reference

1. Chen X, et al. Effects of glucagon-like peptide-1 receptor agonists on cardiovascular outcomes in high-risk type 2 diabetes: a systematic review and meta-analysis of randomized controlled trials. Diabetol Metab Syndr. 2024;16(1):251.

IMPACT OF PRE-PREGNANCY ENDOMETRIOSIS ON POSTPARTUM MENTAL HEALTH OUTCOMES

Women with endometriosis are at a significantly higher risk of being diagnosed with psychiatric disorders such as postpartum depression, anxiety, mood disturbance, and obsessive-compulsive disorder (OCD) during the postpartum period, according to a study presented

at the American Society for Reproductive Medicine's 2024 Scientific Congress and Expo in Denver, Colorado[1].

This retrospective matched-cohort study investigated the potential link between endometriosis and the risk of postpartum psychiatric disorders. The research used data from the TriNetX US Collaborative cohort, which is a large, diverse dataset of de-identified electronic health records (EHRs) from around 45 million individuals across over 50 health care organizations in the US.

A total of 28,462 women aged ≥18 years (average age 33.0 years) who had been diagnosed with endometriosis prior to becoming pregnant and delivered between January 2005 and October 2023 were eligible for inclusion in the study. They were matched with a similar number of women without pre-pregnancy endometriosis (n = 28,462). Patients were followed from the time of delivery until the development of any postpartum psychiatric disorder, patients who discontinued and were lost to follow-up or the end of the study.

Women with pre-pregnancy endometriosis had a 31% higher risk of developing postpartum depression compared to women without endometriosis with HR of 1.31. The risk of developing OCD postpartum was 86% higher in women with endometriosis (HR 1.86). A 41% increased risk of mood disturbances postpartum among those with endometriosis (HR 1.41). The risk of postpartum anxiety was increased by 45% (HR 1.45). Comparable associations were found in women without pre-existing depression prior to pregnancy.

By demonstrating a significant association between pre-pregnancy endometriosis and an elevated risk for postpartum depression, OCD, mood disturbances, and anxiety, this study suggests endometriosis as an independent risk factor for postpartum psychiatric disorders. Lack of awareness of this association may worsen outcomes for mothers with these conditions. Hence, women with a history of endometriosis but without known psychiatric disorders should be proactively screened for mental health issues after childbirth. This may help to identify and address potential postpartum psychiatric conditions early thereby supporting maternal mental well-being.

Reference

1. Jin Hsieh TY, et al. Associations between pre-pregnancy endometriosis and postpartum psychiatric disorders. Fertil Steril. 2024;122(4 Suppl):e24.

Central Obesity and Risk for Pelvic Organ Prolapse

Women with central obesity are at a higher risk of incident pelvic organ prolapse. This risk is particularly pronounced in those younger than 60 years of age or do not have a history of hysterectomy. These findings were published online October 24, 2024, in the journal *Obstetrics & Gynecology*[1].

This prospective study was conducted to ascertain the association between central and general obesity and the risk of incident pelvic organ prolapse. A total of 2,51,143 participants, aged 39 to 71 years, without a history of pelvic organ prolapse from the UK Biobank were enrolled for the study between 2006 and 2010. Baseline data for waist/height ratio and BMI. Central obesity was defined as waist/height ratio ≥0.5. Nearly 61% were postmenopausal and 17% had undergone hysterectomy prior to their enrollment for the present study.

Results showed 9,781 cases of pelvic organ prolapse (POP) over the median follow-up duration of 13.8 years. The risk of POP was increased by 48% among participants with central obesity, independent of BMI, with a HR of 1.48. Approximately 21.7% of all POP cases were attributable to central obesity. The risk was 23% higher among women with overweight without central obesity (BMI 25-29.9 and waist/height ratio <0.5) with HR of 1.23. This accounted for 2.0% of all POP cases that were identified in the study. The association between risk of POP and central obesity was stronger among subjects younger than 60 years (vs. ≥60 years) (57% vs. 39%) and those without a history of hysterectomy (54% vs. 27%).

These findings therefore suggest that central obesity and overweight without central obesity are risk factors for POP. Combining waist-to-height ratio with BMI provides a more accurate assessment of risk for POP compared with using either alone. Higher waist/height ratio among women with the same BMI face a greater risk of POP than those with a normal ratio.

Reference

1. Si K, et al. Association of central and general obesity measures with pelvic organ prolapse. Obstet Gynecol. 2024 Oct 24.

Pregnancy Outcomes in Women with Coexisting PCOS and GDM

Polycystic ovary syndrome (PCOS) and GDM alone increased the risks for complications like pre-eclampsia and preterm birth, their coexistence did not significantly amplify the risks beyond those associated with GDM alone, according to a study of over 2,80,000 women published in *Acta Obstetricia et Gynecologica Scandinavica*[1].

Ragnheidur Valdimarsdottir from the Dept. of Women's & Children's Health, Uppsala University in Sweden and

coauthors conducted this study to determine if the coexistence of GDM and PCOS affects maternal and neonatal outcomes.

A total of 2,81,806 women from Sweden who had singleton births between 1997 and 2015 were examined in the nationwide register-based historical cohort study. Of these, 40,272 had only PCOS, 2,236 had only GDM, while 1,036 had both PCOS and GDM. The control group included 2,38,262 women without PCOS or GDM. Postpartum hemorrhage, gestational hypertension, pre-eclampsia, and obstetric anal sphincter injury were the maternal adverse outcomes examined. The neonatal outcomes were preterm birth, stillbirth, macrosomia, low Apgar score, shoulder dystocia, born small or large for gestational age, birth trauma, neonatal hypoglycemia, meconium aspiration syndrome and respiratory distress.

The study found no significant interaction between PCOS and GDM regarding maternal and neonatal outcomes. PCOS alone was associated with an 18% higher risk for pre-eclampsia with adjusted odds ratio (aOR) of 1.18; the aOR for pre-eclampsia in women with GDM alone was 1.77, while it was 1.86 among women who had both PCOS and GDM. The study reported aORs for preterm birth in the groups analyzed; 1.34 in PCOS-only group, 1.64 in GDM-only group and 2.08 in the group with both PCOS and GDM. The risk of stillbirth was increased 1.5 times in women with PCOS (aOR 1.52), but no such risk was observed in women with GDM (aOR 0.58).

Based on these findings, the study concluded that although the coexistence of PCOS and GDM does not multiply the risk, nevertheless PCOS is an underrecognized pregnancy risk factor, as demonstrated by its association with an increased risk of stillbirth, a risk that was not observed with GDM alone.

Reference

1. Valdimarsdottir R, et al. Polycystic ovary syndrome and gestational diabetes mellitus association to pregnancy outcomes: A national register-based cohort study. Acta Obstet Gynecol Scand. 2024 Oct 30.

Could Semaglutide be a Game Changer in Managing Obesity and Osteoarthritis?

Treatment with once-weekly subcutaneous semaglutide in the dose of 2.4 mg significantly reduced body weight and osteoarthritis-related pain and improved physical function in patients with obesity and knee osteoarthritis, according to the results of the STEP 9 trial published in *The New England Journal of Medicine*[1].

This multicenter study was conducted over 68 weeks at 61 sites in 11 countries with 407 adults with a BMI of 30 or higher and moderate-to-severe knee osteoarthritis, which was clinically and radiologically diagnosed. Their mean age was 56 years, the mean BMI 40.3, and the mean Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain score 70.9. Over 80% of the study population was female.

The participants were randomized 2:1 to receive either once-weekly subcutaneous semaglutide (2.4 mg) or a placebo, as adjunct to counseling on low-calorie diet and physical activity for 68 weeks. The primary end points were the percentage change in body weight and change in the 100-point scale WOMAC pain score from baseline to week 68.

Patients treated with semaglutide had a 13.7% reduction in body weight at week 68 compared to just 3.2% decrease in the placebo group with treatment difference of 10.5. Patients treated with semaglutide had greater reduction in pain. The WOMAC pain score was reduced by an average of 41.7 points with semaglutide compared to a reduction of 27.5 points among the placebo recipients (treatment difference -14.2). Semaglutide also improved physical function as evident by greater improvement in the SF-36 physical-function score, a secondary end point of the study, with an average increase of 12 points compared to 6.5 points with placebo.

Nearly 7% in the semaglutide group (vs. 3% in the placebo group) discontinued the treatment due to adverse events, mainly gastrointestinal. The incidence of serious adverse events was comparable between the two groups.

This trial highlights the role of semaglutide as a promising dual therapy for weight management and alleviating symptoms of osteoarthritis. Semaglutide not only reduced pain, it also improved physical function. Hence, by addressing both obesity and pain, semaglutide may be a potential therapeutic option for patients with obesity and knee osteoarthritis with moderate-to-severe pain.

Reference

1. Bliddal H, et al; STEP 9 Study Group. Once-weekly semaglutide in persons with obesity and knee osteoarthritis. N Engl J Med. 2024;391(17):1573-83.