NCD Newsletter

Jan 2024 - Issue 09

AIR POLLUTION RAISES RISK OF TYPE 2 DIABETES, SAYS LANDMARK INDIAN STUDY

Seven-year study of 12,000 residents of Delhi and Chennai finds link between PM 2.5 particles and increased blood sugar levels

Inhaling polluted air increases the risk of type 2 diabetes, the first study of its kind in India has found. Research conducted in Delhi and the southern city of Chennai found that inhaling air with high amounts of PM 2.5 particles led to high blood sugar levels and increased type 2 diabetes incidence.

PEOPLE WALK ON A ROAD TOWARDS THE INDIA GATE AMID SMOG IN NEW DELHI. INDIA IS ONE OF THE WORLD'S WORST COUNTRIES FOR AIR POLLUTION.

When inhaled, PM 2.5 particles – which are 30 times thinner than a strand of hair–can enter the bloodstream and cause several respiratory and cardiovascular diseases.

The study is part of ongoing research into chronic diseases in India that began in 2010. It is the first to focus on the link between exposure to ambient PM 2.5 and type 2 diabetes in India, one of the worst countries in the world for air pollution.

The average annual PM 2.5 levels in Delhi was 82-100µg/m^3 and in Chennai was 30-40µg/m^3, according to the study, many times the WHO limits of 5µg/m^3. India's national air quality standards are 40µg/m^3.

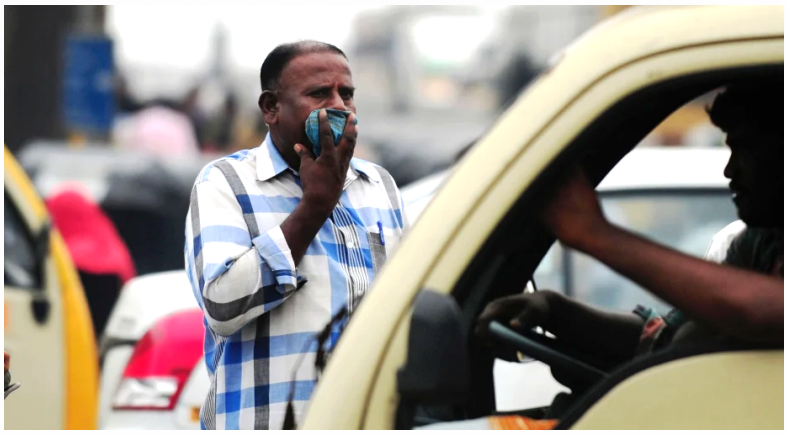
There is also a high burden of non-communicable diseases, including diabetes, hypertension and heart disease in India; 11.4% of the population – 101 million people – are living with diabetes, and about 136 million are pre-diabetic, according to a paper published in the Lancet in June. The average diabetes prevalence in the European Union was 6.2% in 2019, and 8.6% in the UK in 2016. The Lancet study found India's diabetes prevalence to be higher than previous estimations and showed a higher number of diabetics in urban than rural India.
In the BMJ study, the researchers followed a cohort of 12,000 men and women in Delhi and Chennai from 2010 to 2017 and measured their blood sugar levels periodically. Using satellite data and air pollution exposure models, they determined the air pollution in the locality of each participant in that timeframe.

They found that one month of exposure to PM 2.5 led to elevated levels of blood sugar and prolonged exposure of one year or more led to increased risk of diabetes. They found for every 10µg/m^3 increase in annual average PM 2.5 level in the two cities, the risk for diabetes increased by 22%.

"Given the pathophysiology of Indians – low BMI with a high proportion of fat – we are more prone to diabetes than the western population," said Siddhartha Mandal, lead investigator of the study and a researcher at Centre for Chronic Disease Control, Delhi.

The addition of air pollution – an environmental factor – with lifestyle changes in the past 20 to 30 years is fuelling the increasing burden of diabetes, he said.

"Until now, we had assumed that diet, obesity and physical exercise were some of the factors explaining why urban Indians had higher prevalence of diabetes than rural Indians," said Dr V Mohan, chairman of the Madras Diabetes Research Foundation and one of the authors of the paper. "This study is an eye-opener because now we have found a new cause for diabetes that is pollution."



An Indian commuter wears a mask to protect himself against dust and pollution as he waits to cross a road in Chennai.

Another study on the same cohort in Delhi, found average annual exposure to PM 2.5 in Delhi (92µg/m3) led to increase in blood pressure levels and higher likelihood of developing hypertension.

Together, the studies show that the higher than safe levels of PM2.5 in the air in Indian cities cause diabetes and hypertension that could lead to atherosclerosis (the build up of fatty deposits in the arteries), heart attacks and heart failures, said Mandal.

PM 2.5 contains sulfates, nitrates, heavy metals and black carbon that can damage the lining of blood vessels and increase blood pressure by stiffening the arteries. The particles can get deposited in the fat cells and cause inflammation and can also attack the heart muscle directly, said Dr Dorairaj Prabhakaran, cardiologist and executive director of the Centre for Chronic Disease Control and one of the authors of the paper.

Acting as an endocrine disruptor, PM 2.5 hampers insulin production in the body as well as its effect.

In urban India there has been a rise of hypothyroidism, polycystic ovarian syndrome (PCOS) and gestational diabetes. This study shows that pollution may play a part in causing all of these as it disrupts the endocrine system that produces all hormones in the body, said Mohan.

Indian commuters drive amid heavy smog in Delhi.

The researchers are now working to understand the impact of pollution on cholesterol and vitamin D levels in the body, and its impact on the life cycle of individuals, including birth weight, pregnant women's health, insulin resistance in adolescents, and the risk for Parkinson's and Alzheimer's disease, among others.

While its findings are alarming, the study gives scientists hope that bringing down pollution can decrease the burden of diabetes, as well as other non-communicable diseases, said Prabhakaran.

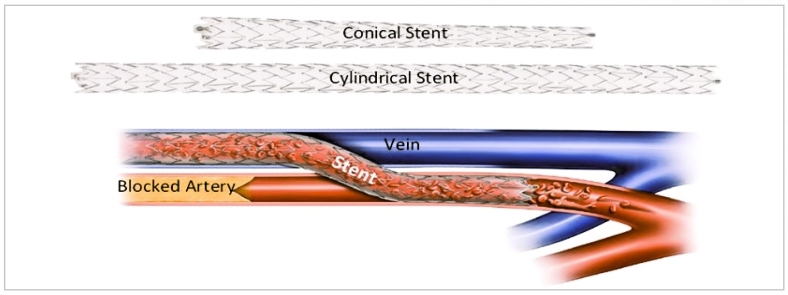
Some public policy initiatives have shown results. Since a public outcry about air pollution in 2016, the central and Delhi government have banned older diesel vehicles, limited construction, built highways that bypass the city, and banned the burning of crops. Reports suggest there was a 22% reduction in PM 2.5 levels between 2016 and 2021.

"This is a modest but welcome reduction. Similar measures adapted to local conditions are urgently needed across the country," said Prabhakaran.

MEDICAL DEVICES

1. LimFlow™ System

Approval Date: September 11, 2023



What is it?

The LimFlow system allows doctors to connect an artery in the calf to a vein near the foot to restore blood flow to the feet in patients with chronic limb threatening ischemia (also known as critical limb ischemia) that are likely to have an amputation and are not good candidates for surgical bypass.

When is it used?

The LimFlow System is used to treat patients with chronic limb-threatening ischemia (also known as critical limb ischemia), which is associated with rest pain, unhealing wounds, amputation and increased mortality. Chronic limb-threatening ischemia results from a collection of fatty substances, such as cholesterol, and calcification that form "plaque" along the lining of the arteries. The plaque formation can reduce, or totally block blood flow to the lower limb, and lead to unhealing wounds in the feet.

2. FDA Approves First Leadless Dual-Chamber Pacing System

Approval date: July 5, 2023

AVEIR DR Dual Chamber Leadless Pacemaker System

The FDA has approved Abbott's AVEIR dual chamber (DR) leadless pacemaker system, the first dual chamber leadless pacing system that treats people with abnormal or slow heart rhythms. Roughly one-tenth the size of a traditional pacemaker, the AVEIR DR leadless pacing system is made up of two devices: the previously approved AVEIR VR single chamber device, which paces the right ventricle, and the now-approved AVEIR AR single chamber device, which paces the right atrium.

The AVEIR DR system incorporates Abbott's novel i2i technology, which provides synchronized or coordinated cardiac pacing between two leadless pacemakers based on the person's clinical needs. The i2i technology utilizes high-frequency pulses to relay messages via the naturally conductive characteristics of the body's blood between each leadless pacemaker. To support dual chamber therapy, each implant communicates beat-to-beat with a paired, co-implanted device

Results from the AVEIR DR i2i Investigational Device Exemption (IDE) study through three-months post-implant showed a 98.3% implant success rate for physicians and more than 97% of people had a successful atrio-ventricular synchrony, so that the upper and lower chamber were beating normally, despite different types of underlying slow heart rhythms.

FDA APPROVALS

1. FDA Approves New Obesity Drug That Will Compete With Wegovy

Approval date: November 8, 2023

Zepbound, which is already sold by Eli Lilly as the diabetes treatment Mounjaro, was shown to reduce patients' weight by as much as one-fifth in drug trials.

Mounjaro, a tirzepatide injection drug, has been used for treating Type II diabetes.

The Food and Drug Administration on Wednesday approved an obesity drug from the company Eli Lilly that will be a direct competitor to the wildly popular Wegovy.

The drug is called tirzepatide and will be sold under the name Zepbound. It joins a class of new medications that are transforming obesity, a condition that affects 100 million American adults and is linked to a spectrum of diseases including diabetes, heart disease, sleep apnea, liver disease, kidney disease and joint pain.

Patients who used tirzepatide lost an average of 18 percent of their body weight, according to the F.D.A., when it was taken at its highest dose in a drug trial. That's compared with Wegovy, manufactured by Novo Nordisk, which produced an average 15 percent weight loss.

The F.D.A. approved Zepbound for people with obesity and for those who are overweight and have at least one obesity-related condition.

2. World's First Chikungunya Vaccine Approved by FDA

Approval date: November 10, 2023

The first vaccine for chikungunya, an emerging mosquito-borne global health threat marked by fever and joint pain, has been granted accelerated approval by the US Food and Drug Administration (FDA).

The vaccine, called Ixchiq, was granted fast-track and breakthrough-therapy designations in June, and the application has now received a priority review designation.

The risk for chikungunya infection is highest in the tropical and subtropical regions of Africa, Southeast Asia, and parts of the Americas, where chikungunya virus-carrying mosquitos are endemic, according to the FDA. However, the chikungunya virus has been spreading geographically, increasing its global prevalence.

At least 5 million cases have been reported globally in the past 15 years, the agency reported yesterday.

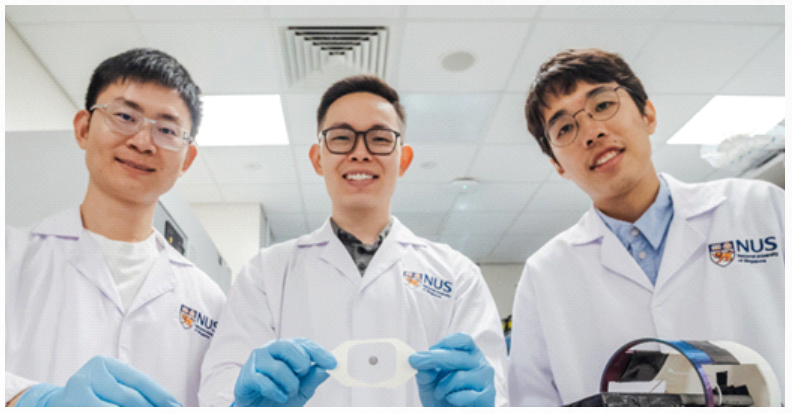
The new vaccine is approved for adults 18 years or older who are at increased risk for exposure to the virus.

NUS scientists develop innovative magnetic gel that heals diabetic wounds three times faster

Mechano-Activated Cell Therapy for Accelerated Diabetic Wound Healing. Advanced Materials, 2023

First-of-its-kind cell therapy promotes wound healing, improves overall wound health and lowers risks of recurrence

Diabetic patients, whose natural wound-healing capabilities are compromised, often develop chronic wounds that are slow to heal. Such non-healing wounds could cause serious infections resulting in painful outcomes such as limb amputation. To address this global healthcare challenge, a team of researchers from the National University of Singapore (NUS) engineered an innovative magnetic wound-healing gel that promises to accelerate the healing of diabetic wounds, reduce the rates of recurrence, and in turn, lower the incidents of limb amputations.



Asst Prof Andy Tay (centre) is holding a plaster pre-loaded with magnetic gel, which promises to accelerate the healing of diabetic wounds, while Dr Shou Yufeng (right) is holding the device for magnetic stimulation. Dr Le Zhicheng (left) is holding a sample of the magnetic gel in liquid form.

Each treatment involves the application of a bandage pre-loaded with a hydrogel containing skin cells for healing and magnetic particles. To maximise therapeutic results, a wireless external magnetic device is used to activate skin cells and accelerate the wound healing process. The ideal duration of magnetic stimulation is about one to two hours.

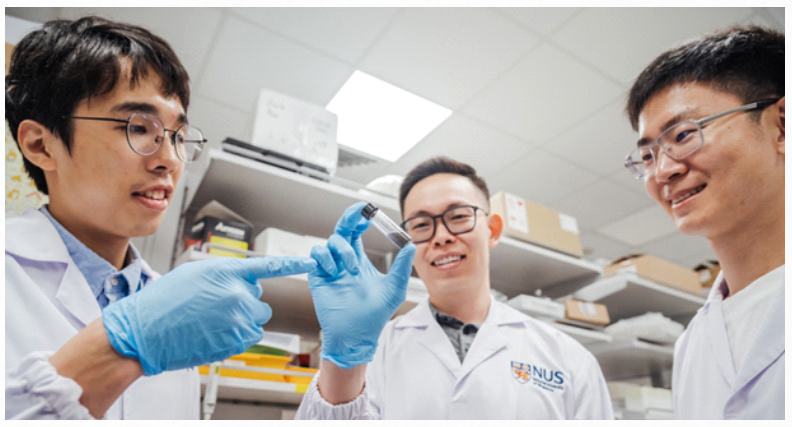
Lab tests showed the treatment coupled with magnetic stimulation healed diabetic wounds about three times faster than current conventional approaches. Furthermore, while the research has focussed on healing diabetic foot ulcers, the technology has potential for treating a wide range of complex wounds such as burns.

"Conventional dressings do not play an active role in healing wounds," said Assistant Professor Andy Tay, who leads the team comprising researchers from the Department of Biomedical Engineering at NUS College of Design and Engineering as well as the NUS Institute for Health Innovation & Technology. "They merely prevent the wound from worsening and patients need to be scheduled for dressing change every two or three days. It is a huge cost to our healthcare system and an inconvenience to patients."

In contrast, the unique NUS invention takes a comprehensive 'all-in-one' approach to wound healing, accelerating the process on several fronts.

"Our technology addresses multiple critical factors associated with diabetic wounds, simultaneously managing elevated glucose levels in the wound area, activating dormant skin cells near the wound, restoring damaged blood vessels, and repairing the disrupted vascular network within the wound," explained Asst Prof Tay.

The NUS team described their innovation in a paper published in the scientific journal, Advanced Materials, on 8 September 2023. The research was conducted in collaboration with scientists from the Agency for Science, Technology and Research, Nanyang Technological University, Sun Yat-sen University and Wuhan University of Technology.



The innovative magnetic hydrogel (held by Asst Prof Tay) contains skin cells for healing and magnetic particles, takes a comprehensive 'all-in-one' approach to wound healing, accelerating the process on several fronts.

Chronic diabetic wounds: A major healthcare challenge

Currently, more than half a billion people globally are living with diabetes and this number is expected to rise significantly. Chronic diabetic wounds such as foot ulcers (one of the most common and hardest to treat wounds) have therefore become a major global healthcare challenge.

Traditional treatments for these wounds are often unsatisfactory, leading to recurring and persistent health issues and -- in a high number of cases- limb amputation.

Every year, there are around 9.1 to 26.1 million cases of diabetic foot ulcer worldwide, and around 15 to 25 per cent of patients with diabetes will develop a diabetic foot ulcer during their lifetime. Singapore has one of the highest rates of lower limb amputation due to diabetes globally, averaging around four per day.

Gentle 'work-out' for skin cells

Skin cells experience mechanical forces continuously from normal daily activities. However, patients with wounds are usually advised not to carry out rigorous activities, such as walking, and this could kill the remaining cells essential for healing.

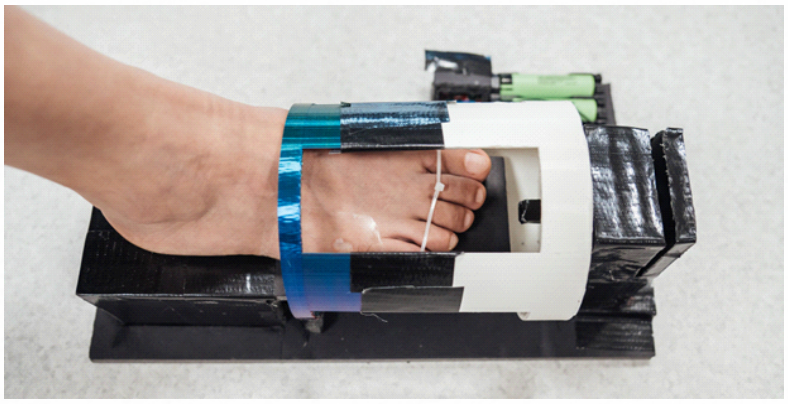
"What our team has achieved is to identify a sweet spot by applying gentle mechanical stimulation," said Asst Prof Tay. "The result is that the remaining skin cells get to 'work-out' to heal wounds, but not to the extent that it kills them."

The specially designed wound-healing gel is loaded with two types of FDA-approved skin cells - keratinocytes (essential for skin repair) and fibroblast (for formation of connective tissue) - and tiny magnetic particles. When combined with a dynamic magnetic field generated by an external device, the mechanical stimulation of the gel encourages dermal fibroblasts to become more active.

Lab tests showed that the increased fibroblast activity generated by the magnetic wound-healing gel increases the cells' growth rate by approximately 240 per cent and more than doubles their production of collagen — a crucial protein for wound healing. It also improves communication with keratinocytes to promote the formation of new blood vessels.

"The approach we are taking not only accelerates wound healing but also promotes overall wound health and reduces the chances of recurrence," added Asst Prof Tay.

The NUS team worked on the project from 2021 to 2023 to demonstrate the viability of this new approach. A patent has been filed for this innovation.



A bandage pre-loaded with magnetic hydrogel is placed on the wound, and an external device is used to accelerate the wound healing process.

Potential game-changer in wound management

While the magnetic wound-healing gel has shown great promise in improving diabetic wound healing, it could also revolutionise the treatment of other complex wound types.

"The magneto-responsive hydrogel, combined with wireless magneto-induced dynamic mechanical stimulation, addresses fundamental challenges in wound healing, such as creating a conducive microenvironment and promoting tissue regeneration," said co-first author of the research paper Dr Shou Yufeng, Research Fellow from the Department of Biomedical Engineering at NUS College of Design and Engineering.

These principles and our technology's adaptability, as well as its general ease of use for patients, means that it can be applied to improve wound healing in various situations beyond diabetes, including burns and chronic non-diabetic ulcers.

The researchers are conducting more tests to further refine the magnetic wound-healing gel to improve its effectiveness. They are also collaborating with a clinical partner to test the effectiveness of the gel using diabetic human tissues.

"This is major step forward in active wound care," said Asst Prof Tay. "Our goal is to provide an effective and convenient wound-healing solution that improves outcomes for millions around the world."

"Wound healing, especially in the field of diabetic foot ulcers, has always been a challenging arena. Diabetic foot patients do not heal as well as normal patients and their healing journey is often prolonged," said Assistant Professor Francis Wong Keng Lin, Consultant, Department of Orthopaedic Surgery, Sengkang General Hospital.

Asst Prof Wong, who is not involved in the study, added, "Advancements in wound healing technologies will reduce the duration of the patient journey and would allow them to return to their lives as quickly as possible, hence improving productivity and quality of life."

PRODUCT UPDATE

1. The legacy effect of hyperglycemia and early use of SGLT-2 inhibitors: a cohort study with newly-diagnosed people with type 2 diabetes

Background: A delay in reaching HbA1c targets in patients with newly-diagnosed type 2 diabetes (T2D) is associated with an increased long-term risk of developing cardiovascular diseases (CVD), a phenomenon referred to as legacy effect. Whether an early introduction of glucose-lowering drugs with proven benefit on CVD can attenuate this phenomenon is unknown.

Methods: Using data derived from a large Italian clinical registry, i.e. the AMD Annals, we identified 251,339 subjects with newly-diagnosed T2D and without CVD at baseline. Through Cox regressions adjusted for multiple risk factors, we examined the association between having a mean HbA1c between 7.1 and 8% or >8%, compared with ≤7%, for various periods of early exposure (0–1, 0–2, 0–3 years) and the development of later (mean subsequent follow-up 4.6 ± 2.9 years) CVD, evaluated as a composite of myocardial infarction, stroke, coronary or peripheral revascularization, and coronary or peripheral bypass. We performed this analysis in the overall cohort and then splitting the population in two groups of patients: those that introduced sodium-glucose transport protein 2 inhibitors (SGLT-2i) during the exposure phase and those not treated with these drugs.

Findings: Considering the whole cohort, subjects with both a mean HbA1c between 7.1 and 8% and >8%, compared with patients attaining a mean HbA1c ≤ 7%, showed an increased risk of developing the outcome in all the three early exposure periods assessed, with the highest risk observed in patients with mean HbA1c > 8% in the 3 years exposure period (hazard ratio [HR]1.33; 95% confidence interval [CI] 1.063–1.365). The introduction of SGLT-2i during the exposure periods of 0–1 and 0–2 years eliminated the association between poor glycemic control and the outcome (p for interaction 0.006 and 0.003, respectively, vs. patients with the same degree of glycemic control but not treated with these drugs).

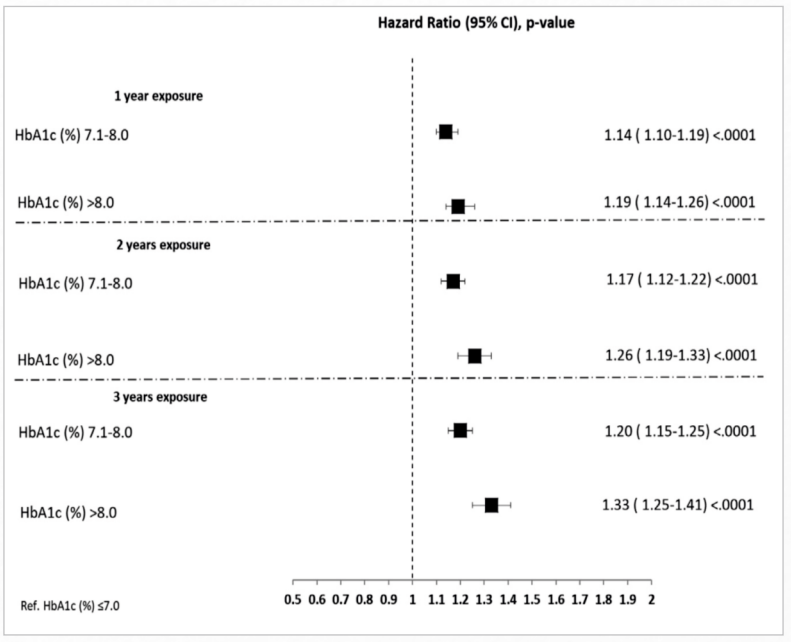


Fig 1 : Poor, early glycemic control and the subsequent risk of cardiovascular diseases. Pseudo-forest plot showing the adjusted hazard ratios (HR) with the relative 95% confidence interval (CI) and the p value, derived from the Cox regression analyses exploring the associations between glycemic

control and the risk of the CVD at follow-up in the whole cohort according to the degree of glycemic control in the three exposure periods assessed. HbA1c ≤ 7% is the reference.

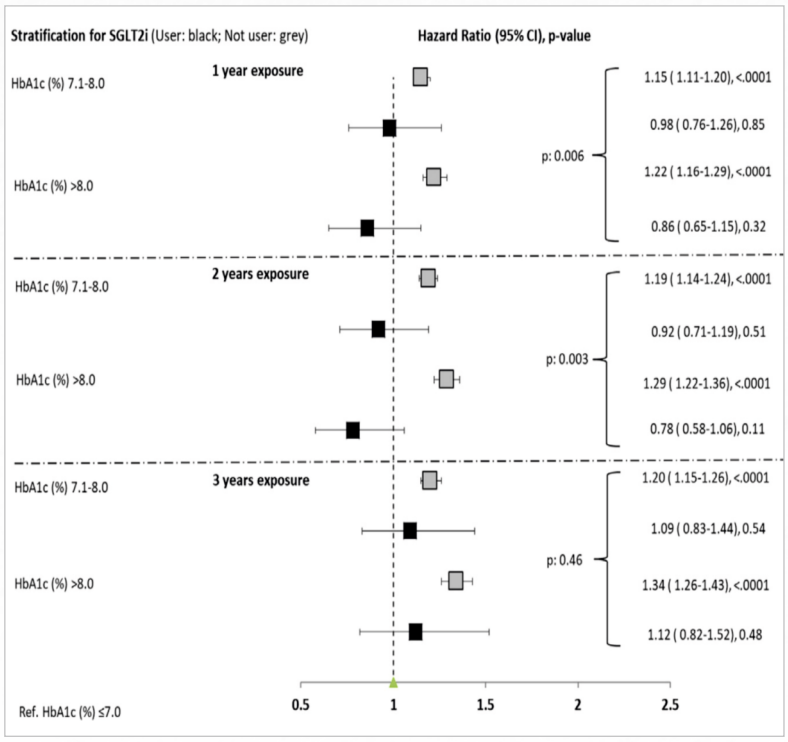


Fig. 2: Early introduction of SGLT-2i attenuate metabolic memory. Pseudo-forest plot showing the adjusted hazard ratios (HR) with the relative 95% confidence interval (CI) and the p value, derived from the Cox regression analyses exploring the associations between glycemic control and the risk of the CVD at follow-up in patients stratified according to use of SGLT-2i during the exposure phase or not users, in the three exposure periods assessed. HbA1c ≤ 7% is the reference.

Interpretation: Among patients with newly diagnosed T2D and free of CVD at baseline, a poor glycemic control in the first three years after diagnosis is associated with an increased subsequent risk of CVD. This association is no longer evident when SGLT-2i are introduced in the first two years, suggesting that these drugs attenuate the phenomenon of legacy effect. An early treatment with these drugs might thus promote a long-lasting benefit in patients not attaining proper glycemic control after T2D diagnosis.

2. Semaglutide reduced cardiovascular events by 20% in certain adults

Findings from a multi-center, international clinical trial reported by a Cleveland Clinic physician show that semaglutide reduced cardiovascular events by 20% in adults with overweight or obesity and established cardiovascular disease who do not have diabetes.

Semaglutide is primarily prescribed for adults with type 2 diabetes but is also approved for chronic weight management in adults with obesity or overweight and have at least one other health issue. In the trial, patients treated with semaglutide lost an average of 9.4% of their body weight and experienced improvements in other risk factors for cardiovascular disease.

Results from the "SELECT-Semaglutide and Cardiovascular Outcomes in Patients with Overweight or Obesity Who Do Not Have Diabetes" trial were presented today during a late-breaking science session at the American Heart Association's Scientific Sessions 2023 and simultaneously published in the New England Journal of Medicine.

In the trial, for patients with preexisting cardiovascular disease and overweight or obesity but without diabetes, weekly injections of semaglutide at a dose of 2.4 mg was superior to placebo in reducing the risk of death from cardiovascular causes, nonfatal heart attack, or nonfatal stroke over an average follow-up of 40 months.

"It is known that overweight and obesity increase a person's risk of cardiovascular events. Yet while reducing cardiovascular disease by treating high cholesterol, high blood pressure, and diabetes is standard practice, the concept of treating obesity to reduce cardiovascular complications has been hampered by the lack of evidence that lifestyle or pharmacologic interventions for overweight or obesity improve cardiovascular outcomes," said Michael Lincoff, M.D., SELECT's lead author and vice chair for research in Cleveland Clinic's Department of Cardiovascular Medicine. "This marks the first pharmacologic intervention for overweight or obesity that's been shown in a rigorous fashion to reduce the risk of cardiovascular events."

More than half the world population is projected to have overweight or obesity by the year 2035. High body-mass index (BMI) is estimated to have accounted for 4 million deaths globally in 2015, more than two thirds of which were caused by cardiovascular diseases.

Semaglutide, a GLP-1 receptor agonist medication initially approved and most frequently prescribed for adults with type 2 diabetes, was also FDA-approved in 2021 for chronic weight management in adults with obesity or overweight with at least one weight-related comorbidity. While the weight loss effects of semaglutide appear to occur primarily through appetite suppression, this drug has other actions which may reduce cardiovascular risk, including improvements in glucose levels, decreases in blood pressure and cholesterol levels and reductions in inflammation, and beneficial effects on heart muscle and blood vessels.

In the SELECT trial, which ran from October 2018 through June 2023, researchers enrolled patients 45 years of age or older who had pre-existing cardiovascular disease and a body mass index of 27 or greater but no history of diabetes. Over 17,000 patients in 41 countries who had previously experienced a heart attack, stroke and/or had peripheral artery disease were enrolled and followed for an average of 40 months after being randomly assigned to receive once weekly injections of semaglutide 2.4 mg or placebo.

In addition to taking either semaglutide or placebo for the trial, all participants also received standard-of-care treatment for cardiovascular disease, such as cholesterol-modifying medications, antiplatelet therapies, beta blockers or other treatments.

Death from a cardiovascular event, nonfatal myocardial infarction (heart attack), or nonfatal stroke occurred during the trial in 6.5% of patients who were treated with semaglutide versus 8.0% of patients who received placebo - a 20% reduction in relative risk by semaglutide. Risk reductions were similar in men and women and across different ethnicities, patient ages and baseline levels of bodyweight.

There were no unexpected safety issues with semaglutide in this trial. More patients discontinued semaglutide (16.6%) than placebo (8.2%), due primarily to gastrointestinal symptoms including nausea and diarrhea. These gastrointestinal symptoms are not uncommon with this class of medications, particularly when the drug is started, or the dose is increased. There was a slightly higher rate of gallbladder disorders in the semaglutide vs. placebo group (2.8% vs. 2.3%, respectively), which has also been previously reported in other studies with GLP-1 agents. Importantly, semaglutide was not associated with higher risks for severe gastrointestinal disorders, pancreatitis, psychiatric disorders or kidney injury.

"There's growing recognition that obesity and overweight are really metabolic diseases, and yet, effective therapies have been quite limited," said Dr. Lincoff. "This study of semaglutide demonstrates the effectiveness of a new pathway to reduce the excess risk associated with obesity of important and potentially deadly cardiovascular complications."

One limitation of the trial is that only patients with pre-existing cardiovascular disease were included. The effects of semaglutide on primary prevention of cardiovascular events in persons with overweight or obesity, but without previous cardiovascular disease, were not studied.

The trial was sponsored by Novo Nordisk, the company that developed semaglutide. Dr. Lincoff has received consulting fees from Novo Nordisk.

3. First Indian Evidence: Triple FDC (DAPA, SITA, MET ER) Yields Better HbA1c Reduction in T2DM Patients Uncontrolled on Existing Therapy

An approach of' using a once-daily triple fixed-dose combination of dapagliflozin, sitagliptin, and metformin ER (extended-release) in Indian type 2 diabetes patients poorly controlled with metformin alone showed greater reductions in glycated Hemoglobulin (HbA1c) and higher proportion of patients achieving glycemic control; without increased risk of hypoglycemia and weight main compared to the conventional once-daily dual combinations of Sitagliptin and Metformin ER or Dapagliflozin and Metformin SR (sustained-release), a study published on Advances in Therapy has reported.

The study, designed in a 16-week, multicenter, randomized, three-arm, open-label, active-controlled, parallel- group, phase 3 clinical study, enrolled 4015

Indian T2D patients poorly controlled on Metformin monotherapy with glycated Hemoglobin (HbA1_c) 8% and 11%, & was conducted across 15 sites in India.

The primary objective of the study was to compare the reduction in HbA1c from baseline to week 16 with dapagliflozin, sitagliptin, and metformin ER compared to Sitagliptin and Metformin SR and Dapagliflozin and Metformin ER. The mean baseline HbA1c was approximately 9% in each treatment group.

Patients were randomized to receive either the FDC (fixed-dose combination) of Dapagliflozin (10mg), Sitagliptin(100mg) and Metformin (1000mu) ER tablets once daily (N=137), or co-administration of Sitagliptin (100mg) and Metformin (1000mg) tablets once daily (N=139) or Dapagliflozin (10mu) and Metformin (1000mg) tablets once daily (N=139). The key results of the study are as follows:

Effect on Glyated Hemoglobin (HbAlc) Levels

The adjusted mean reduction in HbAlc at week 16 was significantly greater with Dapagliflozin, Sitagliptin and Metformin ER (-1.73% [-19.0 mmol/mol]) compared to sitagliptin and metformin SR (-1.28% [-14.1mmol/mol]; difference of-0.46% [-5.1 mmol/mol], p<0.001) and Dapagliflozin and Metformin ER (-1.33% [-14.6 mmol/mol]: difference -0.4% [4.4mmol/mol], p<0.001). (Refer Figure 1)

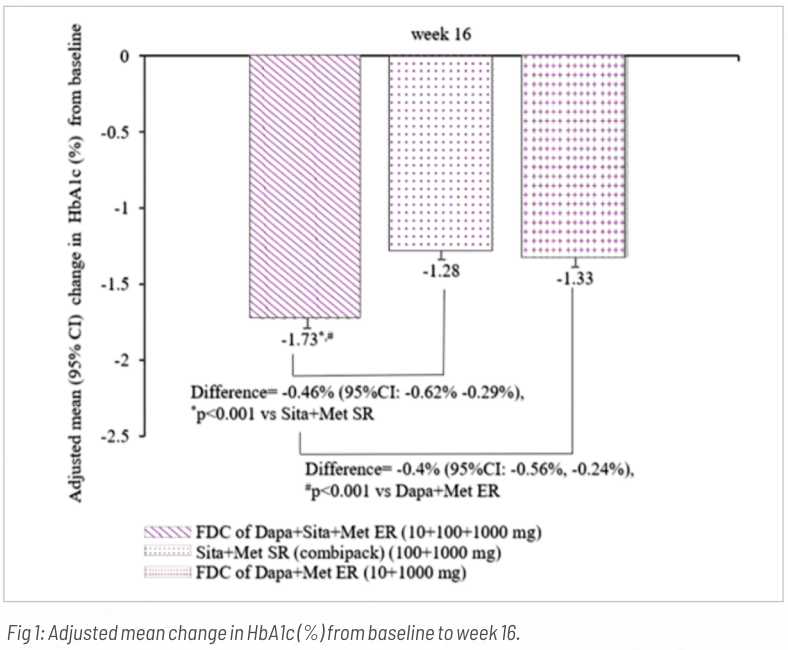


Fig 1: Adjusted mean change in HbA1c (%) from baseline to week 16.

At week 12, the reduction in HbAlc from baseline was significantly greater with Dapagliflozin, Sitagliptin, and Metformin ER compared to Sitagliptin and Metformin SR (-1.15£0.87 vs -0.85£0.70, p=0.0006) and Dapagliflozin and Metformin ER (-1.1520.87 vs -0.94+0.73, p=0.0276).

The triple combination of Dapagliflozin, Sitagliptin and Metformin ER also significantly reduced HbAlc in the subgroup population (baseline HbAlc =9%) at 12 weeks compared to Sitagliptin and Metformin SR (-1.50£0.92 vs -1.03£0.61, p=0.0007) and Dapagliflozin and Metformin ER (-1.16:0.80, p=0.0169). Among this subgroup population, Dapagliflozin, Sitagliptin, and Metformin ER also reduced the HbA lc greater than Sitagliptin and Metformin SR (-2.18+0.97 vs -1.46+£0.73, P<0.001) and Dapagliflozin and Metformin ER (-1.53+£0.79, P<0.001) at 16 weeks. (Refer Figure 2).

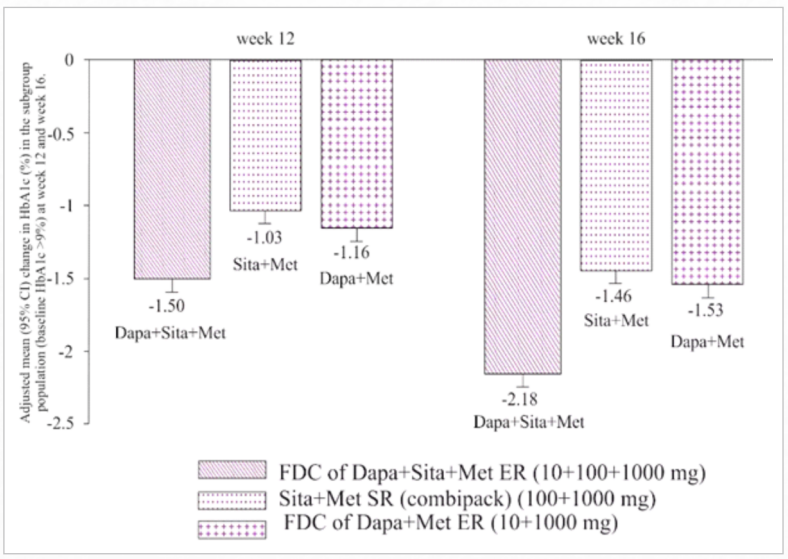


Fig 2: Adjusted mean change in HbA1C (%) in the subgroup population at week 12 and week 16.

Effect on Postprandial & Fasting Blood Glucose Levels

At week 16, Dapagliflozin, Sitagliptin, and Metformin ER showed a significant reduction in postprandial blood glucose compared to Sitagliptin and Metformin ER (-59.5+59.66 mg/dl vs -48+48.17 mg/dl, P=0.0696) and Dapagliflozin and Metformin ER(-44.5+40.73 mg/dl, P=0.0394).

Dapagliflozin, Sitagliptin and Metformin ER also significantly reduced fasting blood glucose compared to Sitagliptin and Metformin SR at 16 weeks (-44.0£33.26 mg/dl vs -35.7£34.44 mg/dl, P=0.0226) and Dapagliflozin and Metformin ER(-36.4+30.76 mg/dl, P=0.0542).

Patients Achieving Target Glycemic Control

The proportion of patients achieving HbA lc <7.0% (53 mmol/mol) at week 16 was significantly higher with Dapagliflozin, Sitagliptin, and Metformin ER (38.5%) versus Sitagliptin and Metformin SR (12.8%) (p<0.001) and Dapagliflozin and Metformin ER(21.3%)(p = 0.0023). (Refer Figure 3)

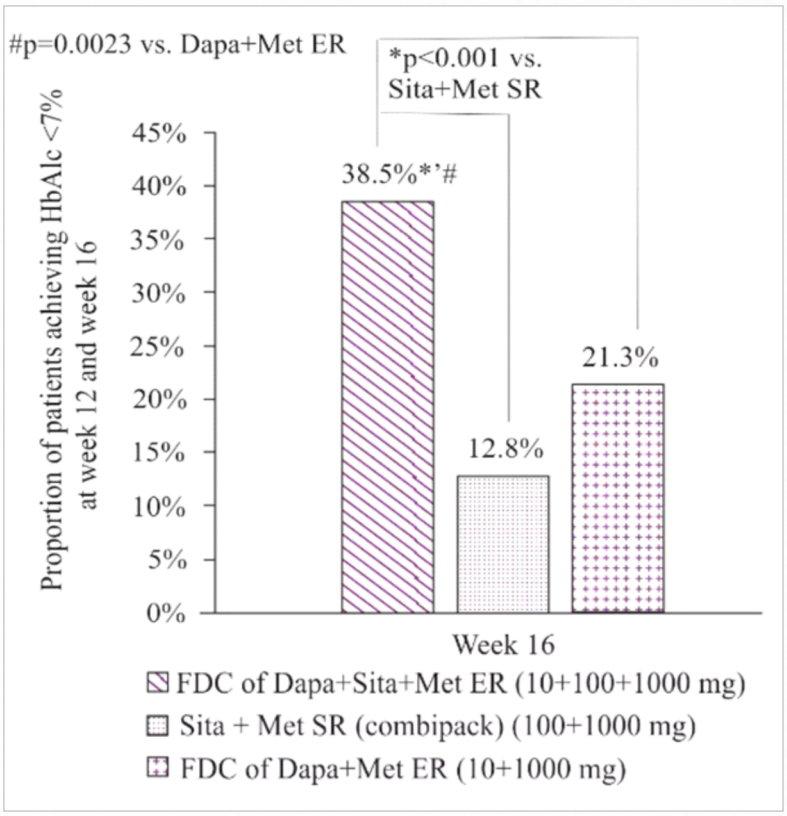


Fig 3: Proportion of patients achieving HbA1c <7% (53 mmol/mol) at week 16.

The mean reduction in body weight from baseline to week 16 was significantly greater in the Dapagliflozin, Sitagliptin, and Metformin ER group when compared with only Sitagliptin and Metformin SR (- 0.69 + 1.67 kgs versus - 0.35 = 1.56 kgs ; p=0.0245).

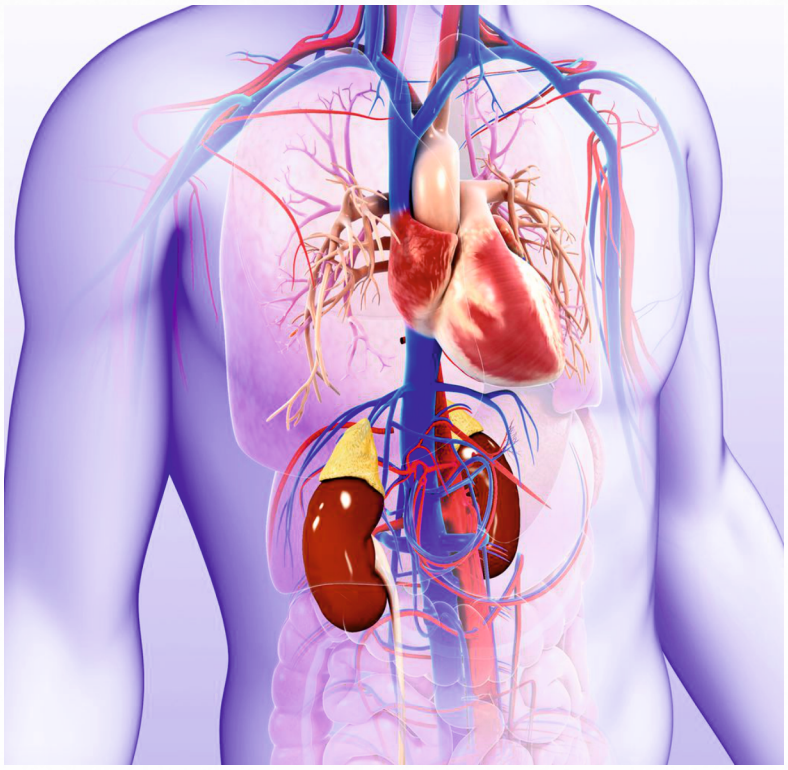
Triple FDC of Dapagliflozin, Sitagliptin, Metformin-Well Tolerated Safety Profile

All drugs were well tolerated, and there were no clinically significant variations in systolic or diastolic blood pressure across treatment groups. During the study, no serious adverse events, fatalities, or severe or life-threatening treatment-emergent adverse events (TEAEs) were reported.

Guideline Recommendations on Triple Therapy for the Management of Type 2 Diabetes:

The triple FDC treatment choice will be in accordance with various guidelines' recommendations. The ADA recommends that treatment intensification not be postponed for individuals who are not meeting treatment goals. The American Diabetes Association (ADA) European Association for the Study of Diabetes (EASD) and the American Association of Clinical Endocrinologists (AACE) recommendations also encourage the inclusion of a third non-insulin agent after weighing the benefits and risks of the new medicine. The ADA and the Research Society for the Study of Diabetes in India (RSSDI) guidelines recommend initiating combination therapy for patients with HbAlc [=1.5% above target]: whereas the AACE guidelines recommend dual or possibly triple-combination pharmacotherapy, usually including Metformin, for newly diagnosed people with T2D and an entrv HbA 1c [9.0% and/or >1.5% above target].

Here's What to Know About Cardiovascular-Kidney -Metabolic Syndrome, Newly Defined by the AHA



Cardiovascular disease often occurs with kidney disease and metabolic diseases, including obesity and type 2 diabetes. And having more than 1 of these conditions multiplies health and mortality risks, particularly due to cardiovascular disease. An American Heart Association (AHA) presidential advisory recently published in Circulation newly defines the adverse interplay among these conditions as cardiovascular-kidney-metabolic (CKM) syndrome.

The advisory provides guidance on how to stage CKM syndrome in patients, predict its cardiovascular outcomes, and effectively manage, prevent, and even reverse it in both adults and children. Evidence is detailed in a separate scientific statement. Together, the publications provide a framework for holistically and equitably improving CKM health in the population, according to the advisory. They also lay the groundwork for a new cardiovascular disease risk calculator that will incorporate the concept of CKM health for the first time.

The Backstory

The advisory notes that the mutually reinforcing harmful relationships among metabolic diseases, chronic kidney disease, and cardiovascular disease are known. However, opinions have varied on how or to what degree these conditions together constitute a syndrome, which suggests a common underlying pathophysiology.

"There has been increasing interest in the interplay among these conditions, but there has not been a clear definition," Chiadi E. Ndumele, MD, PhD, the advisory writing committee chair, said in an interview with JAMA. This has impaired treatment that addresses the entire CKM syndrome–risk spectrum, added Ndumele, who is an associate professor and director of obesity and cardiometabolic research at Johns Hopkins University.

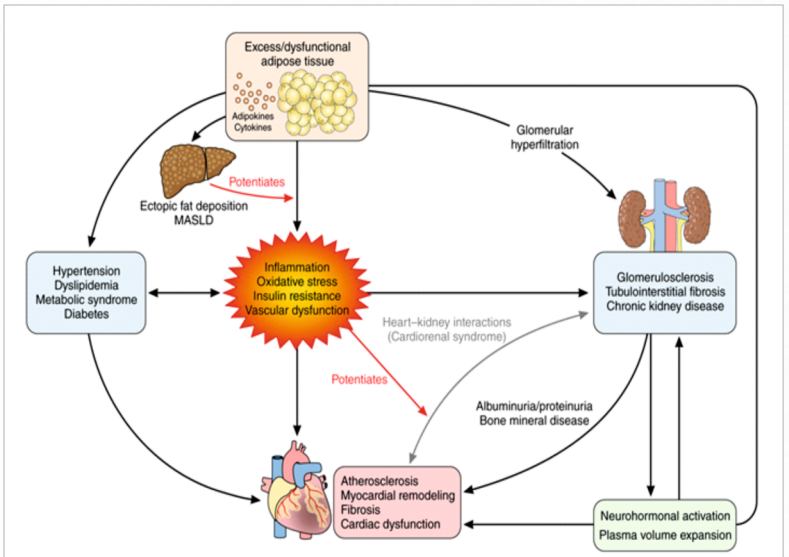
To address the high and increasing prevalence of poor CKM health, the AHA developed a consensus statement to clarify the definition of CKM syndrome and the tools to better detect, prevent, and manage it. They are included in the advisory and the scientific statement, which are the products of a multidisciplinary committee made up of 28 experts in cardiology, nephrology, endocrinology, primary care, and pediatrics.

The advisory attempts to bridge sometimes inconsistent specialty-specific recommendations, Ndumele said. There was a lot of attention given to harmonization across current guidelines. Where there were gaps or a lack of clarity, we identified those areas & then tried to provide clarity wherever possible.

Why This Matters?

Metabolic diseases-such as obesity and type 2 diabetes and chronic kidney disease can damage nearly every major organ system. In particular, they increase the risk of cardiovascular diseases including heart failure, atrial fibrillation, coronary artery disease, stroke, and peripheral artery disease, as well as the chance of premature death. Collectively, heart disease, stroke, kidney disease, and diabetes directly accounted for more than 1 million deaths in the US in 2021, or about 29%. Indeed, the increasing prevalence of CKM-related risks has slowed 5 decades of decline in cardiovascular disease mortality, the advisory notes. And excess weight and its downstream comorbidities directly and indirectly cost an estimated $1.7 trillion annually.

There was a lot of urgency around addressing this challenge, and, at the same time, a growing array of therapeutic options for addressing it, Ndumele said. The clear public health challenge and growing clinical options make this very timely.



Conceptual Diagram of the CKM Syndrome

What Is CKM Syndrome?

In lay terms, the advisory defines CKM syndrome as a health disorder due to connections among heart disease, kidney disease, diabetes, and obesity, leading to poor health outcomes. The syndrome increases the risk of development and progression of cardiovascular disease and includes both those at risk of and those with existing cardiovascular disease.

Adopting this definition helps clarify understanding of these adverse interactions and supports specific constructs for staging, screening, risk stratification, and prevention and treatment, Ndumele said. It also may help more effectively communicate metabolic health factors and their risks to patients in a nonjudgmental way, according to Ashish Sarraju, MD, a preventive cardiologist at the Cleveland Clinic, who was not involved in the advisory development.

How It's Staged?

The staging for CKM syndrome laid out in the advisory reflects its pathophysiology, risk factors, and opportunities for prevention and care:

- **Stage 0:** no CKM risk factors
- **Stage 1:** excess or dysfunctional adiposity-a source of proinflammatory and prooxidative secretions that cause tissue damage and reduce insulin sensitivity
- **Stage 2:** metabolic risk factors-specifically hypertriglyceridemia, hypertension, diabetes, and metabolic syndrome; or moderate- to high-risk chronic kidney disease
- **Stage 3:** subclinical cardiovascular disease with CKM syndrome or risk equivalents-specifically high predicted cardiovascular disease risk or very high-risk chronic kidney disease
- **Stage 4:** clinical cardiovascular disease with CKM syndrome

"The goal is to give more clarity on how to use these therapeutic tools and also better support prevention across the life course," Ndumele said. "With substantial lifestyle changes and significant weight loss, we can even see regression in staging."

Screening and Risk Assessment

Screening for risk factors should begin early in life, the advisory notes, and should increase in frequency if CKM syndrome stages progress. A new risk calculator soon to be published will incorporate CKM health to facilitate cardiovascular risk assessment and outcome prediction, which should start at age 30 for affected patients. Social determinants of health significantly affect risk and should be screened for and considered.

Treatment and Prevention

Excess body fat and related insulin resistance are the root cause of many harms from CKM syndrome, according to the scientific statement. They should be addressed through lifestyle modification and weight loss, the recommendations say. Early use of medications, including sodium-glucose transport protein 2 (SGLT2) inhibitors and glucagon-like peptide 1 (GLP-1) receptor agonists, also may reduce cardiovascular disease risk. Education and support for healthful lifestyles may help improve CKM health in both individual patients and the population.

Access to Care

The advisory emphasizes that holistic care strategies, including value- and volume-based models that support interdisciplinary care, may help reduce care fragmentation and may improve treatment and outcomes. These strategies should address social determinants of health. Forming multidisciplinary teams and community partnerships can help mobilize resources for an effective response.

CASE STUDY - 1

Xanthomas: More than a cosmetic problem

PROF. V K BHARDWAJ

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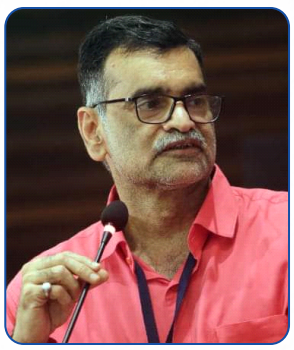


Introduction:

Xanthomas comprise deposits of lipid laden macrophages in dermis. Xanthomas are well circumscribed lesions in the connective tissue of the skin, tendons or fasciae that predominantly consist of foam cells; these specific cells are formed from macrophages as a result of an excessive uptake of low density lipoprotein (LDL) particles and their oxidative modification.

Clinically 5 types of xanthomas have been described:

1). Xanthelasma palpebrum
2). Tendinous xanthomas
3). Tuberous xanthomas
4). Eruptive xanthomas
5). Diffuse plane xanthoma

Usually xanthomas are associated with lipid abnormalities, which can be primary or secondary to a systemic disease. Sometimes lipid abnormality is not evident at presentation but develops over subsequent follow-up. Rare case reports of normolipidemic xanthomas have been described. Sometimes lymphoproliferative disorders manifest as xanthomas.

Xanthelasma is not uncommon. Usually seen in middle aged individuals. it presents as yellowish/skin colored patches on the upper and lower eyelids. May or may not be associated with lipid abnormalities. They are associated with increased risk of atherosclerotic cardiovascular disease.

Tendinous xanthomas present as small papules over tendo-achilles, tendons on dorsum of hands and elbows. They gradually increase in size. Usually they are painless.

Tuberous xanthomas present as small subcutaneous nodules over pressure points of extremities but may be present at other sites.

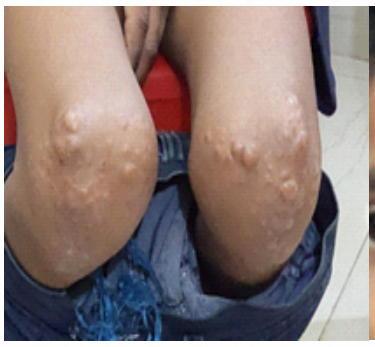
Eruptive xanthoma comes as a crop of skin colored/ purplish nodules over the body. They are manifestation of severe hypertriglyceridemia

Xanthoma striatum palmare is pathognomonic for primary dysbetalipoproteinemia, Diffuse plane xanthomas are frequently associated with paraproteinemia and lymphoproliferative disorders.

Tendinous xanthoma and tuberous xanthoma which develop in children are usually associated with familial hypercholesterolemia. They are associated with 2-4 fold increased risk of ASCVD

Case Description: Here is a case report of tendinous xanthoma in a boy

A 10 year 2 month old boy was referred for evaluation of nodules over elbow joints and knee joints. Pic. 1 and Pic. 2. Painless small nodules were first noticed at the age of 8.5 years which were ignored as they were painless and the child had no apparent problems. The number and size of nodules gradually increased over 1.5 years and the nodules were conspicuous by their increasing number and size. The siblings and parents did not have such nodules anywhere on their body. As per the knowledge of the father none of the relatives on paternal or maternal side suffer from such problems. Child weighed 30 Kg, measured 136.5 cm. He had an average build. His vitals were within normal range. Multiple nodules of varying size , measuring upto 1 cm in largest diameter were present over both elbows, some of them were freely mobile while others were adherent to underlying fibrous tissue.



Investigations: Hematological, liver, renal, and thyroid profiles were within normal range. Abdominal ultrasound showed no abnormalities. Lipid parameters, however, were grossly deranged (see Table 1), confirming the association with xanthoma development.

	Baseline	After 3.5 Months
Total Cholesterol	454 mg/dl	298 mg/dl
HDL Cholesterol	34 mg/dl	32 mg/dl
LDL cholesterol	396 mg/dl	246 mg/dl
Triglycerides	110 mg/dl	100 mg/dl
VLDL Cholesterol	22 mg/dl	20 mg/dl

Table no. 1 Lipid profile at baseline and 3.5 months after statin therapy

Treatment and Follow-up: The patient was prescribed a balanced diet with restricted fried food and increased physical activity. Atorvastatin 20 mg per day was initiated. Follow-up after 3.5 months demonstrated the patient's tolerance to atorvastatin, stable vitals, and improved lipid profile (see Table 1).

He came for follow-up after 3.5 months. He had tolerated atorvastatin.

His vitals were stable Fasting lipid profile was repeated. (Table no.1)

Discussion: The xanthoma are histologically composed of lipid laden macrophages, histiocytes, lymphocytes with evidence of fibrosis. There histological structure has some similarity with atheroma seen in atherosclerotic cardiovascular disease. The lipoprotein present in xanthoma is in equilibrium with plasma lipids. In a study using radio-labeled cholesterol, Bhattacharyya et al found that the exchange of plasma lipids and xanthoma lipids occurs at a rate which is different from what has been reported for atheroma.

Decreasing plasma lipid levels is likely to reduce ASCVD in the individuals, particularly with hypercholesterolemia.

Familial Hypercholesterolemia is an autosomal dominant disorder associated with very high LDL Cholesterol. LDL Cholesterol elevation is more pronounced in Homozygous variant than Heterozygous variant.

Treatment comprises a healthy lifestyle consisting of increased physical activity, avoidance of alcohol and tobacco products. Diet modification involves reduction of dietary fat to 3% of calories, saturated fat to 8% and cholesterol to 100 mg per 1000 calories.

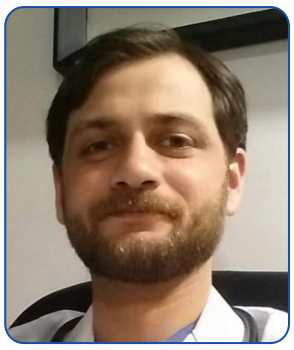
Mainstay of pharmacotherapy is statin use. Pravastatin is approved for use in children above 8 years of age. Atorvastatin, simvastatin and lovastatin are approved for use above 10 years of age. Ezetimibe is also approved for use in children and adolescents.

Conclusion: This case underscores the significance of recognizing and managing tendinous xanthomas in pediatric patients, highlighting the role of early intervention and comprehensive therapeutic approaches in minimizing the risk of atherosclerotic cardiovascular disease.

CASE STUDY - 2

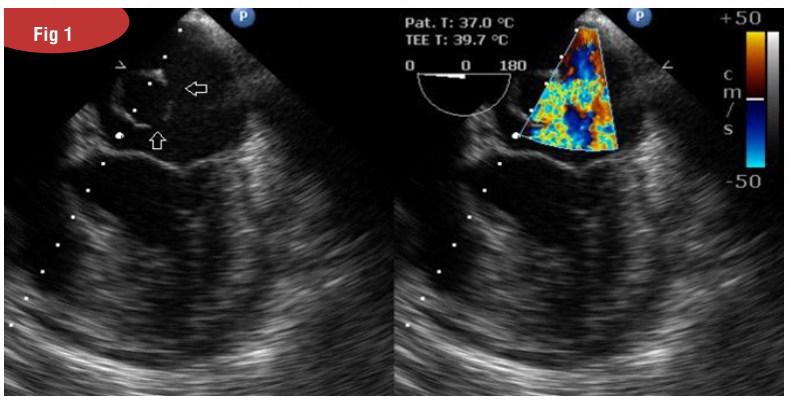
Ruptured Submitral Aneurysm: A Comprehensive Case Study

DR VAIBHAV SHUKLA
DM, Cardiologist, Indore



Introduction: Submitral aneurysm, initially documented in 1812, is an uncommon cardiac anomaly that typically emerges at a young age. Although most common presentation is moderate-severe mitral regurgitation, presenting with gradual worsening dyspnea. Presentation with ventricular tachycardia, thromboembolism, left ventricular diastolic overload, infective endocarditis, left circumflex and left main obstruction has been reported. A congenital maldevelopment resulting in weakness of the posterior mitral fibrous annulus causing formation of a true aneurysm has been considered as an etiology. Diagnosis in utero has been made, supporting a congenital etiology. This case contributes valuable insights by presenting a unique scenario of a ruptured submitral aneurysm extending into the left atrium.

Case Presentation: A 34-year-old male presented with a one-week history of acute breathing difficulty, orthopnea, and expectoration. Clinical examination revealed tachycardia, a third heart sound, pansystolic murmur of mitral regurgitation, and bilateral basal crepitations in the chest, indicative of left ventricular failure. Stabilization was achieved with intravenous diuretics and oral vasodilators.



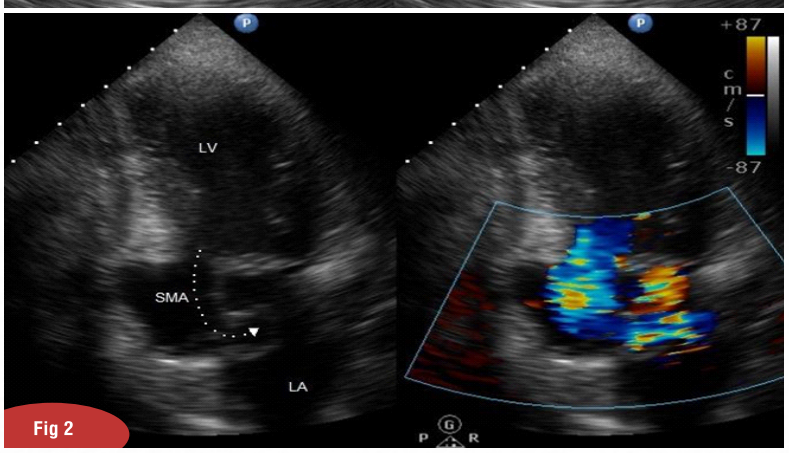


Fig 2

Diagnostic Assessment: Bedside transthoracic echocardiogram revealed a Type I ruptured submitral aneurysm with a single localized neck (Fig 1). The aneurysm exhibited a tunneling effect from the left ventricle to the left atrium. Color contrast demonstrated turbulence at the site of rupture. Subsequent transesophageal echocardiogram further confirmed these findings (Fig 2).

Discussion: The submitral aneurysm is believed to have a congenital origin, stemming from maldevelopment resulting in weakness of the posterior mitral fibrous annulus. Du Toit HJ et al's classification system categorizes the aneurysm into three types based on the extent of involvement:

- Type I: Characterized by a single localized neck.
- Type II: Displays multiple necks.
- Type III: Involves the entire posterior mitral annulus.

Although initially reported in Africans, cases have been documented globally, indicating its presence across diverse races.

Treatment and Outcome: Surgical repair emerged as the recommended course of action for the ruptured submitral aneurysm. However, the patient opted to decline surgery, introducing complexities in managing symptoms and addressing the underlying pathology. A carefully devised medical management plan, including close monitoring, was implemented to optimize the patient's quality of life.

Conclusion: This case underscores the importance of recognizing the diverse presentations of submitral aneurysms and emphasizes the challenges in managing such cases, particularly when surgical intervention is refused. The patient's decision necessitated a nuanced approach to ensure effective symptom management and address the underlying pathology. Continued research and collaborative efforts are imperative to enhance our understanding of the etiology, natural history, and optimal management strategies for this rare cardiac anomaly.

CASE STUDY - 3

Multinodular bilateral adrenal Pheochromocytomas: A Case Report VHL

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Introduction: Bilateral incidental adrenal nodules represent 10–23% of all incidental adrenal nodules. The general approach to these nodules follows the same premise as for unilateral incidental adrenal nodules however there are features unique to bilateral nodules including the differential diagnosis, the diagnostic approach as well as the management. The majority (75%) of bilateral truly incidental adrenal nodules are benign nonfunctioning adenomas however bilateral lesions are more likely to display hormone excess than unilateral lesions with subclinical Cushing's being the most prevalent abnormality followed by Cushing's syndrome, Hyperaldosteronism as well as Congenital Adrenal Hyperplasia (CAH).

Though bilateral pheochromocytomas are less common, a patient presenting with bilateral pheochromocytomas will usually have a germline pathogenic variant and be syndromic. The overall diagnostic approach to bilateral nodules involves determining based on the patients' clinical history and examination as well as the imaging phenotype of each lesion whether the lesions could represent a malignancy, exhibit hormonal excess and whether they could represent a familial syndrome. In patients with bilateral infiltrative lesions, adrenal insufficiency needs to be excluded.

In evaluation of bilateral adrenal masses, age at presentation, presenting symptoms, lesion size, and biochemical features are helpful in delineating varied underlying aetiologies .

Causes: The exact causes of adrenal nodules are unclear. A benign (noncancerous) or malignant (cancerous) nodule, also called a tumor or mass, may develop in one of the adrenal glands that sit atop each kidney. Bilateral adrenal masses may have aetiologies like hyperplasia and infiltrative lesions, besides tumours. Hyperplastic and infiltrative lesions may have coexisting hypocortisolism. Bilateral tumours are likely to have hereditary/syndromic associations. Pheochromocytoma is curable in 90% of cases, yet its diagnosis and localization are among the most challenging problems in clinical medicine. Although only 10% of these tumors are malignant. The clinical hallmark of pheochromocytoma is hypertension, but some patients are normotensive and may even be hypotensive.The recommended initial test include the determination of either plasma free metanephrines or urinary fractionated metanephrines .

Case Presentation: A 18 year female with complaint of fatigue and vertigo with BMI 21.38 kg/m2and Blood Pressure was measured at 200/100mmHg. Patient had no GI/ Urinary complaint and no joint pain & weight was static. No fibromatosis changes observed spider Navie over skin above sternal region.

Patient was referred for ophthalmologist opinion for retinal hemangioblastoma check-up which is part of VHL, and she is having small lesion and advised for observation for same.

No renal, pancreatic, liver cyst observed. Patient's father is hypertensive and no family history of neuroendocrine tumour or adrenal /pituitary lesion.

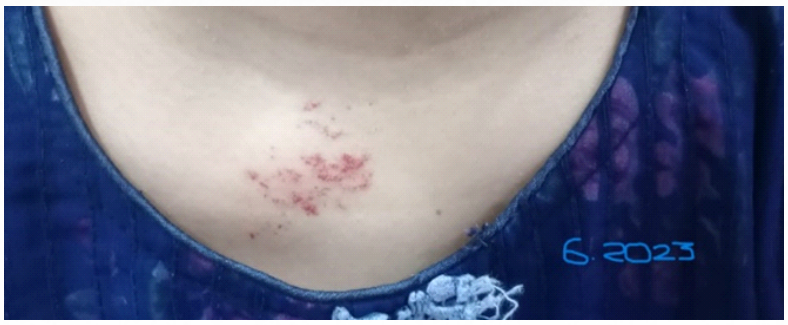
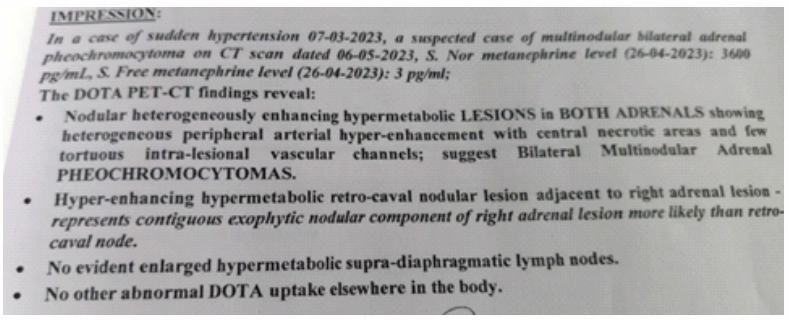


Image: Spider Navie over skin above sternal region

Examination and Investigations: Laboratory findings:
Free Nor metanephrine- 3600(0-180)
C. T. SCAN OF ABDOMEN & PELVIS(TRIPHASIO):
Clinical profile: Young hypertension with elevated nor-metanephrine levels.

Table: Investigation chart

Parameters	Value
I ca+	1.30 mmol/L
PO4-	4.72 mg/dL
S. Cortisol (Morning)	10.01 ug/dL
HBA1c	5.31 %
S. Creatinine	0.80 mg/dL
SGPT	16.69 U
Plasma Free Metanephrine Level	3.0 pg/mL
Plasma Free Nor Metanephrine Level	3600 pg/mL
Na+	142.8 mEq/L
K+	4.44 mEq/L
S. TSH	2.680 uIU/mL
Calcitonin	0.864 pg/mL
Prolactin	14.01 ng/mL



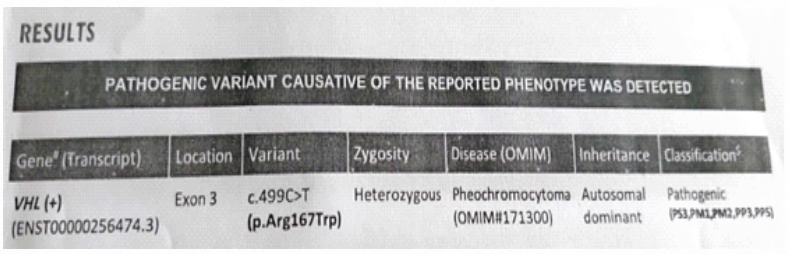
IMPRESSION:

In a case of sudden hypertension 07-03-2023, a suspected case of multinodular bilateral adrenal pheochromocytoma on CT scan dated 06-05-2023, S. Nor metanephrine level (26-04-2023): 3600 pg/mL, S. Free metanephrine level (26-04-2023): 3 pg/ml;

The DOTA PET-CT findings reveal:

- **Nodular heterogeneously enhancing hypermetabolic LESIONS in BOTH ADRENALS showing heterogeneous peripheral arterial hyper-enhancement with central necrotic areas and few tortuous intra-lesional vascular channels; suggest Bilateral Multinodular Adrenal PHEOCHROMOCYTOMAS.**
- **Hyper-enhancing hypermetabolic retro-caval nodular lesion adjacent to right adrenal lesion - *represents contiguous exophytic nodular component of right adrenal lesion more likely than retro-caval node.***
- **No evident enlarged hypermetabolic supra-diaphragmatic lymph nodes.**
- **No other abnormal DOTA uptake elsewhere in the body.**

Image: PET CT Report



RESULTS

PATHOGENIC VARIANT CAUSATIVE OF THE REPORTED PHENOTYPE WAS DETECTED

Gene[1] (Transcript)	Location	Variant	Zygosity	Disease (OMIM)	Inheritance	Classification[2]
VHL (+) (ENST00000256474.3)	Exon 3	c.499C>T (p.Arg167Trp)	Heterozygous	Pheochromocytoma (OMIM#171300)	Autosomal dominant	Pathogenic (PS3,PM1,PM2,PP3,PP5)

Image: Genetic Report

Findings: There were few (at least three on right side and two on left side) nodular hypodense lesions noted in bilateral suprarenal regions, no evident internal calcification noted, both adrenal glands were not seen separately from the lesions. The lesions show areas of arterial phase hyperenhancement with internal non enhancing / necrotic areas and prominent arterial channels traversing lesions. On portal and hepatic venous phase there was mild reduction in density of lesions with 15 minutes delayed phase showing mild washout of contrast. Absolute and relative contrast washout is 72 % and 60 % on right side and 77 % and 59 % on left side respectively. Largest nodule measured 26 x 30 x 30 mm on right side and 37 x 49 x 46 mm on left side. Smaller lesions measured 13 x 11 mm and31 x 17 mm on right side and 25 x 30 mm on left side in axial plane. The lesion causing indentation over renal vessels without encasement.

Diagnosis: In view of arterial phase hyperenhancement within lesions and given clinical, biochemical background findings suggest p/o multinodular bilateral adrenal pheochromocytomas(VHL- Von Hipple Lindau DZ) is likely. Syndromic association needs to be excluded. No evident arterial phase hyper-enhancing lesions in retroperitoneal region or ectopic location in abdomen, pelvic region.

Treatment and Management: First start -Prazosin (2.5 mg) (alpha blockers) given followed by regular BP & pulse monitoring & after that Metoprolol Succinate (23.7 mg) (beta blockers) TDS prescribed for for blood pressure management.

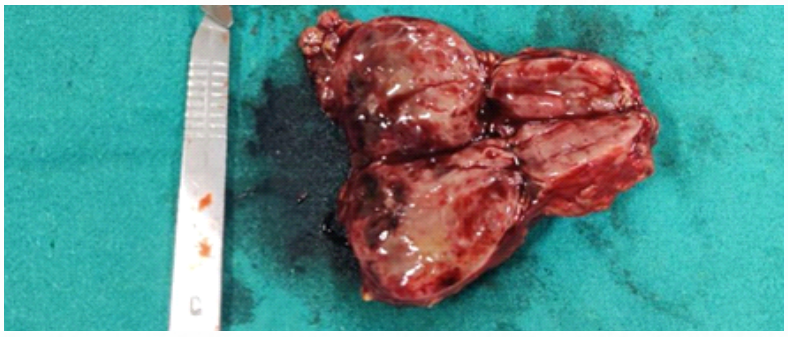


Image: Bilateral Adrenalectomy performed

Follow-Up and Outcomes: After 1 month, patient reported with improved blood pressure 152/100 mmHg. Bilateral Adrenalectomy was performed. Post surgery patient was advised to take Hydrocortisone 10 /20 mg and Fludrocortisone 0.1 mg long term/ lifelong. Periodic investigation was advised post-surgery. Hematinic was prescribed and advised to go for monthly CBC test to check haemoglobin. If it is below 12 mg/dl, patient was advised to continue haematinic for 2 months. Patient was called for follow up after 2 months.

Discussion: Pheochromocytomas are rare, catecholamine-secreting tumors that arise from the adrenal medulla. They are responsible for causing paroxysmal symptoms such as hypertension, palpitations, headaches, and sweating due to excessive release of adrenaline and noradrenaline. The presence of bilateral adrenal pheochromocytomas, particularly in a multinodular form, is even rarer and presents unique challenges in terms of diagnosis and management.

The diagnostic involves measurement of plasma or urinary metanephrines, catecholamines, or their ratios, which are more sensitive and specific than a single measurement. Imaging studies such as CT or MRI of the adrenal glands would likely show the presence of bilateral adrenal nodules.

Surgical resection is the primary treatment for pheochromocytomas. However, bilateral adrenal involvement can complicate the surgical approach. Bilateral simultaneous resection may carry a higher risk due to the potential for inadequate adrenal function postoperatively, necessitating lifelong hormone replacement. Unilateral resection may be considered, but careful evaluation of the other adrenal gland is required to ensure it is not functioning autonomously. After surgery, patients with bilateral adrenal involvement might require hormone replacement therapy, including glucocorticoids and mineralocorticoids, to manage adrenal insufficiency. This poses challenges in terms of finding the right dosage and balancing the potential risks of over- or under-replacement.

Although surgical removal of the tumors can lead to resolution of symptoms, some patients might still experience persistent hypertension postoperatively due to other factors. Close monitoring and appropriate antihypertensive medications are essential to manage blood pressure effectively.

Given the bilateral and potentially multinodular nature of the tumors, there might be an underlying genetic predisposition. It would be important to assess the patient's family history and consider genetic testing for conditions such as multiple endocrine neoplasia type 2 (MEN2) or von Hippel-Lindau (VHL) syndrome.

Conclusion: Multinodular bilateral adrenal pheochromocytomas present a complex diagnostic and management challenge due to their rarity and the potential for adrenal insufficiency post-surgery. The prognosis for patients with bilateral adrenal pheochromocytomas largely depends on early diagnosis, successful surgical intervention, and effective postoperative management of hormonal imbalances and blood pressure control. Regular follow-up appointments, including hormone level monitoring and imaging studies, are necessary to ensure recurrence is detected promptly, and any hormonal imbalances are addressed.

HEALTHY LIVING

People Who Stay Up Late May Have a Greater Risk of Diabetes, Study Finds

People who prefer to go to bed late and wake up late may be putting their health at risk, according to a new study.

It's no secret that the quality of someone's sleep habits impacts their wellbeing.2 But evidence also points to the timing of someone's nightly routine as a factor in overall health and lifestyle.

The new study, published in the Annals of Internal Medicine journal, found that night owls, or people with "evening chronotypes," were more likely to have unhealthy lifestyle habits and to develop diabetes.

"People with 'night owl' are at a 72% increased risk of developing diabetes-and that's a substantial increased risk when we compare them to early birds," Sina Kianersi, DVM, PhD, first study author and postdoctoral research fellow at Brigham and Women's Hospital and Harvard Medical School, told Health.

The research team also found that night owls were more likely to smoke, exercise infrequently, and engage in other negative lifestyle behaviors.

Kianersi explained that because the study was done in a large cohort of middle-aged female nurses, there may be some limitations to its applicability. However, the research builds on the general idea that a person's sleep preferences can have major implications for their health.

"The effect of shift work [on] our metabolism and insulin resistance have been in the literature within the last decade or more," Betul Hatipoglu, MD, professor of medicine at Case Western Reserve University School of Medicine, told Health in an email. "However the article describes that the increase was observed in day shift workers. That is an interesting observation."

Here's what experts had to say about the link between sleep preferences and overall health, why night owls might be at a higher diabetes risk, and what people can do to ensure their chronotype doesn't get in the way of their wellbeing.

Comparing Night Owls and Early Birds

To understand the relationship between chronotype and diabetes, Kianersi & his team gave over 60,000 female nurses a survey where they could rank their sleep preferences on a spectrum-about 35% of the participants identified as definite early birds, while about 11% identified as definite night owls.

When the study started, none of the participants had a history of cancer, cardiovascular disease, or diabetes. They were asked to report any new diabetes diagnosis until the study ended in 2017.

Researchers also used a questionnaire to determine the nurses' lifestyle in six areas: alcohol use, body mass index (BMI), physical activity levels, smoking status, sleep duration, and diet.

Overall, self-proclaimed night owls tended to also have a less healthy lifestyle based on these factors.

According to the questionnaire, night owls tended to smoke more, have an unhealthy sleep duration, and not meet exercise recommendations. There was also a significant association between being a night owl and having a poorer diet and a higher BMI.

Kianersi explained that the other major finding from the research was that night owl nurses saw a 72% increased risk of diabetes. But, once unhealthy lifestyle behaviors were accounted for, the additional diabetes risk for this chronotype dropped to 19%.

This means night owls' lifestyle is largely to blame for making their diabetes risk worse, Kianersi said, though their risk, in general, was still elevated.

These aren't necessarily novel findings-recently published studies have found that being a night owl could put someone at an elevated risk of diabetes and cardiovascular disease, and that night owls are more likely to use tobacco & alcohol.

But, according to Kianersi, the link between lifestyle factors and night owls' elevated diabetes risk is what sets this study's findings apart from previous research.

Are Night Owls' Internal Clocks to Blame?

Unhealthy lifestyle behaviors account for most of night owls' elevated diabetes risk, which aligns with what scientists already know about the disease.

The Centers for Disease Control and Prevention list the following as risk factors for type 2 diabetes:

- Being overweight
- Exercising infrequently
- Smoking
- Lack of sleep

These factors were also reflected in the study.

However, even after accounting for these behaviors, night owls were still at a 19% increased risk of diabetes as compared to early birds.1 It's not totally clear why this is the case, though this stat could indicate that "there might be something [beyond] lifestyle that is causing this relationship," Kianersi said.

One possibility is that this increased risk is driven by night owls' biology, or more specifically, the way that their internal body clocks deviate from their everyday schedules.

Other research has found that misalignment between someone's circadian rhythm and their sleeping or eating schedule can negatively affect appetite-regulating hormones, glucose metabolism, and mood.

These changes in hormones make night owls more prone to insulin resistance and metabolic syndrome, Hatipoglu explained.

Night owls also tend to get less sleep during the work week and more on weekends, which could be a concern as irregular bedtimes have been associated with a higher risk of hypertension.

The study did find that diabetes risk was higher for night owl nurses who did not do shift work-meaning they likely had to work, at least to some degree, in the mornings. This could imply that if a person's circadian rhythm, or body clock, is misaligned with their daily routine, it may worsen their health.

"The best scenario for our health is to follow our internal body clock," said Kianersi. "If you are a night owl, you prefer to go to bed late at night-if you have work that syncs to your body clock, then that is healthy for us. But if you're an early bird, then working late [at] night, it's going to be a little bit hazardous."

How Can Night Owls Stay Healthy?

The new findings may seem alarming for people who prefer to go to bed and wake up later, however, there's a silver lining-the lifestyle factors largely driving night owls' increased diabetes risk can be changed.

"It is good news [for] night owls," Kianersi said. "Even though they have an increased risk of diabetes, maybe if they just adjust some of their poor health habits, these increases can substantially be decreased."

Rather than trying to become an early bird, a much simpler solution is for night owls to make small lifestyle adjustments in the six categories included in the study.

This would mean aiming to get at least 150 minutes of moderate-to-vigorous physical activity each week, eating a nutritious diet, getting between 7 and 9 hours of sleep each night, lowering tobacco and alcohol consumption, and keeping a healthy weight.

Reducing screen time and managing stress might also help people get better sleep and lower their health risks, Hatipoglu added.

Beyond the individual, big picture implications of this type of research could be a shift toward more personalized or flexible work hours, Kianersi said, so that early birds and night owls could have a schedule that better aligns with their internal clock.

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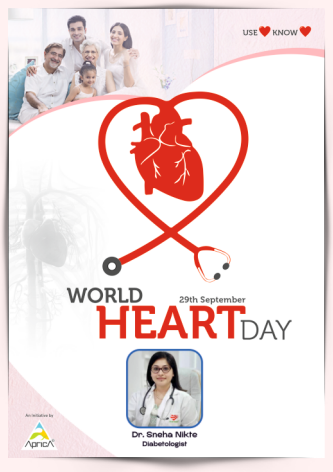

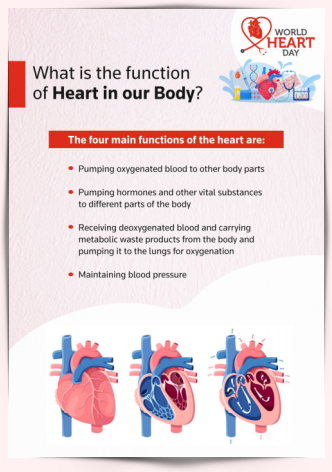

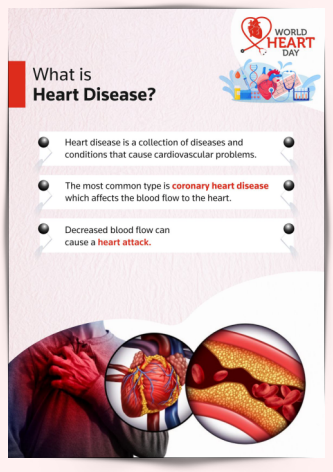

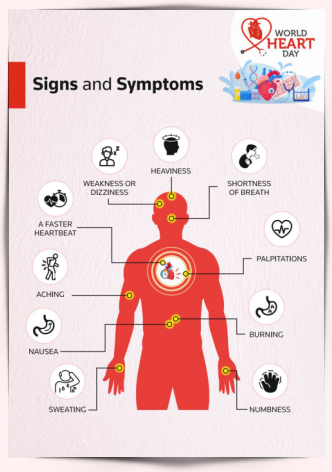

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