News and Views

Impact of Age on Cushing's Disease

A study published recently in the *Journal of Clinical Endocrinology & Metabolism* has found that older patients with Cushing's disease exhibit fewer classical features of the condition compared to younger patients[1].

The study from the US sought to determine the age-related differences in the clinical presentation, tumor characteristics, and surgical outcomes of Cushing's disease using data from the Registry of Adenomas of the Pituitary and Related Disorders (RAPID), which collects data from 11 sites in the United States. A total of 608 patients who underwent transsphenoidal tumor resection for Cushing disease between 2003 and 2023 were evaluated. The age of the participants ranged from 10 to 79 years; nearly 82.0% of the subjects were female. The median age at the time of surgery was 44 years.

Researchers found that older patients presented with larger tumors, more comorbidities such as hypertension, diabetes, hyperlipidemia, coronary artery disease, chronic obstructive pulmonary disease (COPD). They also faced a higher risk of postoperative complications, including thromboembolic events (deep vein thrombosis or venous thromboembolism).

They exhibited greater frailty and showed higher Knosp grades along with increased postoperative cortisol and adrenocorticotropic hormone (ACTH) nadirs. The Knosp classification is used to assess the likelihood of cavernous sinus invasion in pituitary macroadenomas.

Older patients presented with fewer classical features of Cushing's disease. Older age was also associated with lower preoperative 24-hour urinary free cortisol levels, lower Ki-67 proliferation indices (a marker of cell proliferation; high values indicate greater likelihood of tumor growth and spread) and arginine vasopressin deficiency. Conversely, younger patients presented more frequently with hallmark symptoms such as weight gain, abdominal striae, facial rounding, acne, hirsutism, menstrual irregularities, and dorsocervical fat pad, whereas obstructive sleep apnea and infections were more common with advancing age.

These findings suggest an inverse relationship between age and the hallmark symptoms of Cushing's disease. The age-dependent differences in clinical presentation, tumor behavior, and surgical risks, as observed in this study, reinforce the need for increased clinical awareness when assessing and diagnosing Cushing's disease in elderly patients. Furthermore, it underscores the need for tailored diagnostic and management approaches for different age groups.

Reference

1. Salcedo-Sifuentes JE, et al. Cushing's disease clinical phenotype and tumor behavior vary with age: diagnostic and perioperative implications. J Clin Endocrinol Metab. 2025 Jan 2:dgae904.

Risk Factors for Endometrial Polyps in Asymptomatic Postmenopausal Women

One-third of asymptomatic, postmenopausal women who underwent hysterectomy for uterovaginal prolapse have endometrial polyps, according to a study published in the February 2025 issue of the *American Journal of Obstetrics & Gynecology*[1]. Those using menopausal hormone therapy and women with a higher body mass index (BMI) were particularly at risk for developing these polyps.

This study aimed to determine the prevalence of endometrial polyps in postmenopausal women without symptoms of bleeding and to identify risk factors linked to their occurrence. The study, with a cross-sectional design, examined the prevalence of endometrial polyps in 317 asymptomatic, postmenopausal women who underwent hysterectomy for uterovaginal prolapse. Women who had a hysterectomy for other indications, including postmenopausal bleeding, were not included in the study. Eligible patients received care at a single medical facility in Washington state between 2009 and 2018. The primary outcome was the identification of endometrial polyps through pathology. Risk factors for the presence of polyps were analyzed using both univariate analysis and multivariate regression.

Out of the 317 women included in the study, 106 (33.4%) had endometrial polyps. The average size of the polyps was 13 mm, and the average endometrial thickness was 1.4 mm. The majority (78%) of cases had a single polyp. Two participants (1.89%) were found to have premalignant and malignant lesions; one had endometrial intraepithelial neoplasia and the second had endometrial carcinoma. Baseline clinical and demographic characteristics, such as the

presence of fibroids, endometriosis, and adenomyosis, were comparable between women with and without endometrial polyps.

The likelihood of having polyps was significantly associated with a higher BMI with odds ratio (OR) of 1.06. Similarly, the use of menopausal hormone therapy was associated with greater probability of having endometrial polyps (OR 1.67).

Clinicians should therefore be aware of the possibility of endometrial polyps in postmenopausal women undergoing hysterectomy for uterovaginal prolapse, even in the absence of symptoms. "Although the risk for malignancy seems to be low, more investigation is warranted to truly quantify the lifetime risk" conclude the authors.

Reference

1 Weigel GM, et al. Prevalence of and risk factors for endometrial polyps among asymptomatic postmenopausal women with uterovaginal prolapse. Am J Obstet Gynecol. 2025;232(2):196.e1-196.e6.

Type 2 Diabetes and Fracture Risk: An Under-recognized Complication

Diabetes duration of ≥10 years, glycated hemoglobin (HbA1c) and/or the presence of at least one microvascular complication such as diabetic retinopathy, nephropathy, or neuropathy increase the risk of any fracture, major osteoporotic fractures and hip fractures. These findings from a recent study were published in the journal *Diabetes, Obesity and Metabolism*[1].

The aim of this study was to find out if duration of diabetes, level of glycemic control, and presence of microvascular complications were associated with an increased risk of fractures at specific anatomical sites in patients with type 2 diabetes.

The study examined data of all patients with type 2 diabetes, aged ≥30 years, from the overall Clinical Practice Research Datalink (CPRD) GOLD cohort between 1987 and 2018. Based on the duration of diabetes, patients were categorized as <2 years, 2 to <5 years, 5 to <8 years, 8 to <10 years, and ≥10 years. Also, based on the most recent HbA1c in the year preceding their enrollment in the present study, patients were grouped as <6%, 6% to <7%, 7% to <8%, 8% to <9%, and ≥9%. The primary outcome was the occurrence of a fracture. Major osteoporotic fractures were defined as a fracture of the hip, vertebrae, humerus or the forearm (radius or ulna).

A total of 121,959 participants formed the study group with male preponderance. Their mean age was 63.0 years, the mean BMI was 31.9 kg/m^2, and mean HbA1c was 8.4%.

The risk of any fracture including major osteoporotic fractures was increased among patients who had diabetes for more than a decade with an adjusted hazard ratio (aHR) of 1.16 and 1.14, respectively. Diabetes duration of >8 years was associated with an increased risk of hip fractures compared to the diabetes duration of <2 years (aHR 1.32). HbA1c level of <6% was associated with a higher risk of any fractures (aHR 1.16), major osteoporotic fractures (aHR 1.21) and hip fractures (aHR 1.35) compared to HbA1c levels in the range of 6% to <7%. The risk of any fracture, major osteoporotic fractures and hip fractures was lower in the group with HbA1c between 7% and <8% with aHRs of 0.91, 0.88, and 0.78, respectively versus HbA1c value between 6% and <7%. In the group with HbA1c ≥8%, the risk of fractures was similar to the group with HbA1c between 6% and <7%.

The study also found that the presence of one or two microvascular complications was significantly associated with an increased risk of any fracture (aHR for one microvascular complication) as well as major osteoporotic fractures (aHR for one microvascular complication 1.13). Only the presence of two microvascular complications notably increased the risk of hip fractures (aHR 1.28) compared to patients without any microvascular complications. When associations with individual microvascular complications were evaluated, specifically retinopathy was associated with a higher risk of any fracture, major osteoporotic fractures, humerus, clavicle, and lower leg fractures.

No such associations were found for ankle, scapula, skull or tibia/fibula fractures. These findings demonstrate increased fracture risk associated with poor glycemic control, microvascular complications, and even stringent HbA1c targets. While stricter glycemic control may help in reducing other diabetes-related complications, on the flip side, it might increase susceptibility to fractures. It also emphasizes that patients should be monitored for microvascular complications.

Hence, implementing fracture-prevention strategies, especially in patients with these risk factors, such as optimizing glycemic control without stringent targets, DEXA scanning to measure bone mineral density and management of neuropathy to prevent fall risks may reduce the burden of fractures.

Reference

1. van Hulten V, et al. The association of type 2 diabetes-related characteristics with fracture risk at different sites. Diabetes Obes Metab. 2024;26(11):4887-96.

Can Self-Monitoring of Urinary Na/K Ratio Improve Salt Reduction Efforts?

Self-monitoring with the urinary sodium/potassium (Na/K) ratio meter, ≥3 times in a day, may be effective in lowering salt intake among patients who find it challenging to reduce their salt consumption, according to findings of a single center, nonrandomized controlled study published in the journal *Hypertension Research*[1].

This study examined the effectiveness and feasibility of a self-monitoring intervention in 160 patients with chronic kidney disease, hypertension, or heart disease who find it hard to reduce their salt consumption. A Na/K ratio meter that measured the urinary Na/K ratio was utilized for this purpose. All the selected participants received follow-up care at the outpatient clinic of Dokkyo Medical University Nikko Medical Center in the city of Nikko in Japan.

The 80 participants in the treatment (T) group received the device to measure their urinary Na/K ratio for a mean duration of 25.1 days. They were instructed to measure it for a minimum of thrice daily and keep it below 2.0, while the control group of 80 subjects was not given the Na/K ratio meter. Both groups received salt reduction education and guidance about home blood pressure measurement.

Almost half (48.8%) of the T group patients could achieve three measurements per day over a mean follow-up period of 13 months. Self-monitoring with the urinary Na/K ratio meter led to a significant reduction in salt intake, which decreased by 1.9 g/day by the second visit ($p < 0.001$). No change was evident in the control group.

The Na-to-K ratio is now increasingly being recognized as a more reliable indicator of the risk of cardiovascular diseases (CVD) and CVD-related mortality than measuring either Na or K intake individually.

Urinary Na-to-K ratio has demonstrated a strong predictive value for hypertension and CVD[2] and thus salt intake. It is easier to measure and also obviates the inconvenience of collecting 24-hour urine samples without any loss of urine.

References

1. Shimoyama M, et al. Effects of salt intake reduction by urinary sodium to potassium ratio self-monitoring method. Hypertens Res. 2024;47(7):1852-60.
2. Mirmiran P, et al. Urinary sodium-to-potassium ratio: a simple and useful indicator of diet quality in population-based studies. Eur J Med Res. 2021;26(1):3.

Prognostic Significance of Silent Mucus Plugs in COPD

Nearly 40% of patients with COPD, who are current or former smokers but who do not have the characteristic mucus-related symptoms such as cough, phlegm, have silent airway mucus plugs detected on computed tomography (CT) scan, according to a study published in the journal *Chest*[1].

This study focused on assessing the risk and protective factors as well as the implications of silent airway mucus plugs in patients with clinically diagnosed COPD. Participants from the multicenter COPDGene cohort formed the study group. Chest CT scans were used to quantify the number of pulmonary segments with mucus plugs and calculate the mucus plug score ranging from 0 to 18. Based on the score, the participants were categorized into three groups (0, 1-2, ≥3). Multivariable linear and logistic regression models were used to assess the risk and protective factors for silent mucus plugs and their associations with disease severity.

The total number of participants in the study was 4,363. A subgroup of 1,739 patients did not have cough or phlegm; of these, 627 (36%) were found to have mucus plugs on CT. Older patients (OR, 1.02) and female patients (OR 1.40) were at higher risk of silent mucus plugs than those who had symptomatic mucus plugs. The risk was also higher among Black patients (OR, 1.93).

After adjusting for potential confounders such as age, BMI, and smoking status, the presence of silent mucus plugs among individuals without cough or phlegm (compared to their absence) was independently associated with worse clinical outcomes, which included a shorter 6-minute walk distance, lower resting arterial oxygen saturation, decreased forced expiratory volume in 1 second (FEV1) % predicted, a greater extent of emphysema, increased airway wall thickness, and greater odds of experiencing a severe exacerbation within the past year.

This study has demonstrated a significant association between mucus plugging and poorer functional, structural, and clinical outcomes, suggesting their potential role in disease severity. Mucus plugging is more a consequence of impaired mucus clearance than hypersecretion. Hence, CT scan for mucus plugs should be a part of routine evaluation of COPD patients.

The authors suggest that "airway mucus plugging may be a distinct phenotype of COPD and could be an imaging biomarker". Detection of mucus plugs

in asymptomatic COPD patients warrants careful evaluation and management, as their presence is indicative of more severe disease and worse prognosis.

Reference

1. Mettler SK, et al. Silent airway mucus plugs in COPD and clinical implications. Chest. 2024;166(5):1010-9.

Association Between Hyperglycemia, Diabetes Duration and Heart Failure

Increased levels of HbA1c, fluctuations in HbA1c, and a history of severe hypoglycemia are all significant risk factors for heart failure in patients with type 2 diabetes, suggests a study published September 13, 2024 in the journal *Diabetes, Obesity and Metabolism*[1].

This study from Australia systematically reviewed longitudinal studies investigating the association of glycemic risk factors such as HbA1c, HbA1c variability, hypoglycemia, and diabetes duration with heart failure in patients with type 2 diabetes. The objective was to explore the link between these factors and the risk of heart failure in these patients.

The final analysis included 40 studies involving 4,102,589 participants. Analysis showed a 15% increased risk of heart failure for each 1% increase in HbA1c, a 2% increased risk for each additional year of diabetes and a 43% increased risk for individuals with a history of severe hypoglycemia. A 20%-26% increased risk of heart failure was observed for each unit increase in the metrics of HbA1c variability (HbA1c standard deviation, coefficient of variation, and average successive variability). All included studies scored high in the risk of bias assessment indicating that issues such as selection bias, confounding factors, and reporting bias might have influenced the results. Results from Egger's test showed the presence of publication bias suggesting that studies reporting strong associations between HbA1c levels and heart failure risk were more likely to be published, while those with negative or weaker findings might have been underreported or not reported. After adjusting for publication bias, a 14% increased risk of heart failure per percentage point increase in HbA1c was observed on trim-and-fill analyses.

This study has highlighted the contribution of glycemic risk factors and duration of diabetes to the increased risk of heart failure in patients with type 2 diabetes. Early intervention and proactive management of these risk factors to achieve stable glycemic levels, reducing HbA1c variability and avoiding severe hypoglycemic episodes may minimize the risk and improve patient outcomes.

Reference

1. Tabesh M, et al. The association of glycaemic risk factors and diabetes duration with risk of heart failure in people with type 2 diabetes: a systematic review and meta-analysis. Diabetes Obes Metab. 2024(12):5690-700.

Factors Influencing Adenomyosis Progression

Presence and/or worsening of painful symptoms, such as severe dysmenorrhea, dyschezia and chronic pelvic pain, as well as the presence of focal adenomyosis of the outer myometrium in women with adenomyosis increase the risk of disease progression, according to a study published in the *International Journal of Gynecology & Obstetrics*[1].

This prospective, observational, cohort study was undertaken at a tertiary referral center in Italy to assess the clinical progression of adenomyosis using ultrasound and clinical data over a period of 1 year. Patients diagnosed with adenomyosis via ultrasound from May 2022 to August 2022 were enrolled for the study. Demographic, clinical, and ultrasound data were collected at baseline (T0). Data for these parameters was again gathered at 12 months (T1).

The study group was categorized into two groups based on the progression of adenomyosis at T1: the Progression Group with patients who experienced a significant increase in uterine volume, specifically greater than 20% and the Stability/Regression Group with patients whose uterine volume either decreased or increased by 20% or less at T1. Both groups were similar in terms of baseline data.

In the study, the overall rate of adenomyosis progression, the primary study outcome, was 21.3%, with 47 out of 221 patients showing a significant increase in uterine volume (>20%) at T1. The rate was higher (30.7%) in hormonally untreated women, whereas it was lower (18.3%) in hormonally treated women.

The secondary study outcomes were clinical factors associated with the progression of adenomyosis. Presence of focal adenomyosis of the outer myometrium, moderate to severe dysmenorrhea, chronic pelvic pain, dyschezia, and worsening of chronic pelvic pain were associated with progression of adenomyosis.

This study has identified specific clinical symptoms and features that were linked to a greater likelihood of disease progression over time. Their presence in a patient with adenomyosis might help identify at-risk patients allowing more tailored follow-ups and individualized management strategies. Also, the rate of progression was lower among hormonally treated

women suggesting that hormonal treatment may play a role in reducing the progression of adenomyosis.

Reference

1. Borghese G, et al. Progression of adenomyosis: rate and associated factors. Int J Gynaecol Obstet. 2024;167(1):214-22.

Outcomes of Early PPROM

Around 26% of women with very early preterm prelabor rupture of membranes (PPROM) before 23 weeks of gestation, who received expectant management had children who survived to hospital discharge. However, both maternal and neonatal morbidity and mortality rates were high. These findings from a UK study were published in *BMJ Medicine*[1].

The aim of this prospective observational study was to examine the perinatal and maternal outcomes with PPROM occurring before 23 weeks of gestation. The study was conducted using the UK Obstetric Surveillance System (UKOSS), which comprised a national population-based cohort from all 194 obstetric units in the UK. The study period spanned from September 2019 to February 2021.

A total of 326 women with singleton pregnancy and 38 with multiple pregnancies with PPROM between 16 + 0 and 22 + 6 weeks + days of gestation were selected for the study.

The primary outcome measures for the fetus included live birth, survival to hospital discharge, and serious morbidity, which was defined as either requiring supplemental oxygen at 36 weeks postmenstrual age or experiencing an intraventricular hemorrhage grade 3 or 4, or both. For the mother, the outcomes included sepsis, hospitalization to an intensive care unit, surgery to remove the placenta, and death. Pregnancy termination rates for medical reasons were included in the clinical data.

A worst-best range was computed with the assumption that all terminations for medical reasons and those with missing data would have died (minimum value) or all would have been liveborn (highest value). The researchers calculated the perinatal outcomes with all terminations of pregnancy for medical reasons omitted.

The live birth rate was 44% in the group with singleton pregnancies with rates ranging from 30% to 62%. The perinatal survival rate to hospital discharge was 26%, with a range of 17%-53% and the percentage of newborns that lived without serious morbidity was 18%, with a range of 12%-48%. Maternal sepsis developed in 12% of patients with singleton pregnancies, whereas among those with multiple pregnancies, the maternal sepsis rate was 29%, which was statistically significant with p = 0.004. Twenty percent of women with singleton pregnancy and 16% of those with twin pregnancies required surgery to remove the placenta. Five participants developed severe sepsis; of these, 3 required intensive care, while two passed away.

This study highlights the complexities and challenges associated with expectant management of PPROM, particularly before 23 weeks of gestation. The risk of maternal sepsis is a significant concern in these pregnancies. Hence, the critical need for close maternal monitoring, early detection of chorioamnionitis, timely delivery and proper antibiotic therapy in these patients. The authors emphasize the need for careful counseling of families with PPROM, as well as the importance of updating clinical guidelines based on current data. They further advocate the need for further research in maternal sepsis since it poses a significant risk to both the mother and the newborns.

Reference

1. Goodfellow L, et al. Preterm prelabour rupture of membranes before 23 weeks' gestation: prospective observational study. BMJ Med. 2024;3(1):e000729.

Is 2,500 the New 10,000? Revisiting the Step Goal

Walking as little as 2,500 to 3,000 steps per day yields significant health benefits in terms of reduced mortality and incident heart disease, according to a new research published in the *Journal of American College of Cardiology*[1]. Walking faster adds to the beneficial outcomes[1,2].

This study was a meta-analysis of published evidence (up to October 2022) with the objective to investigate the relationship between daily step counts and adverse outcomes. Twelve studies involving 1,11,309 adults, aged 62.5 years (mean) and comprising 60.8% women were selected for analysis. None of the participants had a history of known heart disease. All-cause mortality and incident heart disease were the primary endpoints of the study. There were 4.4% deaths during a median follow-up period of 77.8 months and 1.4% incident heart disease during 72.9 months of follow-up.

Analysis of data revealed a marked decrease in risk for death due to any cause with a daily step count of 2,517 compared to 2,000 steps per day with aHR of 0.92. The risk of new onset of heart disease was also reduced in participants who took a daily step count of 2,735 compared to 2,000 steps per day with aHR of 0.89.

The risk of all-cause mortality was reduced by 36% among participants who took 6,000 (median) steps per day (vs. median of 3,166 steps per day). The highest risk reduction (50%) was observed for those who took 10,000 (median) steps per day compared to the participants who were least active (median of 3,166 steps per day). Compared with the least active participants, the risk of CVD was lower by 42% among the participants with 6,000 (median) steps per day and by 58% among those with 10,000 (median) steps per day[2].

The risk of all-cause mortality and incident heart disease declined further in a nonlinear manner as step count increased to 8,763 steps per day for all-cause mortality (aHR: 0.40) and 7,126 steps per day for incident heart disease (aHR: 0.49). However, an increase in daily step count further than these had no significant impact on the two study endpoints.

A notable finding of the study was a decline in the risk for all-cause mortality as the step count per minute (cadence) increased from low to intermediate or high. Gender had no impact on the dose-response. The risk of all-cause mortality reduced by further 20% with median step per minute count of 63 and 88 compared to 29 steps per minute. The researchers also examined the impact of devices used to measure step count. They found that risk reduction was significant for hip-worn accelerometers compared with pedometers and wrist-worn accelerometers.

This study has demonstrated a dose-response association of steps per day with clinical outcomes. It has identified the minimum step count and the optimum step count to reduce the adverse health outcomes.

The American Heart Association (AHA) as well as the Centers for Disease Control and Prevention (CDC) recommend a daily step count of 10,000 steps per day for a healthy heart and overall health. This study illustrates that this number is not sacrosanct as the benefits were significant even at a step count of ≥2500, which is less than 10,000 steps per day. Failure to achieve the 10,000-step mark may be disheartening for many. For some, for instance, persons with osteoarthritis, reaching this goal may be a daunting task. The take home message from this study is that it is important to be physically active; even some amount of physical activity is better than none. Hence, all patients must be encouraged to be more active for optimum cardiovascular health. Walking, and brisk walking at that, is the simplest, most inexpensive and an effective form of exercise.

"Although step volumes beyond this level were not associated with additional health benefits, there is no reason to discourage individuals from such behavior, as a highly physically active lifestyle may provide other benefits, such as joy, improved quality of life, and better sleep and mental health," write the authors[2].

References

1. Stens NA, et al. Relationship of daily step counts to all-cause mortality and cardiovascular events. J Am Coll Cardiol. 2023;82(15):1483-94.
2. TCTMD News. Available at: https://www.tctmd.com/news/mortality-cvd-benefits-seen-relatively-low-daily-step-counts, dated Sept. 8, 2023. Accessed October 6, 2023.

Predictors of Hemoptysis in Nontuberculous Mycobacterial Pulmonary Disease

Patients with nontuberculous mycobacterial pulmonary disease (NTM-PD), who have a history of tuberculosis (TB), high C-reactive protein (CRP) levels, and reduced % predicted forced vital capacity (FVC) are at a greater risk of developing clinically significant hemoptysis, which is associated with an increased likelihood of all-cause mortality.

This study assessed the incidence of clinically significant hemoptysis, the risk factors contributing to hemoptysis and its association with all-cause mortality in 506 patients with NTM-PD. Data for patients enrolled in a prospective observational cohort study between July 2011 and May 2023 was analyzed in the present study.

Results showed that 43 patients (8.5%) experienced clinically significant hemoptysis, requiring interventions like bronchial artery embolization or surgical resection, with an incidence rate of 2.1 cases per 100 person-years.

The major risk factors identified included a past history of TB (incidence rate ratio [IRR] 1.91), elevated CRP levels (IRR, 1.20 per 1 mg/dL increase), and lower % predicted FVC (IRR, 0.81 per 10% increase). Of note, clinically significant hemoptysis was associated with a higher risk of all-cause mortality (aHR, 2.39).

This study has identified risk factors for clinically significant hemoptysis in patients with NTM-PD. It also suggests clinically significant hemoptysis as a potential risk factor for mortality in these patients underscoring its implications for patient outcomes. These findings highlight the need for early identification and management of at-risk patients to improve survival rates.

Reference

1. Hyung K, et al. Clinically significant hemoptysis and all-cause mortality in patients with nontuberculous mycobacterial pulmonary disease. Respir Med. 2025;237:107946.