NCD Newsletter

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# 20% DIABETICS GO BLIND, SUFFER KIDNEY FAILURE, NERVE DAMAGE

One out of five patients with diabetes in the country has complications affecting the body's small blood vessels that could eventually lead to kidney failure, blindness or severe nerve damage, says an all-India study that followed up over 6,000 patients for over three years.

The study, which was recently published in the peer-reviewed medical journal, 'Endocrinology, Diabetes & Metabolism', focused on management of diabetes after a patient was diagnosed and put on medication.

In real-world settings, we found people couldn't achieve the level of control they wanted and, hence, complications related to diabetes were high," said Dr Shalini Menon, one of the authors of the study.

Diabetes, a chronic health condition that affects how the body turns food into energy, is known to affect one's heart, nerves, kidneys, eyes, foot, among other organs. The study, which was sponsored by a pharma major, found that the patient pool had other health problems other than diabetes - around 60% were obese and 80% had hypertension and six of 10 had high levels of cholesterol, suggesting a higher risk of heart attacks. "The study recorded 54 deaths due to cardiovascular disease in these three years," said the doctor.

Senior endocrinologist and author of the study, Dr Shashank Joshi, said the main finding of the study was the poor A1c test results. The A1c blood test measures one's average blood sugar levels over the past three months. "There seems to be some inertia in hitting hard and hitting early," he said, pointing to poor medicine schedules.

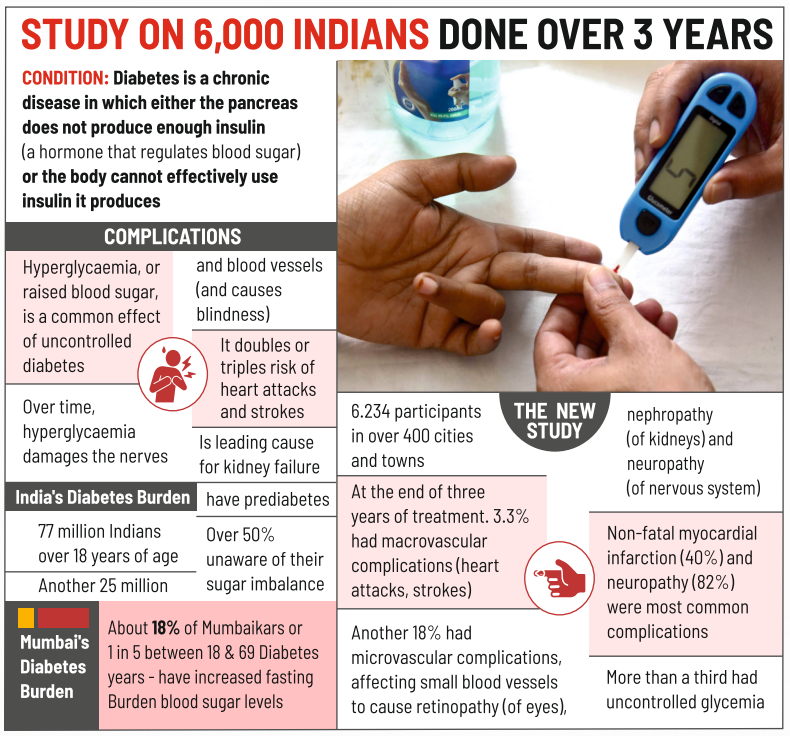
Dr Joshi said non-fatal myocardial infarction, or heart attacks, was reported in 40% of patients while neuropathy was the most common complication.

Dr Tushar Bandgar, head of the endocrinology department at KEM Hospital, Parel, and wasn't associated with the study, said the real problem with diabetes lay with changing lifestyles and poor prevention strategies.

"The number of diabetes cases in the country is only increasing. This reflects the fact that we are not doing enough on prevention," he said. "If there are more cases of diabetes, there are bound to be more complications. It is not as if there are not adequate drugs. It is just a matter of poor control and prevention," he said.

While diabetes affected barely 3% of the population until three decades back, it now affects almost 9% of India's adult population. "People are eating more and have picked up addictions such as tobacco or alcohol," he said.

Dr Joshi added that those with diabetes not only have to check their eyes and heart function once a year, they also have to check for albumin in urine and lipid levels every three months. "People also need to exercise, diet and sleep adequately," he added.



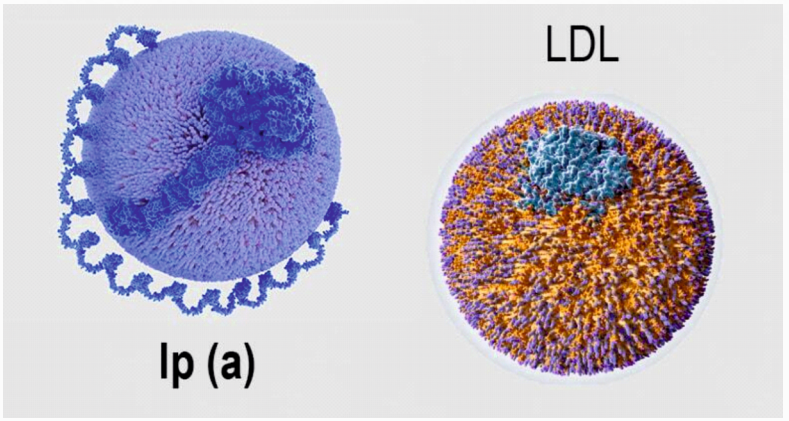

## Lp(a) Packs a More Powerful Atherogenic Punch Than LDL

A UK Biobank analysis confirms that LDL is more abundant and drives most ASCVD risk, but Lp(a) carries a powerful punch.

Lipoprotein(a), the low-density lipoprotein (LDL)-like particle that is currently the focus of so much enthusiastic research, is significantly more atherogenic than LDL cholesterol, according to a genetic analysis and a second corroboratory study.

While LDL cholesterol particles are much more abundant than Lp(a), and as such remain the biggest contributor to atherosclerotic cardiovascular disease (ASCVD) risk, Lp(a) is more than six times more atherogenic than LDL on a per-particle basis, report Elias Björnson, PhD (University of Gothenburg, Sweden), and colleagues in a study published online ahead of the January 23, 2024, issue of the Journal of the American College of Cardiology.

"Our data, what it really shows us and what we're trying to emphasize, is that LDL cholesterol is still the most important risk factor, but there are several risk factors in addition to LDL cholesterol," senior investigator Jan Borén, MD, PhD (University of Gothenburg), told TCTMD. "And Lp(a) is a very important risk factor."




The search for a drug that lowers Lp(a) and reduces the risk of ASCVD has been likened to the Holy Grail in contemporary prevention circles. It's an attractive target for physicians, researchers, and drug manufacturers because it's highly genetically determined and large observational studies, including genetic analyses, have shown that higher levels are linked with ASCVD and calcific aortic valve disease.

There are several small-interfering RNA (siRNA) therapies in development that target LPA, the gene that encodes for apolipoprotein(a), which is an essential component needed by the liver to make Lp(a). These include the injectables lepodisiran (Eli Lilly), olpasiran (Amgen), and zerlasiran (Silence Therapeutics),

as well as an oral small molecule inhibitor, muvalaplin (Eli Lilly), in early testing. Pelacarsen (Novartis/Ionis Pharmaceuticals), an antisense oligonucleotide (ASO) is furthest along in development, with data from the Lp(a) HORIZON cardiovascular outcomes study expected in 2025.

"A lot of focus has been on LDL cholesterol for many, many years," said Borén. "We know that lowering our total plasma cholesterol has been very successful in lowering the risk of myocardial infarction. However, even though we have [patients] at optimal LDL cholesterol values, we still have a highly significant residual risk of cardiovascular disease. Many people have been working trying to explain what lipoproteins account for the residual risk."

That research has focused on the role of triglyceride-rich lipoproteins, their remnants, and Lp(a), he added.

**"LDL cholesterol is still the most important risk factor, but there are several risk factors in addition to LDL cholesterol."**

According to Borén, it's vital to understand the atherogenicity of the different lipoproteins relative to LDL cholesterol when developing new interventions, but Lp(a) remains a challenge for several reasons. For one, it's difficult to accurately gauge its plasma concentration because of calibration issues with different assays. The field has been hampered by these technical difficulties, as well as by the fact that there are different Lp(a) isoforms, which makes it hard to calculate the genetic variant effect sizes on Lp(a).

**Comparing Apples to Apples**

To overcome these issues, researchers took a different approach and focused on apolipoprotein B (apoB) instead. Lp(a) is formed by the addition of apo(a) to apoB on LDL particles. LDL cholesterol, Lp(a), and other remnant particles each contain one molecule of apoB: this allowed investigators to relate the change in apoB to the respective change in coronary heart disease risk.

"We would then compare apoB in LDL versus apoB in Lp(a), comparing apples to apples instead of apples to something else," said Borén.

The study population included 502,413 people enrolled in the UK Biobank study. In a genome-wide association study, researchers identified two clusters of genetic variants associated with Lp(a) and LDL cholesterol concentrations. These included 107 single nucleotide polymorphisms (SNPs) associated with Lp(a) concentrations and 143 SNPs linked to LDL cholesterol concentrations. In these two clusters, they assessed the relationship of genetically predicted variations of apoB in the Lp(a) and LDL particles with coronary heart disease (MI and coronary revascularization).

They found that the odds of a coronary event were 28% higher for every 50-nmol/L increase in apoB levels in Lp(a). In contrast, each 50-nmol/L increase in apoB in LDL cholesterol was associated with a 4% higher risk. A replication analysis from a case-control study confirmed the finding, showing a higher risk for coronary heart disease with each 50-nmol/L increase for apoB in Lp(a). Similarly, a polygenic risk that ranked individuals according to differences in apoB in Lp(a) versus apoB in LDL cholesterol showed that the hazard of coronary heart disease was significantly higher with every 50-nmol/L increase in apoB in Lp(a).

The researchers also assessed the relative per-particle atherogenicity for Lp(a) compared with LDL cholesterol. The relative atherogenicity-assessed as the coronary heart disease risk quotient-was 6.6 times higher per unit of apoB in Lp(a) compared with apoB in LDL cholesterol. In the case-control replication cohort, Lp(a) appeared to be nearly four times more atherogenic.

A second study published in JACC and led by Nicholas Marston, MD, MPH (Brigham and Women's Hospital, Boston, MA), tackled a nearly identical question, with researchers estimating the cardiovascular risks associated with Lp(a) versus the non-Lp(a) apoB-containing particle.

Here, Marston and colleagues turned to patients without preexisting ASCVD in the UK Biobank who were not taking lipid-lowering therapy and who had apoB and Lp(a) measurements. In 355,912 participants (mean age 56 years; 57.0% women), each 100-nmol/L increase in non-Lp(a) apoB was associated with a 5% higher risk of major cardiovascular events. In contrast, each 100-nmol/L increase in Lp(a) was associated with a 24% higher risk.

**Potency of Lp(a)**

To TCTMD, Borén stressed that LDL cholesterol is the more abundant particle and is responsible for the largest extent of patient risk, but the present study helps understand the contribution of Lp(a) on a per-particle basis.

Right now, there aren't a lot of strong data to explain why Lp(a) is such a potent particle when it comes to ASCVD. He noted that apo(a) in the Lp(a) particle carries oxidized phospholipids, which are not present on the LDL particle. Basic science and animal models have suggested that oxidized phospholipids are an important driver of atherosclerotic plaque formation.

In an editorial, Sotirios Tsimikas, MD (University of California San Diego, La Jolla, and Ionis Pharmaceuticals), and Vera Bittner, MD, MSPH (University of Alabama at Birmingham), said the study by Borén and colleagues overcomes some of the complexities associated with measuring Lp(a), but these results will need to be confirmed in other databases, particularly those with a more diverse patient population with and without ASCVD. Another limitation is that plasma Lp(a) concentrations can be influenced not just by variants at the LPA locus, which the researchers studied, but also at APOE, LDLR, CETP, and APOH, which weren't studied.

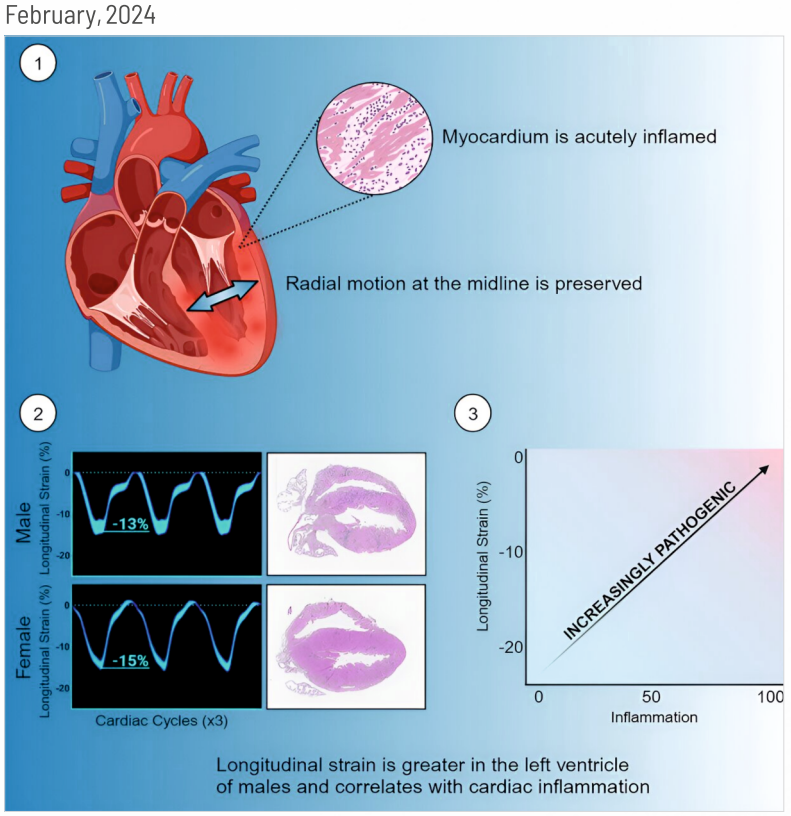
Still, Tsimikas and Bittner, based on the relative atherogenicity of the two particles, estimate that an Lp(a) concentration of 250 nmol/L would be akin to an LDL cholesterol level of 100 mg/dL. Moreover, they calculate, if the Lp(a)-lowering therapies are to achieve a 20% relative reduction in ASCVD risk, they'd need to cut Lp(a) levels by 32 to 101.5 mg/dL (or 80 to 254 nmol/L).

"This level of reduction is feasible with all RNA-based Lp(a) drugs in development," they write.

## MEDICAL DEVICES

### 1. New 4D imaging may detect poor pumping in deadly heart disease

February, 2024




Mayo Clinic researchers have unveiled a groundbreaking 4D echo imaging method that stands to revolutionize the detection and management of acute myocarditis, a serious and often fatal heart disease. Published in iScience, the study reveals how this innovative technology measures cardiac strain, providing a nuanced understanding of heart dysfunction during myocarditis.

The novel 4D echo imaging method for measuring cardiac strain proves beneficial for patients with myocarditis in several ways:

- **Early Detection:** The technology allows for early detection of subtle changes in heart function during acute myocarditis, enabling timely intervention and treatment.
- **Sex-Specific Insights:** By identifying sex differences in cardiac strain, the device offers a personalized approach to understanding and managing myocarditis, considering the distinct risks and manifestations in men and women.
- **Prediction of Heart Failure:** The ability to predict which patients are more likely to suffer from heart failure provides valuable information for clinicians, enabling proactive measures and specialized care for those at higher risk.

- **Assessment of Treatment Efficacy:** The device aids in assessing the effectiveness of novel treatments and drugs, facilitating faster and more accurate evaluation in preclinical models before translating to human trials.
- **Mitigation of Long-Term Damage:** Early assessment using cardiac strain allows for prompt treatment, potentially mitigating long-term, irreversible heart damage in patients with myocarditis.
- **Improved Clinical Outcomes:** The findings emphasize the importance of considering sex differences in cardiac function, contributing to more tailored and effective clinical approaches for patients with suspected myocarditis.

## 2. PALMAZ MULLINS XD Pulmonary Stent

The PALMAZ MULLINS XD Pulmonary Stent is a stainless-steel mesh tube that can be placed inside a narrowed pulmonary artery (blood vessel in the lung) and expanded to widen it.

**How does it work?**

The stent is compressed and placed on a small, thin tube with a deflated balloon at the tip called a balloon catheter. It is then inserted through a person's skin into a blood vessel in the groin. Together, the catheter and stent are guided to the inside of the narrowed location of the pulmonary artery. The balloon is then inflated to expand the stent against the pulmonary artery wall, which widens the narrowed part of the artery. The balloon is then deflated, and the catheter is removed from the body. The stent permanently stays in the body to hold the vessel open.

**When is it used?**

The PALMAZ MULLINS XD Pulmonary Stent is used to reopen a narrowed pulmonary artery in children who weigh at least 10 kg (22 lb.) and have two ventricles (pumping chambers) in their heart.

**What will it accomplish?**

The PALMAZ MULLINS XD Pulmonary Stent widens a narrowed pulmonary artery. In a clinical study of 108 patients, 103 patients (95.4%) had at least a 50% increase in pulmonary artery diameter after the stent was implanted and the stent placement decreased pressure in the pulmonary artery, reducing how hard the heart must work to move blood to the lungs.

**When should it not be used?**

The stent should not be used in people:

- Who have an active infection.
- Who have an aneurysm, dissection, or in-situ thrombus (blood clot) formation at the treatment site.
- In whom there is an inability to cross the narrowed vessel segment safely.
- Who have a vessel too small for the delivery system.

# FDA APPROVALS

## FDA approves the first and only medicine for children and adults with one or more food allergies

February 16th, 2024

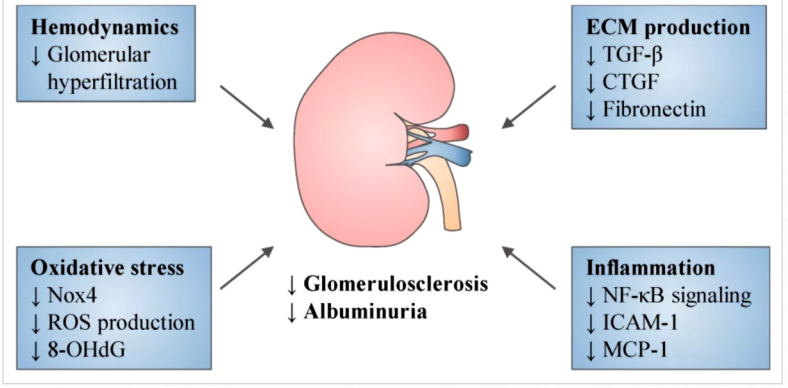
On February 16, 2024, the FDA approved Xolair® (omalizumab) for the reduction of allergic reactions, including anaphylaxis, that may occur with accidental exposure to one or more foods in adult and pediatric patients aged 1 year and older with IgE-mediated food allergy. People taking Xolair for food allergies should continue to avoid all foods they are allergic to (commonly referred to as "food allergen avoidance"). Xolair should not be used for the emergency treatment of any allergic reactions, including anaphylaxis.


**Highlights:**

- Xolair is the first and only FDA-approved medicine to reduce allergic reactions in people with one or more food allergies.
- The approval is based on data from the NIH-sponsored Phase III OUtMATCH study, which showed a significantly higher proportion of food allergy patients as young as 1 year treated with Xolair could tolerate small amounts of peanut, milk, egg and cashew without an allergic reaction, compared to placebo.
- Immunoglobulin E (IgE) mediated food allergies are the most common type and are typically characterized by the rapid onset of symptoms following exposure to certain food allergens.
- About 3.4 million children and 13.6 million adults in the United States have been diagnosed with IgE-mediated food allergies, based on estimates for 2024.
- Safety findings were consistent with the known safety profile of Xolair across its additional indications and in previous clinical trials.

# TRIAL UPDATES

## 1. SGLT2 Inhibitors may slow progression of Diabetic Retinopathy: JAMA




Diabetic nephropathy and diabetic retinopathy share many similarities in pathophysiological processes. Preclinical studies have shown that sodium-glucose cotransporter 2 inhibitors (SGLT2is) have a protective role in the risk of diabetic retinopathy.

A study was done to compare the risk of sight-threatening retinopathy associated with SGLT2is and other second-line glucose-lowering medications (including pioglitazone, sulfonylureas, and dipeptidyl peptidase-4 inhibitors [DPP-4is]) in patients with type 2 diabetes (T2D).

This cohort study in Taiwan applied a new-user and active-comparator design. Patient demographic and clinical data were obtained from the National Health Insurance Research Database. Adult patients with newly diagnosed T2D from January 1, 2009, to December 31, 2019, were recruited and followed up until December 31, 2020. Propensity score matching was used to identify pairs of patients treated with SGLT2i vs DPP-4i, SGLT2i vs pioglitazone, and SGLT2i vs sulfonylurea from January 1, 2016, to December 31, 2019. Data were analyzed between August 18, 2022, and May 5, 2023.

The main outcome was sight-threatening retinopathy in participants. Cox proportional hazards regression models were used to assess the relative hazards of sight-threatening retinopathy between the matched case and control groups.

**Results**

A total of 3,544,383 patients with newly diagnosed T2D were identified. After 1:1 propensity score matching, 65 930 pairs of patients treated with SGLT2i vs DPP-4i, 93 760 pairs treated with SGLT2i vs pioglitazone, and 42 121 pairs treated with SGLT2i vs sulfonylurea were identified. These matched patients

included 236 574 males (58.6%), with a mean (SD) age of 56.9 (11.8) years. In the matched cohorts, SGLT2i had a significantly lower risk of sight-threatening retinopathy than DPP-4i (adjusted hazard ratio [AHR], 0.57; 95% CI, 0.51-0.63), pioglitazone (AHR, 0.75; 95% CI, 0.69-0.81), and sulfonylureas (AHR, 0.62; 95% CI, 0.53-0.71). The Kaplan-Meier curves showed that SGLT2i was associated with a significantly lower cumulative incidence of sight-threatening retinopathy than DPP-4i (3.52 vs 6.13; P <.001), pioglitazone (4.32 vs 5.76; P <.001), and sulfonylureas (2.94 vs 4.67; P <.001).

This cohort study found that SGLT2i was associated with a lower risk of sight-threatening retinopathy compared with DPP-4i, pioglitazone, and sulfonylureas. This finding suggests that SGLT2i may play a role not only in reduced risk of diabetic nephropathy but also in the slow progression of diabetic retinopathy in patients with T2D.

## 2. Tirzepatide: A 'Rising Star' in T2D Renal Protection

A meta-analysis showed that all doses of tirzepatide, a novel twincretin molecule, reduced albuminuria levels without affecting renal function in patients with type 2 diabetes (T2D).

**METHODOLOGY:**

- A meta-analysis of eight randomized controlled trials compared the effects of tirzepatide and control treatment (placebo or any active comparator) on albuminuria levels and renal function in patients with T2D.
- The pooled data included 6226 patients with T2D who received tirzepatide (5, 10, or 15 mg) and 3307 participants in the control group who received placebo, semaglutide, or insulin.
- The primary outcome was the difference in absolute change in urinary albumin-creatinine ratio (UACR) from baseline between the tirzepatide and control groups.
- The secondary efficacy endpoint was the comparative change in estimated glomerular filtration rate (eGFR) between the two groups.

**TAKEAWAY:**

- Overall, tirzepatide reduced UACR by ~27% (mean difference [MD], −26.9%; P < .001) compared with controls.
- The reduction in UACR was consistent across all tirzepatide doses (5 mg: MD, −23.12%; 10 mg: MD, −27.87%; 15 mg: MD, −27.15).
- Benefits of tirzepatide were even more pronounced in patients with increased albuminuria levels (UACR ≥ 30 mg/g) at baseline (MD, −41.42%; P < .001) than in controls.
- However, tirzepatide vs control treatment did not have a significant effect on eGFR levels (P = .46), which indicated no negative effect of tirzepatide on renal function.

**IN PRACTICE:** Tirzepatide seems to be a 'rising star' for the prevention and delaying of chronic kidney disease and related, surrogate renal outcomes in patients with T2DM," the authors wrote.

**SOURCE:**
Paschalis Karakasis, MD, Aristotle University of Thessaloniki, Thessaloniki, Greece, led this study, which was published online on December 20, 2023, in the journal Diabetes, Obesity and Metabolism.

## 3. SGLT2 Inhibitors use tied to lower risk of kidney stones in patients with type 2 diabetes:

The use of SGLT2 inhibitors in adults with type 2 diabetes (T2D) may lower nephrolithiasis risk compared with GLP-1 receptor agonists or DPP4 inhibitors, a recent study has revealed.

The study findings, published in JAMA Internal Medicine, may help inform decision-making when prescribing glucose-lowering agents for patients at risk for developing nephrolithiasis.

The cohort study comprised 1 378 462 commercially insured adults with T2D initiated treatment with sodium-glucose cotransporter 2 inhibitors (SGLT2is), glucagon-like peptide 1 receptor agonists, or dipeptidyl peptidase 4 inhibitors.

Those initiating SGLT2i treatment had a lowered risk of developing nephrolithiasis compared with those initiating the other two treatments.

There has been an increasing prevalence of kidney stones worldwide. Kidney stones are associated with substantial costs, cardiovascular disease, kidney function decline, and fractures. Type 2 diabetes is associated with an elevated risk of kidney stones.

SGLT2 inhibitors, a newer class of glucose-lowering agents with demonstrated renoprotective and cardiovascular benefits in clinical trials, might lower the risk of nephrolithiasis by altering urine composition and increasing urine volume. However, no studies have investigated the association between SGLT2i use and nephrolithiasis risk in patients receiving routine care in the US. To fill this knowledge gap, Julie M. Paik, Brigham and Women's Hospital, Boston, Massachusetts, and colleagues aimed to investigate the association between SGLT2i use and nephrolithiasis risk in clinical practice.

For this purpose, they conducted a new-user, active comparator cohort study using data from commercially insured adults (aged ≥18 years) with type 2 diabetes who initiated treatment with GLP-1 receptor agonists, SGLT2 inhibitors, and DPP4 inhibitors between 2013 and 2020.

The primary outcome was nephrolithiasis diagnosis by the International Classification of Diseases codes in the outpatient or inpatient setting. New users of SGLT2 inhibitors had a 1:1 propensity score matched to new users of DPP4 inhibitors or GLP-1 receptor agonists in pairwise comparisons. Incidence rates, rate differences (RDs), and estimated hazard ratios (HRs) were calculated.

After 1:1 propensity score matching, 716 406 adults with T2D initiating an SGLT2i or a GLP-1RA (mean age, 61.4 years for both groups; 51.4% versus 51.2% female; 48.6% versus 48.5% male) and 662 056 adults initiating an SGLT2i or a DPP4i (mean age, 61.8 vs 61.7 years; 47.4% versus 47.3% female; 52.6% vs 52.7% male) were included.

**The study led to the following findings:**

- Over a median follow-up of 192 days, the risk of nephrolithiasis was lower in patients initiating an SGLT2i than among those initiating a GLP-1RA (14.9 vs 21.3 events per 1000 person-years; HR, 0.69; RD, -6.4) or a DPP4i (14.6 vs 19.9 events per 1000 person-years; HR, 0.74; RD, -5.3).
- The association between SGLT2i use and nephrolithiasis risk was similar by sex, race and ethnicity, history of chronic kidney disease, and obesity.
- The magnitude of the risk reduction with SGLT2i use was larger among adults aged younger than 70 years versus those aged 70 years or older (HR, 0.85; RD, −3.46 per 1000 person-years).

These results suggest that nephrolithiasis risk could be a consideration when deciding among glucose-lowering agents for patients with type 2 diabetes," the researchers concluded.

**Reference:** Paik JM, Tesfaye H, et.al., Sodium-Glucose Cotransporter 2 Inhibitors and Nephrolithiasis Risk in Patients With Type 2 Diabetes. JAMA Intern Med.

## 4. Comparable clinical outcomes of radial artery grafts versus right internal mammary artery grafts during CABG, suggests study

A recent study published in the American Heart Journal compared the radial artery (RA) versus the right internal mammary artery (RIMA) as a second conduit during coronary artery bypass grafting.

The researchers revealed that RIMA and RA conduits for coronary artery bypass grafting (CABG) were associated with comparable 5-year major adverse cardiac and cerebrovascular events (MACCE), immediate postoperative complications, and 5-year survival after propensity score matching (PSM).

CABG remains the gold standard for treating obstructive atheromatous disease within the coronary arteries, with excellent short- and long-term postoperative outcomes. A left internal mammary artery (LIMA) graft is standardly used in revascularization of the left anterior descending coronary artery, however, there has been no clarity on the consensus on the best secondary conduit for additional grafting.

Eishan Ashwat, Division of Cardiac Surgery, Department of Cardiothoracic Surgery, University of Pittsburgh, and colleagues aimed to compare the clinical outcomes of radial artery grafts during CABG to those of the right internal mammary artery grafts.

For this purpose, they conducted a retrospective, single-institution cohort study of isolated CABG with multiple grafts between 2010-2022. PSM was performed using a 1:1 match ratio to balance graft cohorts.

Long-term postoperative survival was compared among RA and RIMA groups. Similarly, MACCE were compared among both cohorts, with MACCE comprising myocardial infarction (MI), death, stroke, and coronary revascularization. Kaplan-Meier estimation was performed for mortality, while cumulative incidence estimation was used for MACCE.

8,774 patients underwent CABG. Of those, 1,674 patients who underwent multi-arterial CABG were included in the analysis. 326 patients received RA grafts, and 1,348 received RIMA grafts.

**The study led to the following findings:**

PSM yielded a cohort of 323 RA patients and 323 RIMA patients.

After matching, groups were well-balanced across all baseline variables.

There were no significant differences in immediate postoperative complications or long-term survival, with 5-year survival estimates of 89.5% for the RA group versus 90.1% for the RIMA group.

There was a non-significant trend toward a higher incidence of MACCE at 5 years in the RA group compared to the RIMA group (31.3% in the RA group versus 24.1% in the RIMA group), especially after 1-year follow-up (21.6% in the RA group versus 15.1% in the RIMA group).

For RA patients, there were higher rates of repeat revascularization in the 5-year postoperative period (14.7% in the RA group versus 5.3% in the RIMA group), particularly in the territory revascularized by the RA during the index operation (45.7% in the RA group versus 10.3% in the RIMA group).

"The findings showed that RA and RIMA secondary conduits for CABG were associated with comparable deep sternal wound infection, operative mortality, 5-year survival, and 5-year MACCE," the researchers wrote.

**Reference:** Reference:Ashwat, E. et.al,. Radial Artery versus Right Internal Mammary Artery as a Second Conduit during Coronary Artery Bypass Grafting. American Heart Journal.

## CASE STUDY - 1

### Acromegaly with retinitis pigmentosa: A rare association

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**ABSTRACT**

Acromegaly or gigantism is a disorder of excess growth hormone. Most common etiology is Pituitary Adenoma which is detected on MRI. Visual disturbances are common in these macroadenoma due to compression of optic chiasma. Unusual findings like Rubeosus Iridis and Retinitis Pigmentosa are very rarely described in this disorder. We hereby present similar case with these findings in a patient first time diagnosed as GH secreting Pituitary tumor.

**Introduction**

Retinal pigmentary changes have been described as an isolated entity and alongside many other endocrine disturbances as early as 1972 by J.M. Smail. Lawrence -Moon- Beidl Syndrome also dictates similar association of Retinitis Pigmentosa and endocrine disorders such as obesity and hypogonadism. Literature is sparse regarding association of Acromegaly and Retinitis Pigmentosa which we have described in this case report.

**Case Report**

We encountered a 47-year-old male patient, resident of district Ratlam in Central India, who presented with complaints of chronic headache, chronic cough and diminished visual acuity. On initial examination his vitals were within normal limits. Physical features favouring gigantism including frontal bossing, macroglossia, enlarged extremities and prognathism were obvious. (Figure 1)

Endocrine workup revealed normal Thyroid and Gonadotropin levels and surprisingly normal serum Prolactin levels too. Growth hormone levels and IGF-1 assays could not be processed due to unavailability at our centre. Other laboratory parameters were within normal limits except HbA1c in prediabetes range. MRI revealed Pituitary Macroadenoma with indentation of Optic Chiasma superiorly and bilateral Internal carotids laterally. (Figure 2)

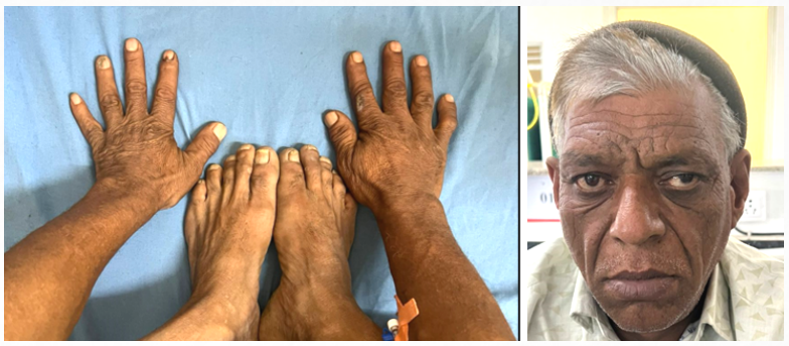

Figure 1. Coarse facial and limb features of gigantism

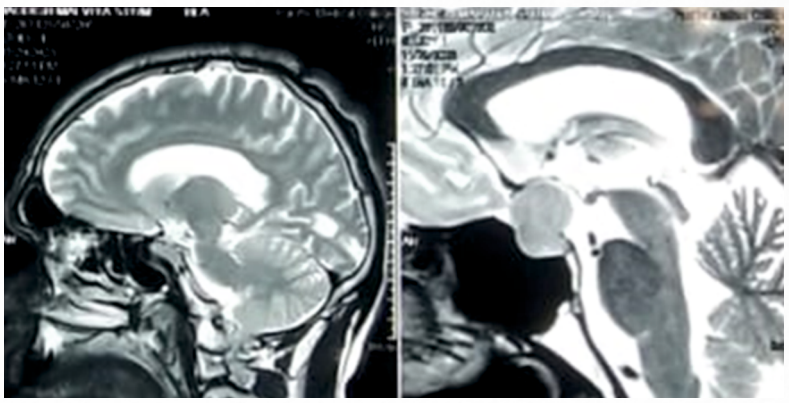

Figure 2. MRI pituitary showing Macroadenoma with suprasellar extension

Ocular examination revealed Bilateral inferolateral lenticular displacement along with Rubeosus Iridis. Bilateral fundus examination revealed primary pigmentary changes of Retinitis Pigmentosa. (Figure 3)

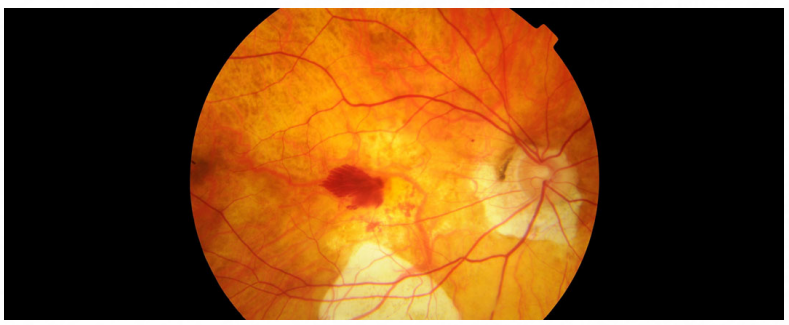

Figure 3. Fundus photograph with retinal degenerative and pigmentary changes

Left eye had no vison and right eye only tubular vision was present on visual field charting. (Figure 4)

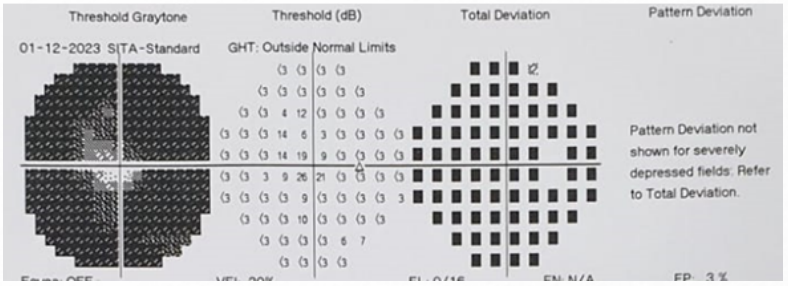


Figure 4. Perimetry showing restricted tubular vision in Rt eye

Patient was thus advised for immediate Neurosurgical intervention in view of imminent vision loss and referred to specialist centre for the same. He was lost to follow up thus postoperative evaluation is still pending.

**Discussion**

GH secreting pituitary adenoma is rare amongst all pituitary tumors. Due to excessive IGF-1 and IGFBP-3 levels neovascularisation is often seen in various body tissues. Similar changes are also seen in eye as Severe proliferative retinopathy and Iris neovascularisation. It is a well known clinical entity and is also seen in our patient as Rubeosus iridis.

What is not well described is retinal changes in the form of pigmentary degeneration along with pituitary tumours. There are some scattered case reports of the same in patients with Acromegaly and Chromophobe adenoma. We thus found this unusual association in our patient and felt the need for reporting it. Histological reports are still awaited and we cannot deny the likelihood of Chromophobe adenoma causing Acromegaly in this patient. It might also be an association by chance. Thus we need more literature and case reports with similar findings to correlate both the clinical findings. Diminished visual acuity in this patient can be attributed both to the retinal changes and direct chiasmal compression. However repeat perimetry in postoperative follow up is required to assess the same.

**Summary**
Pituitary macroadenoma causing Acromegaly and Retinal Pigmentary changes is an unusual finding. GH secreting pituitary tumours and retinal changes may be an association by chance or involvement of MSH secreting cells in pituitary. Detailed histologic examination of the pituitary tumour mass is thus the answer to the above mystery.

## CASE STUDY - 2

### Atypical extrapyramidal manifestation of atypical antipsychotic with serotonergic antidepressant

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**Introduction**
Typical antipsychotics being antidopaminergics are known to produce extrapyramidal side effects such as drug induced parkinsonism, acute dystonia, akathisia and tardive dyskinesias. Rabbit syndrome(RS) is another extrapyramidal condition that affects patients on antidopaminergic therapies. Around 2.3-4.4% of patients on typical antipsychotics may develop this condition though isolated reports of RS exist with atypical antipsychotics and antidepressant drugs. Rabbit syndrome is characterized by vertical rhythmic motion of the mouth and lips, resembling chewing movements of a rabbit. The onset of RS is usually late and occurs within months to years of underlying therapy. The movements seen are rapid, involuntary, occur at a frequency of nearly 5Hz and are usually in the vertical plane. Characteristically, tongue is spared in cases of RS, a feature that distinguishes it from tardive dyskinesias.

**Reason for the report**
To report the case of an elderly male on haloperidol and escitalopram who presented with atypical form of RS with relatively acute onset jaw tremor with horizontal movements and with conspicuous tongue involvement causing confusion in the diagnosis.

**Case presentation**
A 65-year-old man with newly diagnosed hypertension presented with abnormal movements of the jaw and tongue of 7 days duration, hampering his daily activities, and causing social embarrassment. Drug history revealed that he was taking amlodipine 10mg daily for hypertension, haloperidol 0.25mg twice daily and escitalopram 10mg daily for insomnia for the past two months on the advice of a local medical practitioner. The course of the movements during sleep or under stress could not be confirmed as the patient lived alone. On examination, movements of around 5Hz frequency and rhythmic in nature were present in the perioral area. Similar frequency tremor was evident in tongue. Bradykinesia and rigidity were absent and there was no involvement of the trunk or extremities. Remaining neurological and other system examination were normal. In view of an extrapyramidal syndrome caused by haloperidol and absence of features of depression or anxiety, haloperidol was stopped, and oral trihexyphenidyl 2mg thrice daily was started. The patient improved significantly in 10 days-time. Trihexyphenidyl was eventually stopped after 3 weeks and clonazepam 0.5mg on as needed basis was started for insomnia.

**Discussion**
The differentials considered in the current case were Rabbit syndrome (RS) and tardive dyskinesias (TD). The tongue is spared in classic cases of RS though rare cases of RS with lingual involvement exist. The condition improves dramatically after drug discontinuation and administration of central anticholinergics. Dopaminergic drugs are generally not useful in Rabbit Syndrome. Rabbit syndrome is often confused with tardive dyskinesias involving the orolabial region. In contrast to Rabbit syndrome, orolabial tardive dyskinesias are slower, less rhythmic, involve the tongue, and may have truncal and limb involvement. Onset of TD is also delayed, occurring after months to years of antipsychotic therapy, but the condition worsens with use of anticholinergics as opposed to Rabbit syndrome. In the present case, the high frequency rhythmic chewing-like movement and rapid response to trihexyphenidyl administration closely resembled Rabbit syndrome. However, movements had a relatively acute onset and occurred within seven weeks of initiation of haloperidol, were more in the horizontal plane and were associated with tremors in tongue. Drug-induced Parkinsonism (DIP) was considered as another possibility in this case, but DIP usually starts within days to months of antipsychotic use and has other features such as bradykinesia and rigidity, which were absent in the present case. Rabbit syndrome has clinical similarity with drug induced bruxism which is characterized by clenching of jaw, tooth grinding, jaw pain, jaw spasm, facial pain, headaches, and sleep disorders. Other than jaw tremor causing tooth grinding, no other feature suggestive of bruxism was present in the patient. Drug induced bruxism has been associated classically with anticonvulsants and antidepressants particularly the selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine and sertraline, though cases exist with dopamine blockers also. The condition usually requires cessation of culprit drug or addition of other neurological drugs with partial agonistic action on 5-HT1a receptors, such as buspirone. No report to our knowledge exists of improvement of SSRI associated bruxism with trihexyphenidyl. Though the patient in present case was taking escitalopram which can mechanistically induce bruxism, the same was however not discontinued and the condition improved with trihexyphenidyl suggesting SSRI induced bruxism to be less likely in this case. The exact pathogenesis of Rabbit Syndrome or similar extrapyramidal syndromes is unclear but disturbances in the movement circuits of basal ganglia in the form of acute dopamine blockade have been projected as possible mechanisms. Among drugs received by the patient, chances of development of RS are more with haloperidol. The drug is a potent conventional antipsychotic agent with increased propensity to cause dopamine receptor blockade. However, the patient was also taking the antidepressant escitalopram which works via inhibition of serotonin reuptake and has alone been implicated in a few cases of rabbit syndrome. The drug has been associated with isolated tongue tremors which resolve spontaneously without drug discontinuation as was observed in the present case. The third drug the patient had been on in the same time frame was amlodipine which is a L type calcium channel blocker, anti-hypertensive agent. Although otherwise safe, it has been associated with rare cases of new onset tremors mimicking DIP. The association of amlodipine with rabbit syndrome and tongue tremors is not known at present. Though escitalopram and amlodipine were not stopped, a possibility of pharmacodynamic drug interaction with haloperidol resulting in atypical extrapyramidal manifestations cannot be excluded. Though the patient in the current case did not have features completely matching any of the discussed extrapyramidal syndromes, the high frequency rhythmic chewinglike movement and rapid response to trihexyphenidyl administration more closely resembled Rabbit syndrome. The early onset of symptoms after two months of haloperidol therapy, movements more in the horizontal plane and the associated tongue involvement were atypical features of the case. The tongue involvement was believed to be secondary to escitalopram use.

**Outcome**
The syndrome resolved after discontinuation of haloperidol. Tongue tremor with serotonergic drugs resolves spontaneously as was noticed in this case.

**Conclusion**
Typical antipsychotic drugs such as haloperidol can produce atypical extrapyramidal features with concomitant serotonergic antidepressants. A thorough drug history of neurological as well as non-neurological drugs should be taken to delineate any synergistic or additive interaction that increases the vulnerability of an individual towards atypical extrapyramidal symptoms.

## CASE STUDY - 3

### Wandering large left atrial thrombus

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**Introduction**
Rheumatic heart disease (RHD) is still prevalent in developing countries. Left atrium (LA) thrombus is associated with RHD having varying clinical presentation. We report a case of mobile left atrial mass in middle aged women as a presenting feature of RHD.

**Case study**

A 42-year-old lady presented with exertional dyspnea and palpitations since 2 months. She did not have any past history of heart disease. Clinical examination revealed a severely breathless patient, electrocardiogram was suggestive of atrial fibrillation (AF) with fast ventricular response. She had a loud pulmonary component of second heart sound with mid diastolic murmur at the apex. Echocardiography and color Doppler study showed severe calcific rheumatic mitral stenosis (MS) with mild mitral regurgitation, moderate tricuspid regurgitation and moderate pulmonary arterial hypertension (Calculated Pulmonary artery systolic pressure was 50 mmHg). In addition, there was large spherical mass in the LA cavity, which was moving freely throughout the left atrium like a pinpong ball. (Fig. 1a & b). In view of perceived risk of embolism, the patient was referred for urgent surgical intervention. While being prepared for surgery she developed mild facio-brachial weakness secondary to cardioembolic stroke. During surgery spherical, smooth, 12 g mass was found in LA with no attachment to the LA wall (Fig. 1c). In addition, there was a layered thrombus in LA (Fig. 1d). The mass and clot were removed and mitral valve was replaced with metallic prosthesis (Medtronic 29 mm). Histopathological examination of the mass confirmed the diagnosis of thrombus (Fig. 1e).

**Discussion & Conclusion**

LA thrombus inpatients with RHD isusually seen withs evere MS in a dilated LAand/orAF. It is seen in 17% of patients with severe MS, and the risk doubles with AF. Most of the thrombi are seen in LA appendage, but in 2% of cases it may extend to LA body. Although LA thrombi are quite common in MS with AF, the presence of free floating mass is quite unusual. Usually, the free floating thrombi are small in size, ball-shaped and have endothelial-like superficial layer, which reduce the propensity to aggregate platelets and therefore, rarely cause systemic thromboembolism. In our case, although echocardiographic features of mass like smooth, spherical and echogenicity were more in favor of myxoma, but histopathological examination showed hemorrhagic tissue consistent with finding of thrombus. Hence, it might be speculated that the mass was initially attached to LA wall but subsequently got detached. Due to the risk of systemic embolism, emergent surgery should be the norm in such cases.

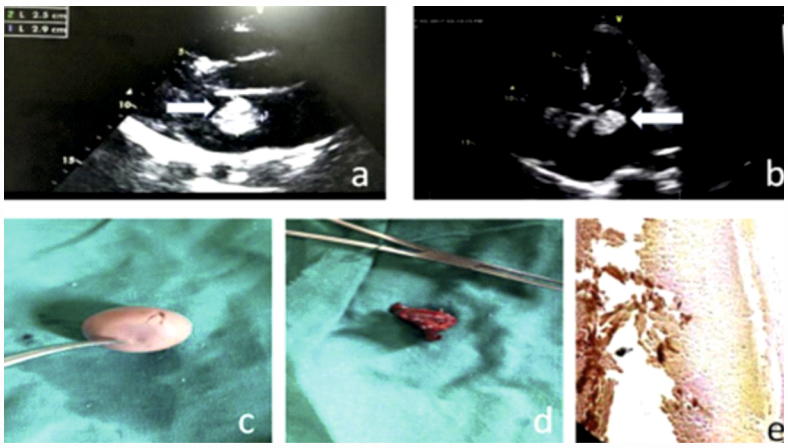


Fig. 1.
a. Parasternal long axis echocardiographic view showing (white thick arrow) large wandering mass in left atrium free from wall.
b. Apical four chamber view showing (white thick arrow) ball and valve phenomenon caused by mass.
c. Smooth spherical 12 g mass removed during surgery.
d. Layered thrombus in LA.
e. Histopathological examination of mass confirmed thrombus.

Bansal M et al described a case of mobile large LA thrombus in case of RHD who had undergone balloon mitral valvuloplasty. The patient underwent surgery, which confirmed the mass to be a large thrombus. Open mitral commissurotomy was performed along with removal of the thrombus, and the patient had an uneventful recovery. Darwazah AK et al reported case of a middle aged woman with rheumatic MS with history of successful closed mitral valvotomy. On examination, a hugely enlarged LA occupied by a thrombus was demonstrated by transthoracic echocardiography. Surgery was performed and a huge organized thrombus was removed and mitral valve was replaced with St. Jude Medical valve 31-mm.

Aoyagi S reported a case of LA thrombus with normal mitral valve in a patient who had nephrotic syndrome and AF. They related the occurrence of thrombus to the hypercoagulable state associated with the nephrotic syndrome and AF. Nosaka S et al described a similar case of LA thrombus in a case of myocardial infarction and AF. Oryoji A et al and Ohkado A et al also reported similar cases with AF. Most of the reported cases had underlying atrial fibrillation or coagulation disorders and the symptoms were related to thromboembolism. Echocardiography especially transesophageal echo is very sensitive in detecting the free floating nature. We would like to emphasize that large mobile LA thrombi rarely may be found on echocardiography in newly diagnosed cases of RHD without any previous history, hence a high index of suspicion and appropriate evaluation helps in reaching correct diagnosis and management in these cases. A few case reports of mobile LA thrombus in RHD have been reported already, but rarely this has been reported in a newly diagnosed case of RHD.

## CASE STUDY - 4

### Marfan Syndrome: A case report

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**Introduction**

Marfan syndrome is a complex and hereditary connective tissue disorder with diverse clinical manifestations affecting multiple organ systems, primarily the cardiovascular, skeletal, and ocular systems. Named after the French pediatrician Antoine Marfan, who first described the condition in 1896, Marfan syndrome arises from mutations in the FBN1 gene, leading to defects in the production and structure of fibrillin-1, a critical component of the extracellular matrix.

This syndrome exhibits considerable variability in its presentation, making diagnosis challenging. However, characteristic features often include tall stature, long limbs, joint hypermobility, and a predisposition to certain cardiovascular abnormalities such as aortic root dilatation, aortic dissection, and mitral valve prolapse. Skeletal manifestations may include scoliosis, chest wall deformities, and arachnodactyly, while ocular involvement commonly encompasses lens dislocation, myopia, and retinal detachment.

Despite its rarity, Marfan syndrome holds significant clinical importance due to its potential for life-threatening cardiovascular complications, particularly aortic dissection, which remains a leading cause of morbidity and mortality in affected individuals. Early diagnosis and comprehensive management are crucial to mitigate these risks and optimize patient outcomes.

**Case Presentation**

A 21-year-old male presented with symptoms of palpitations and exertional dyspnea. The patient exhibited typical features of Marfan syndrome including tall stature, joint laxity, and cardiovascular abnormalities such as aortic root dilation and aortic regurgitation. Vital signs showed sinus tachycardia with a pulse rate of 100 beats per minute and blood pressure of 120/60 mmHg. ECG demonstrated left ventricular hypertrophy. Echocardiography revealed cardiomegaly with significant left ventricular enlargement and a markedly dilated aortic root measuring 53.9 mm, along with a large reverse flow jet into the left ventricle indicative of aortic regurgitation. CT aortic angiography confirmed gross dilation of the aortic root with a maximum diameter of 6.7 cm. These findings were consistent with Marfan syndrome.

Figure 1: Wrist hypermobility

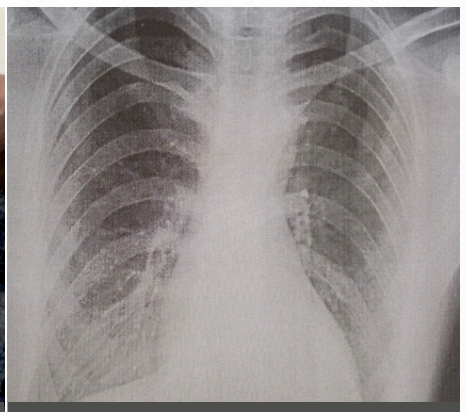


Figure 2: Chest X-ray

**Investigations and Diagnosis**

Diagnostic evaluation included 2D echocardiography with color Doppler, which revealed left ventricular enlargement, aortic root dilation, and aortic

regurgitation. Measurements of interventricular septum thickness (IVS) and posterior wall thickness (PWLV) were consistent with concentric hypertrophy. The aortic root diameter, left atrial diameter (LA), left ventricular end-diastolic diameter (LVEDd), and left ventricular end-systolic diameter (LVESd) were significantly enlarged. Left ventricular mass was elevated, and left ventricular ejection fraction (LVEF) was within normal limits. These findings, along with the clinical presentation, led to a diagnosis of Marfan syndrome.

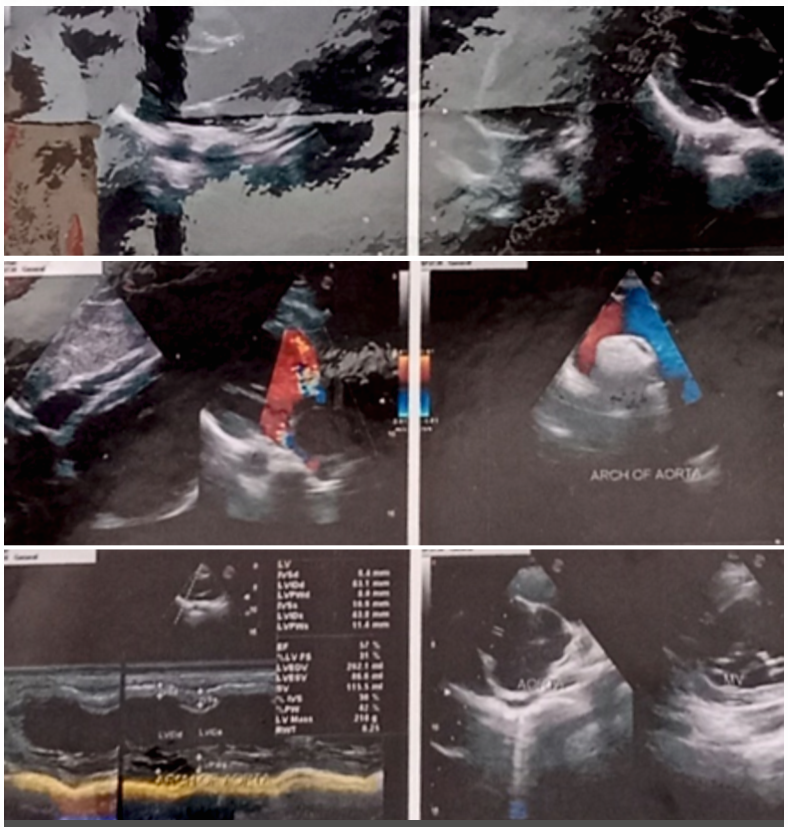



Figure 3: Echocardiographic findings of a dilated aortic root

**Management**

Management of Marfan syndrome involves a multidisciplinary approach aimed at addressing cardiovascular complications and optimizing patient outcomes. Here the patient was prescribed with Tab (Metoprolol Succinate (25mg) + Ramipril (2.5mg)) and Tab {Furosemide (20mg) + Spironolactone (50mg)} ½ biweekly. Regular cardiac monitoring with echocardiography is essential to assess aortic dimensions and function, with consideration for surgical intervention in cases of severe aortic dilation or dissection risk. Additionally, orthopedic evaluation is necessary to address skeletal abnormalities and joint laxity, while ophthalmologic assessment is important for monitoring and managing ocular manifestations.

**Conclusion**

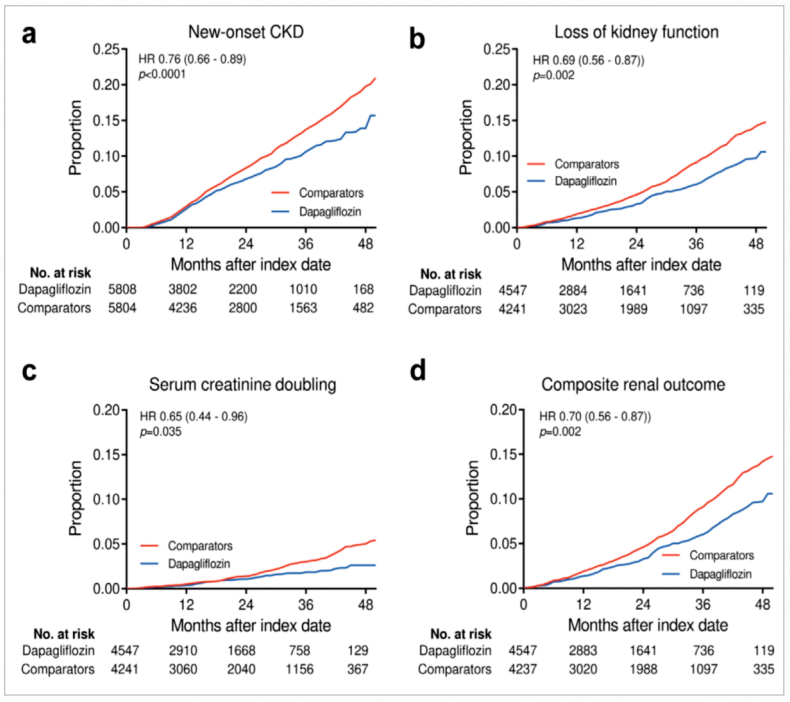
Marfan syndrome presents with characteristic cardiovascular manifestations, including aortic root dilation and aortic regurgitation, which require prompt recognition and management to prevent life-threatening complications. This case highlights the importance of a comprehensive diagnostic approach involving clinical examination, ECG, echocardiography, and imaging studies for accurate diagnosis and appropriate management of Marfan syndrome. Early intervention and multidisciplinary care are essential to improve patient outcomes and quality of life in individuals with Marfan syndrome.

## For the kidneys of patients with type 2 diabetes, long-term protection with dapagliflozin

The DARWIN-Renal Study highlighted that the use of dapagliflozin compared to other classes of diabetes drugs protects the kidneys already within 6 months of starting treatment The results of the clinical study published in The Lancet Regional Health Europe.

In a groundbreaking revelation for the treatment of Type 2 diabetes, the DARWIN-Renal Study has demonstrated the remarkable efficacy of dapagliflozin in safeguarding renal function. Over a span of two and a half years, dapagliflozin showcased a significant reduction in the decline of estimated glomerular filtration rate (eGFR), a crucial indicator of renal filtering capacity, compared to other drug classes available for diabetes treatment, including GLP-1 receptor agonists.

The study, spearheaded by the Italian Society of Diabetology (SID), marks a milestone as the first and largest real-world comparative study in Italian diabetology. Angelo Avogaro, President of SID, underscores the study's findings as pivotal for diabetes management, emphasizing dapagliflozin's potential in curtailing the onset of chronic kidney disease. Notably, dapagliflozin exhibited a remarkable 24% reduction in the relative risk of new-onset chronic kidney disease and a 31% decrease in the loss of kidney function compared to alternative diabetes medications.




Professor Gian Paolo Fadini, the coordinator of the project and a distinguished expert in Endocrinology at the University of Padua, sheds light on the comprehensive nature of the DARWIN RENAL study. Involving 50 specialized diabetes centers across Italy and encompassing over 12 thousand individuals with Type 2 diabetes, the study yielded compelling evidence in favor of dapagliflozin's renal protective effects.

Moreover, Raffaela Fede, Medical Director of Astrazeneca Italy, underscores the collaborative effort between Astrazeneca and SID, highlighting the DARWIN project's extensive scientific contributions. The findings elucidate dapagliflozin's pivotal role in preserving renal health in individuals with Type 2 Diabetes, even in those at low renal risk, thus offering unprecedented renal protection.

The study's data underscore the importance of early intervention with dapagliflozin, showcasing greater protection against the decline in renal function, elevated levels of albuminuria, and adverse renal outcomes leading to dialysis and transplantation. Notably, the study indicates that only 22 subjects would require treatment with dapagliflozin for five years to prevent a composite renal endpoint, further solidifying its status as a cornerstone in diabetes management.

In essence, the DARWIN-Renal Study heralds a new era in diabetes care, emphasizing dapagliflozin's indispensable role in preserving renal function and mitigating the risk of chronic kidney disease. Thanks to the collaborative efforts of Italian researchers and the robust scientific endeavors of SID and Astrazeneca, individuals with Type 2 diabetes can now look forward to enhanced renal protection and improved health outcomes.

## Most commonly misdiagnosed medical conditions

The prospect of misdiagnosing a patient's medical condition will put a lump in any doctor's throat. However, the error seems remarkably common, with some estimates pegging misdiagnoses among 12 million Americans, or 1 in every 20 patients, each year. Let's take a look at some commonly misdiagnosed conditions.

**Stroke**

Failure to diagnose stroke quickly can lead to lost opportunity to initiate time-sensitive treatments.

In 2% to 26% of patients, stroke is underdiagnosed (ie, false-negative cases or "stroke chameleons"), and in 30% to 43% of patients, stroke is overdiagnosed (ie, false-positive cases or "stroke mimics").

**Common stroke mimics include:**

- Migraine
- Epileptic seizures or postictal states
- Psychogenic disease or conversion disorder
- Toxic-metabolic abnormalities (eg, hyperglycemia and systemic infection)
- Demyelinating disease

Because atypical stroke presentations, including posterior circulation stroke syndromes, are often misdiagnosed, additional efforts are needed to improve diagnoses in these cases. According to the authors of one review article: "Additional strategies to improve the accuracy of stroke diagnosis should focus on rapid clinical reasoning in the time-sensitive setting of acute ischemic stroke and identifying imperfections in the healthcare system, which may contribute to diagnostic error."

In other words, physicians should be on the lookout for stroke, because time is of the essence.

**Irritable bowel syndrome**

Irritable bowel syndrome (IBS) is marked by altered bowel habits with abdominal pain devoid of an organic pathological process or specific motility/structural abnormalities. Change in bowel habits, with diarrhea, constipation, or both, is the main symptom in IBS. This condition is the most common reason for referral to a gastroenterologist.

**Symptoms of IBS with diarrhea can be mistaken for:**

- Dietary causes (eg, alcohol, lactose, sorbitol, fructose, caffeine, fatty foods, fat substitutes, and gas-producing foods)
- Inflammatory bowel disease (eg, Crohn's disease or ulcerative colitis)
- Malabsorption (eg, celiac disease)
- Drug toxicity (eg, antibiotics, NSAIDs, and ACE inhibitors)
- Infections
- Ovarian cancer
- Endometriosis
- Colorectal cancer
- Carcinoid

**The differential diagnosis for IBS with constipation includes:**

- Dietary causes (eg, lack of fiber)
- Immobility
- Drug toxicity (eg, opiates, antidepressants, and calcium-channel blockers)
- Neurological (Parkinson's disease, multiple sclerosis, and spinal cord injuries)
- Endocrine disease (eg, diabetes, hypothyroidism, and hypercalcemia)
- Colorectal cancer
- Ovarian cancer
- Bowel obstruction
- Diverticular disease

**Carpal tunnel syndrome vs thoracic outlet syndrome**

When presenting with shoulder pain, carpal tunnel syndrome (which involves impingement of the median nerve at the wrist) can easily be confused with thoracic outlet syndrome. However, the co-occurrence of these two syndromes in a single patient is extremely rare.

Thoracic outlet syndrome is a constellation of disorders marked by abnormal compression of arterial, venous, or neural structures in the base of the neck. Symptoms rarely develop until adulthood, and typically result from impingement of the brachial plexus. They include pain, paresthesia, and numbness. Symptoms of ischemia and venous compression secondary to compression of the subclavian artery are uncommon and may predict emboli.

**Systemic lupus erythematosus vs rheumatoid arthritis**

Systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) are both systemic autoimmune diseases that attack the body, leading to inflammation and tissue damage. The pathogenesis and mechanisms of SLE and RA, however, are not fully known.

Due to the similarity of symptoms, differentiating and treating these diseases is challenging. In the early stages of disease, 80% of patients with SLE or RA have fever and fatigue, making it difficult to distinguish these diseases at this point. However, researchers of one study showed that in the middle to late stages of these conditions, complement C3 and C4 levels were significantly decreased in patients with SLE, while patients with RA had heightened CRP levels.

**Lyme disease**

Lyme disease, which is caused by the spirochete Borrelia burgdorferi, is the most common vector-borne illness in the United States. It is also difficult to diagnose because symptoms are often nonspecific, and clinical presentation varies based on the stage of the illness.

Presentation can include erythema migrans, carditis, central nervous system disease, and arthritis. Despite clinical presentation, most patients with Lyme disease are cured of clinical symptoms following 2 to 4 weeks of treatment with antimicrobials.

Even the diagnosis of erythema migrans, which is pathognomonic for Lyme disease, can sometimes be challenging because the rash doesn't always appear, or it may be confused with an insect bite, ringworm, cellulitis, nummular eczema, or granuloma annulare.

However, rapid and prolonged extension of erythema migrans when left untreated helps to separate this characteristic rash from differential causes of rash.

On a related note, other causes of carditis include viral agents, specifically Coxsackie enteroviruses. The differential diagnosis for arthritis is long and includes bacterial septic arthritis, and rheumatologic and oncologic processes. Many physicians erroneously believe that nonspecific symptoms in patients, such as arthralgias and fatigue, call for antibody testing for Lyme disease. Indeed, most patients who receive the test do so under these circumstances. Antibody tests for Lyme disease, however, can be highly nonspecific and yield many false positives, thus resulting in unnecessary treatment.

**Multiple sclerosis**

The misdiagnosis of multiple sclerosis (MS) is an important issue among neurologists, with MS specialist neurologists frequently encountering patients who have received misdiagnoses of MS-sometimes for 10 or more years.

Although a large number of rare genetic, metabolic, vascular, and inflammatory disorders are often posited as part of the differential diagnosis for MS, the conditions most often mistaken for it are common: migraine, fibromyalgia, and functional neurologic disorders. These alternative diagnoses are based on MRI scans done to investigate white matter lesions.

The misdiagnosis of MS can have serious repercussions, including exposure to MS disease-modifying agents, which can result in patient harm, as well as litigation.

On a final note, with a diagnosis of exclusion, misdiagnosis is a common pitfall. For example, IBS is a diagnosis of exclusion, which means that it can only be diagnosed when everything else on the list of differential diagnoses is ruled out. Other examples of diagnoses of exclusion include panic attack, diastolic heart failure, Bell's palsy, anorexia tardive (ie, later-life anorexia), phantom tooth pain, Alzheimer's disease, functional vision loss, psychogenic cough, hypertensive encephalopathy, chronic bronchitis, and pyoderma gangrenosum.

## The 5 most curious medical stories of 2023

**Can Brain Bleeds Be Contagious?**

Recipients of blood donated by someone who later experienced multiple brain bleeds, a condition closely associated with cerebral amyloid angiopathy, are three times more likely to suffer brain bleeds themselves. This raises the possibility of an unknown infectious agent being involved. The findings are from an analysis of records of more than a million people in Sweden and Denmark who received a blood transfusion between 1970 and 2017. While there are currently no preventive measures in place, "this article seems to be a warning. At this point, the probability has shifted strongly away from cerebral amyloid angiopathy being a purely random disease and is leaning towards it being an infectious disease. It may be time to identify some of the unusual suspects", said F. Perry Wilson, an epidemiology master and professor of medicine at Yale School of Medicine in New Haven, United States, who was not involved in the study.

**Nobel Laureate Who Turned Explosives into Medicine Dies**

Dr Ferid Murad, the American physician and pharmacologist who won the Nobel Prize in 1998 for discovering that nitroglycerine and other vasodilators act by releasing nitric oxide gas, passed away on September 4 at the age of 86.

The transformation of nitroglycerine from an explosive agent to a cardiovascular drug, saving millions of lives, is one of the most curious stories in medicine. Discovered by the Italian physician and chemist Ascanio Sobrero in the 1840s, nitroglycerine was stabilised and then turned into dynamite by Alfred Nobel, a fact that Sobrero always regretted. Nitroglycerine's entry into medicine can be attributed to homeopaths who began prescribing it in low doses for headaches based on Sobrero's observations, noticing it lowered blood pressure instead of relieving headaches; and 19th century workers handling dynamite, who noticed it alleviated chest pain. From the late 1870s, William Murrell and Fancourt Barnes promoted the use of nitroglycerine and amyl nitrate for angina, a practice that expanded during the early decades of the 20th century.

**Impostor Syndrome Is Common With Doctors**

Impostor syndrome, a psychological construct characterised by a persistent belief that personal success is undeserved and not due to one's own effort, skills, or abilities, is a common phenomenon among doctors, especially during transition periods such as entering medical school, starting a residency, or facing a new professional challenge, wrote Dr Paolo Spriano, a medical editor and member of the National Training Society for General Practitioners in Italy. Studies suggest that the phenomenon is associated with burnout and interferes more in the lives of paediatricians and emergency physicians than in other specialists. Strategies to mitigate it include sharing concerns with trusted colleagues, combating perfectionism, and practising self-compassion.

**Unexpected Pathogens: Infection After Iguana Bite and Python Parasitic Worm in the Brain**

Mycobacterium marinum was identified in a painful lesion of a 3-year-old American girl bitten on the hand by an iguana 5 months earlier during a vacation in Costa Rica, with no apparent major consequences. The bacterium is a slow-growing nontuberculous mycobacterium with an incubation period of up to 9 months and is found in freshwater and saltwater. The literature had reported that the bacterium causes opportunistic infections in humans who swim, work in aquariums, or have fish tanks, but never from bites. Meanwhile, neurosurgeons in Australia made an unusual discovery while conducting an open brain biopsy on a 64-year-old patient who had an abnormal image detected in the right frontal lobe. They found a live 80 mm-long helminth, Ophidascaris robertsi, an intestinal nematode parasite of the carpet python (Morelia spilota). It is believed that the woman may have ingested larval eggs from wild vegetables she collected and consumed without prior cooking in an area where this snake species resides. Both patient were successfully treated, as reported in separate articles in Emerging Infectious Diseases.

**Smart Necklaces Prevent Drownings and Help Quit Smoking**

The era of necklaces serving solely as ornaments has come to an end. A US emergency physician, Dr Graham Snyder, conceived and developed a child's necklace (SEAL SwimSafe) that triggers an alarm when it remains submerged in water for too long. It has already been used to protect more than 10,000 children in swimming pools. Drowning is the leading cause of death in children aged 1 to 4 and the second leading cause in those aged 5 to 14. Meanwhile, US scientists designed a device that attaches to the neck, detects smoking events (like lighting a cigarette or taking a puff) and promotes smoking cessation interventions for users identified as at higher risk of relapse, such as by sending text messages with recommendations.

## HEALTHY LIVING

### 1. Hair Loss Confirmed to be Another Risk of Smoking

**TOPLINE:** Men who smoke are more likely to develop and experience progression of male-pattern hair loss (androgenetic alopecia).

**METHODOLOGY:**

- Investigators undertook a systematic review and meta-analysis using data of 4462 men from eight observational studies conducted in Europe, Asia, and Oceania.
- The main outcomes were the incidence and progression of male-pattern hair loss according to smoking status.

**TAKEAWAY:**

- Relative to men who had never smoked, those who had ever smoked were 82% more likely to develop male-pattern hair loss ($P < .05$).
- There was also a suggestion of a dose effect whereby men who smoked heavily (at least 10 cigarettes daily) had 96% higher odds of developing the condition than peers who smoked less heavily ($P < .05$).
- Among men with male-pattern hair loss, the odds of progression from stage I-III to stage IV-VII were 27% higher in ever-smokers vs never-smokers ($P < .05$).
- Smoking intensity was not significantly associated with disease progression.

**IN PRACTICE:**

"Findings from the current study - which is the first meta-analysis to our knowledge reviewing the association between androgenetic alopecia and the extent of smoking - can guide further research and update clinical practice guidelines," the authors write. "Our patients with male pattern baldness need to be educated about the negative effects of smoking, given the fact that this condition can have a profound negative psychological impact on those who suffer from it".

**References**

Gupta AK, Bamimore MA, Talukder M. A meta-analysis study on the association between smoking and male pattern hair loss. J Cosmet Dermatol. Published online January 4, 2024. doi:10.1111/jocd.16132

### 2. High Salt Intake Linked to Increased Risk for Kidney Disease


People who habitually add salt to their meals at the table may unknowingly be risking their kidneys, according to a study utilizing UK Biobank data. Chronic salt additions are associated with an elevated risk of developing chronic kidney disease (CKD), as revealed by researchers led by Rui Tang, a doctoral candidate in epidemiology at Tulane University in New Orleans, Louisiana. The study was published in JAMA Network Open.

**Large Study Sample**

In a population-based cohort study comprising over 460,000 UK Biobank participants aged 37-73 years, Tang and colleagues explored the association between adding table salt to food and increased CKD risk.

Participants indicated how often they added salt to their meals: Never or rarely, sometimes, often, or always. The follow-up period exceeded a decade, and median duration was 11.8 years. During this time, approximately 22,000 new CKD cases were documented. Data analysis revealed a significantly higher CKD risk among those who frequently added salt.

The extent of risk elevation varied with the frequency of salt additions. Even occasional salters had a 7% higher risk than those who never or rarely added salt. For frequent salters, the risk increased by 12%, and for those who always added salt, it rose to 29%. These results were adjusted for age and gender.

**Worse Overall Health**

The research group noted that individuals who frequently added salt were generally less healthy, adopting an unhealthier lifestyle and having lower

socioeconomic status. They exhibited higher body mass index (BMI), were more likely to smoke, had diabetes or cardiovascular diseases, and had reduced estimated glomerular filtration rate (eGFR) at the beginning of the study. Moreover, their Townsend Deprivation Index, indicating material deprivation, was higher.

Considering these factors, the researchers adjusted the results not only for age and gender but also for ethnicity, Townsend Deprivation Index, eGFR, BMI, smoking status, alcohol consumption, physical activity, elevated cholesterol levels, diabetes, cardiovascular diseases, hypertension, infectious diseases, immune system disorders, and the use of nephrotoxic medications.

**Association Persists**

Even after accounting for these factors, a significant, albeit attenuated, association between salt additions and CKD risk remained. The risk increased by 2% for occasional salters, 5% for frequent salters, and 6% for those who always added salt.

The research group led by Tang concluded that adding salt to meals could be associated with an increased risk for CKD in the general population. However, they highlighted several limitations that should be considered when interpreting the study results.

**Reducing Salt**

Primarily, self-reported frequency of salt addition doesn't precisely reflect actual salt consumption. While earlier studies validated the accuracy of this variable, the researchers acknowledged the possibility that frequent salt addition may merely be a marker for an unhealthy lifestyle.

Nevertheless, the authors speculated that reducing the frequency of salt additions to meals could contribute to lowering CKD risk in the general population. They suggested validating their results in post hoc analyses or follow-up studies from clinical trials.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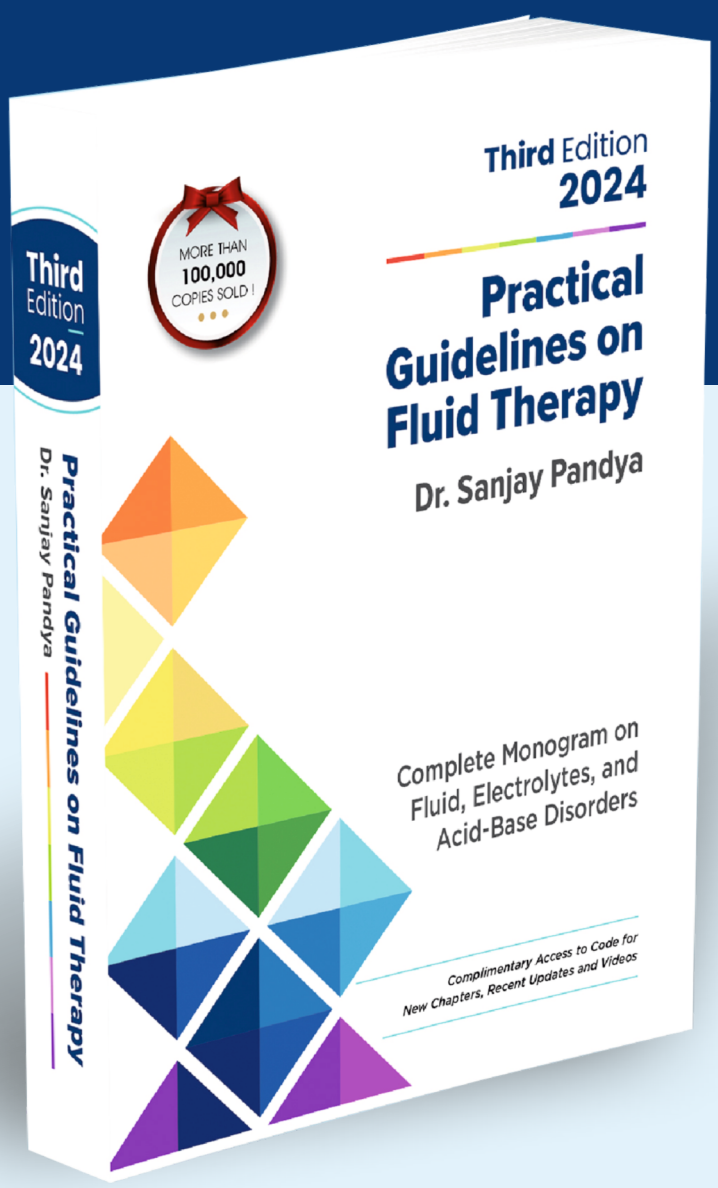


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# Celebrating World Kidney Day: Reflecting on 9 Breakthroughs in Kidney Disease Research of 2023


As we commemorate World Kidney Day, it's essential to reflect on the remarkable strides made in the field of nephrology over the past year. In 2023, the landscape of kidney disease research witnessed significant advancements, ranging from innovative diagnostic tools to groundbreaking treatment modalities. In this special edition, we delve into nine pivotal breakthroughs that have reshaped our understanding of kidney health and disease management. From the creation of a comprehensive atlas of human kidney cells to the development of novel predictive models, each discovery brings us closer to a future where kidney disease can be better managed and treated.

## Here are nine of the biggest headlines from the nephrology research field from 2023.

**Breakthrough #1:** New atlas of human kidney cells to help unlock kidney disease research | National Institutes of Health (NIH)

In July, the National Institutes of Health (NIH) announced it had created a "comprehensive atlas of the human kidney." By comparing cells from healthy kidneys to those from diseased or injured kidneys, researchers created a "map" or model of the human kidney. This model was created as part of the Kidney Precision Medicine Project (KPMP) with support from NIH's National Institute of Diabetes and Digestive and Kidney Disease. The goal of precision medicine and the kidney model is to create new drugs and treatments that target the specific cause of a disease. Not all kidney diseases or acute kidney injuries affect the kidneys in the same way and this model will help scientists to better treat or prevent different types of kidney disease.

**Breakthrough #2:** Report redefines overlapping risks of heart and kidney diseases | American Heart Association

The American Heart Association (AHA) submitted a presidential advisory defining and officially declaring cardiovascular-kidney-metabolic (CKM) syndrome as a specific health condition. This condition acknowledges the overlap between cardiovascular (heart) disease, kidney disease, type 2 diabetes and obesity, breaking the condition into different stages with prevention and treatment guidelines for each stage. Find out more about what experts describe as a paradigm change in this AKF blog post.

**Breakthrough #3:** Feasibility of an implantable bioreactor for renal cell therapy using silicon nanopore membranes | Nature Communications

The Kidney Project a national research project led by the University of California San Fransisco to create a bioartificial kidney announced progress this year. The plan for the implantable device includes two key parts: (1) a bioreactor and (2) a hemofilter. The hemofilter will filter the blood to remove waste and toxins. However, the kidney performs other important functions for the body, too, including managing the level of certain hormones and reabsorbing water and other needed nutrients after the blood has been filtered. The bioreactor will perform these critical jobs, using a combination of kidney cells and silicone membranes. In August, the Kidney Project researchers published their findings that they had successfully implanted the bioreactor in healthy pigs. The next step would be FDA trials, first in animals and eventually in humans.

**Breakthrough #4:** Pig kidney works a record 2 months in donated body, raising hope for animal-human transplants | AP News

The University of Alabama at Birmingham (UAB) successfully transplanted a genetically modified pig kidney for the first time in August 2023, which functioned as a healthy human kidney would for the seven days of the study. The New York University (NYU) Langone Health hospital also transplanted a pig kidney into the body of a brain-dead man, Maurice "Mo" Miller, which survived for two months. This is the longest a pig kidney has functioned in a human body to date and scientists are hopeful this may mean they can eventually begin trials to transplant one into a living human.

**Breakthrough #3:** Global Coalition on Aging Finds Chronic Kidney Disease A Troubling Blind Spot Among Chronic Diseases in the US- Global Coalition On Aging

The Global Coalition on Aging (GCOA), the World's Leading Business Voice on Aging, conducted a survey of 1,000 Americans 18 years and older and discovered a surprising lack of awareness and understanding about chronic kidney disease. Despite the growing rate of kidney disease in U.S., over half of the participants (58%) had no awareness of the disease at all. Even respondents who regularly saw doctors did not have an awareness of the disease. GCOA recommended several steps to increase awareness, some of which AKF has already undertaken including bringing stakeholders together to discuss concerns within the kidney community.

**Breakthrough #6:** Millions of lives and billions of dollars: the need for earlier intervention in chronic kidney disease

As part of the Patient Access Initiative (PAI), AKF published a white paper called "Reimagining Kidney Care: From Crisis to Opportunity," that examines the dire kidney disease trends in the U.S. The paper also highlights the potential benefits of creating policies that prioritize "upstream care." Upstream care is an approach to health care that puts an emphasis on addressing the root of a medical problem rather than the symptoms. It focuses on earlier detection and intervention of a disease rather than treating it once it has become more advanced. The paper shows how this approach could have benefits for Americans' health and its economy. Find out more in this AKF blog post.

**Breakthrough #7:** New Non-Invasive Test Uses AI and Retinal Scans To Accurately Predict Risk of Chronic Kidney Disease | AP News

A new noninvasive retinal scan that uses an artificial intelligence (AI) deep learning algorithm called Reti-CKD "showed superior prediction of future CKD risk compared to the conventional [estimated glomerular filtration rate (eGFR)] or urine test." The test can accurately predict kidney disease risk because the kidneys and retina (the light-sensitive layer of eye tissue innermost in the eye and is an extension of the brain) have similar micro blood vessels. Concerns about the micro blood vessels in the retina, therefore, can be predictive of possible problems with the micro blood vessels in the kidneys, putting the person at greater risk for kidney disease.

**Breakthrough #8:** Risk Calculator for Early-Stage CKD May Soon Enter US Market (medscape.com)

Dr. Naveep Tangri, a nephrologist and professor at the University of Manitoba, is the founder of Klinrisk, Inc., a company that is developing and commercializing a new predictive tool for kidney disease called the Klinrisk model. Using 20 lab-measured variables from routinely ordered tests, it can predict the risk of an adult with early-stage CKD developing either a 40% or greater drop in eGFR or kidney failure. Since the Klinrisk model uses information from tests a primary care doctor may already give, Dr. Tangri says it is ready for any health system, insurance company or clinic to implement.

**Breakthrough #9:** Exercise during hemodialysis improved physical function of patients with kidney failure

A study found that, after 12 months, patients who participated in endurance and resistance exercises during their hemodialysis treatments had improved physical function compared to those receiving standard treatment. The study included 917 patients and found that those who did the exercises during dialysis also reported an improved quality of life and had fewer hospitalizations.

We hope to see even more progress in the kidney disease research and treatment space in 2024!

At Aprica Healthcare Ltd. we explore these remarkable achievements and envision a world where kidney health is prioritized and celebrated. We Apricans, are committed to improving disease management and raising awareness. We offer personalized patient information leaflets for CKD on this **World Kidney Day** for your patients.

We encourage you to reach out to our TBMs, ABMs or Medical department and get your personalized PIL on this World Kidney Day
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