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Global Health
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Diabetes Management
Advances in the Management of Type 2 Diabetes in Adults

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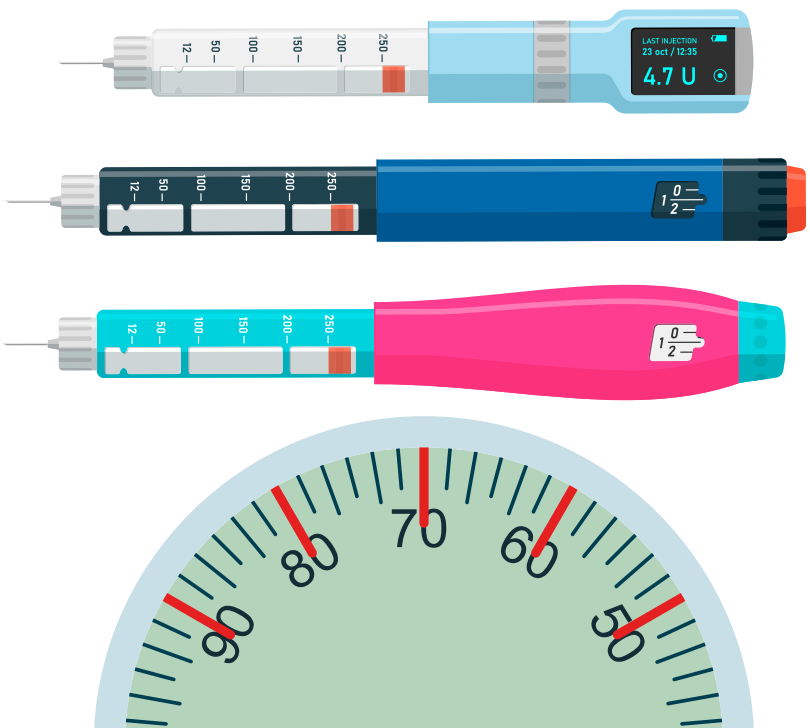

Shaping the future of healthcare

SIEMENS Healthineers

CONTENTS

September 2023

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Healthcare professionals, armed with knowledge, dedication, and a patient-centered mindset, are poised to make a profound difference in the lives of individuals living with diabetes, ensuring that they receive the best care and the brightest future possible.

CONTENTS

September 2023

The Brief

In the quest to diagnose and prevent dementia, the UKBDRS offers a promising tool for initial screening. High-risk individuals may benefit from further assessments like cognitive testing or genetic screening.

Page 10

VIEWS & REVIEWS

The Role of 18 F- Fluorodeoxyglucose Positron Emission Tomography with Low Dose Computed Tomography for Evaluation of Fever of Unknown Origin

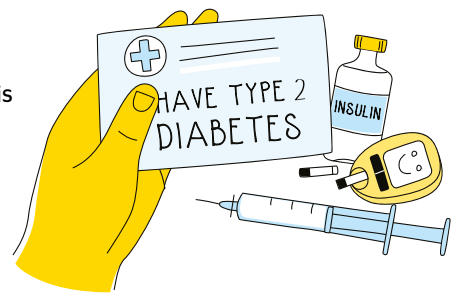
15

VIEWS & REVIEWS

Advances in the Management of Type 2 Diabetes in Adults

The past decade has seen multiple developments in each aspect of the management of diabetes. This review focuses specifically on recent advances in the management of hyperglycaemia in diabetes, including drug and non-drug treatments.

21



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Feature

40 DENGUE OUTBREAK

COULD A NEW TOOL STOP A DENGUE OUTBREAK BEFORE IT EVEN STARTS?

In 2022, Vietnam went through one of its worst dengue outbreaks. According to the World Health Organization (WHO), there were more than 360,000 reported cases of dengue and 140 deaths in Vietnam. By comparison, in 2021, Vietnam recorded 72,880 cases and 27 deaths.

IN EVERY ISSUE

ON THE COVER

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Prologue

Democratizing Diabetes Treatment: From Breakthroughs to Access

Diabetes, a chronic metabolic disorder affecting millions worldwide, has long been a significant public health concern. However, recent advancements in treatment options, exemplified by medications like Wegovy and Ozempic, herald a new era in diabetes management that holds the potential to transform the lives of individuals grappling with this condition. It is crucial that we not only celebrate these breakthroughs but also strive to ensure equitable access to these novel modalities for all, recognizing the profound public health implications of diabetes.

The advent of Wegovy and Ozempic represents a remarkable stride in diabetes management. These medications, categorized as GLP-1 receptor agonists, stimulate insulin release, slow digestion, and reduce appetite. What sets them apart is their dual impact on diabetes and obesity, addressing two major health crises in tandem.

Yet, the true challenge lies in democratizing access to these advanced treatments, transcending socio-economic barriers. Diabetes, particularly type 2, disproportionately affects disadvantaged populations with limited healthcare access. Thus, policymakers and healthcare stakeholders must collaboratively craft strategies to make these therapies universally accessible.

From a public health perspective, diabetes is an exigent concern. Its complications, spanning heart disease, kidney failure, blindness, and limb amputation, exact a significant toll. Moreover, diabetes places an immense economic burden on society, escalating healthcare expenses and diminishing productivity. Consequently, tackling diabetes extends beyond individual health—it is integral to broader public health objectives.

The COVID-19 pandemic has underscored the vulnerability of those with underlying conditions like diabetes. Effectively managing and preventing diabetes is now more crucial than ever. In addition to the promising strides in diabetes care, this issue of AMJ extends attention to two other pressing health issues—dengue fever and dementia.

Dengue fever remains a formidable health challenge, predominantly in developing nations. This mosquito-borne disease can lead to severe complications and fatalities, disproportionately affecting marginalized communities. Mitigating dengue's impact necessitates robust vector control, improved healthcare infrastructure, and heightened public awareness.

Dementia, characterized by cognitive decline, afflicts millions globally, with numbers projected to rise. While dementia often accompanies aging, it is not an inevitable aspect of growing older. Addressing dementia demands a comprehensive approach—early diagnosis, caregiver support, and concerted research into treatments and prevention.

These issues—diabetes, dengue fever, and dementia—paint a multifaceted picture of global health. By spotlighting these topics, we aspire to foster awareness, galvanize action, and propel ongoing research and innovation. Together, we can enhance the well-being of individuals and communities worldwide, steering them toward healthier, brighter tomorrows.

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Case Reports

Editorial

A Focus on Diabetes, Dengue Fever, and Dementia

This edition of *AMJ* embarks on a journey through the intricate web of global health, with a spotlight on three pivotal areas: Diabetes, Dengue Fever, and Dementia. These topics, while distinct, converge in their profound impact on public health and the urgent need for innovation and equitable access to care.

Diabetes, a metabolic disorder, has witnessed remarkable advancements in recent times. Medications such as Wegovy and Ozempic, both GLP-1 receptor agonists, have revolutionized diabetes management. These therapies not only regulate blood sugar levels but also hold promise in addressing the co-occurring obesity crisis. Yet, the ethical imperative remains clear: we must ensure that these breakthrough treatments are accessible to all, transcending socio-economic disparities.

The global burden of diabetes extends beyond individual health, cascading into healthcare systems and economies. As we celebrate progress in diabetes care, we must unite in our commitment to make these advances available to everyone.

Dengue fever, a persistent threat in developing nations, demands a concerted effort in vector control, healthcare infrastructure improvement, and public awareness. It serves as a stark reminder that infectious diseases continue to be a global concern. In this context, innovative tools like E-DENGUE offer a ray of hope. By harnessing technology and collaborative research, we can better protect communities worldwide, working toward a future where dengue outbreaks are rare rather than recurrent.

Dementia, characterized by cognitive decline, affects millions globally, with numbers projected to rise. While aging is a risk factor, dementia is not an inevitable part of growing old. In the quest to diagnose and prevent dementia, the UKBDRS offers a promising tool for initial screening. High-risk individuals may benefit from further assessments like cognitive testing or genetic screening. Early diagnosis, caregiver support, and ongoing research into treatments and prevention are vital components of addressing this complex issue.

Our journey through these topics—diabetes, dengue fever, and dementia—reveals the interconnectedness of global health challenges.

In addition to these critical topics, we have included challenging clinical cases that are clinically challenging case studies that will enrich your clinical acumen.

Happy reading!

Dr Geetha Philips, MD, FRCP

Phenylephrine: Decongestant in Cold and Flu Medicines Doesn't work, says FDA

Phenylephrine, a decongestant commonly found in cold and flu medicines, has been deemed ineffective by an advisory panel to the Food and Drug Administration (FDA). This unanimous decision has raised concerns about the potential removal of phenylephrine from the market. The FDA's independent Nonprescription Drugs Advisory Committee voted unanimously, asserting that "orally administered phenylephrine is not effective as a nasal decongestant at the monographed dosage (10 mg of phenylephrine hydrochloride every 4 hours) as well as at doses up to 40 mg (dosed every 4 hours)." However, the committee did acknowledge that phenylephrine remains effective in nasal sprays and drops, although these are less commonly used.

Several advisers highlighted that patients taking phenylephrine were essentially postponing their path to finding an effective remedy. Maria Coyle, the chairwoman of the panel and an associate professor of pharmacy at Ohio State University, stated, "I think we clearly have better options in the over-the-counter space to help our patients, and the studies do not support that this is an effective drug."

Dr. Leslie Hendeles, a pharmacist from the University of Florida in Gainesville, who, along with colleagues, initially petitioned the FDA in 2007 to remove the drug from the market, emphasized, "If you have a stuffy nose and you take this medicine, you will still have a stuffy nose."

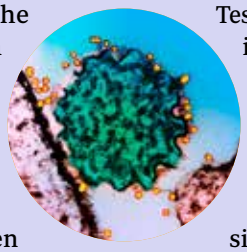
100 Children Per Month Die in Sudan from Preventable Diseases

Sudan is facing a heart-wrenching humanitarian crisis, as preventable diseases claim the lives of around 100 children every month, according to a report by the United Nations. Armed conflicts have displaced more than five million people in the region, exacerbating the dire situation. Between May 15 and September 14, approximately 1,200 children under the age of five succumbed to a deadly combination of suspected measles outbreaks and severe malnutrition in nine internally displaced persons' camps located in Sudan's White Nile state. Additionally, reports of cholera, dengue, and malaria cases have emerged in various parts of the country, heightening concerns of impending epidemics.

The World Health Organization (WHO) stated that children under five bear the brunt of the crisis, constituting nearly 70% of all cases and 76% of all deaths. Sudan's healthcare system is on the brink of collapse due to a severe lack of funding and essential resources.

Nipah Virus: Kerala State in India Acts Swiftly to Control Fresh Outbreak

In response to the re-emergence of the potentially deadly Nipah virus, the Indian state of Kerala has taken swift action by closing schools, offices, and public transport in the Kozhikode district. This decision, made on September 13, was taken as a precautionary measure to prevent the virus from spreading further. To date, there have been two deaths and six confirmed cases linked to the virus. Tests conducted at the National Institute of Virology in Pune have confirmed that a 49-year-old man in Kerala, who passed away on August 30, was a victim of the Nipah virus. The state's second victim, a 40-year-old man, succumbed to the virus on September 11. This marks the fourth occurrence of a Nipah virus outbreak in Kerala since 2018.



The brief

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Climate change is affecting the prevalence of dengue in Dhaka

One of the world's densest cities.The streets of Uttara, a suburb of Dhaka that has expanded rapidly over the past 20 years, are sprayed with insecticide to exterminate mosquitoes during an outbreak of dengue. This process of 'fogging' is unlikely to have much success in preventing an outbreak from spreading as it targets only adult mosquitoes, leaving eggs and larvae unharmed.Despite its limited efficacy, the fumigation process gives communities a sense of reassurance that some effort is being made to protect them.

Screening tool uses 11 risk factors to predict dementia with up to 80% accuracy

In the quest to diagnose and prevent dementia, the UKBDRS offers a promising tool for initial screening. High-risk individuals may benefit from further assessments like cognitive testing or genetic screening.

A new risk scoring tool has emerged on the medical horizon, offering a promising avenue for early dementia detection with an impressive 80% accuracy rate, a staggering 14 years ahead of its usual diagnosis timeline. This breakthrough, known as the UK Biobank Dementia Risk Score (UKBDRS), brings hope to millions worldwide who currently grapple with the relentless progression of dementia—a neurodegenerative condition that erodes memory and cognitive abilities. With no known cure for dementia, prevention becomes paramount in mitigating its profound impact on individuals' overall health and quality of life.

Research has indicated that addressing a set of 12 key risk factors, such as low education levels, smoking, and hypertension, could potentially prevent up to 40% of dementia cases. While previous prognostic models aimed at predicting dementia risk exist, they often come riddled with limitations. For instance, a 2019 systematic review of 61 dementia risk scores found that only eight had been validated through external samples, and even these displayed inconsistent performance in external validation. Most of these models predominantly catered to North American populations, leaving their applicability in other demographic groups uncertain.

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Enter the UKBDRS, a game-changing dementia risk score composed of 11 risk factors. To evaluate its reliability, researchers tapped into healthcare data from the UK Biobank, analyzing information from 220,762 individuals with an average age of 60 over a 14-year period. This data exploration revealed 11 robust predictors of dementia risk: age, education level, parental history of dementia, material deprivation, history of diabetes, stroke, depression, hypertension, high cholesterol, living alone, and gender.

Remarkably, when tested against the remaining 20% of the UK Biobank data, the UKBDRS exhibited an impressive 80% accuracy in predicting dementia incidence. Its efficacy remained undiminished when applied to external data from the Whitehall II study, accurately predicting 77% of dementia cases among the participants, who were followed for 17 years.

Interestingly, the UKBDRS's predictive abilities rivaled those of APOE testing, a genetic biomarker evaluation for dementia. While APOE testing predicted 83% of dementia cases in the UK Biobank sample and 79% in the UK Whitehall II study, the UKBDRS outperformed three other widely used dementia risk scores that had undergone external validation.

Intriguingly, the research also raised questions about gender disparities in dementia risk. Traditionally, Alzheimer's disease and other dementia forms have been considered more prevalent among women due to their longer life expectancy. However, men may face higher dementia risks due to lifestyle factors like smoking, excessive alcohol consumption, and occupational exposure to toxins, coupled with a greater tendency to neglect medical care.

Psychosocial variables, such as material deprivation and living alone, were identified as additional contributors to dementia risk. These factors can indirectly impact brain health by affecting access to healthcare, physical activity, and cognitive stimulation, all of which are vital for maintaining cognitive function.

The Promise of GLP-1 Agonists in Diabetes Management

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The journey of GLP-1 Agonists and Ozempic in diabetes management has been marked by remarkable advancements and promising developments. These drugs have redefined the way healthcare professionals approach the treatment of type 2 diabetes and obesity, offering a comprehensive and personalized approach that goes beyond glycemic control.

In the dynamic landscape of diabetes management, the last few decades have witnessed remarkable advancements in treatment options. Among these innovations, GLP-1 agonists, with Ozempic (semaglutide) at the forefront, have been transforming the lives of individuals grappling with this chronic condition.

Healthcare professionals in the field of diabetes care are continuously seeking innovative therapies that efficiently control blood glucose levels and address the multifaceted challenges confronted by patients.

GLP-1 Agonists and Ozempic

The intertwined epidemics of obesity and type 2 diabetes present substantial global health and economic burdens. Recent pharmacotherapeutic advances have given rise to innovative medications addressing not only glycemic control but also substantial weight loss. A notable breakthrough is Ozempic (semaglutide), a GLP-1 receptor agonist (GLP-1 RA), demonstrating promising efficacy in managing type 2 diabetes while inducing significant weight loss.

A Comprehensive Approach

Traditional treatments for type 2 diabetes primarily emphasize glucose control, often neglecting the critical issue of weight management. Obesity significantly exacerbates insulin resistance and impairs glycemic control. Consequently, there is an urgent need for pharmacological interventions that not only enhance glycemic control but also address the obesity epidemic. Ozempic (semaglutide), a GLP-1 RA, represents a promising pharmaceutical that offers a comprehensive approach to managing type 2 diabetes, addressing both hyperglycemia and obesity.

Mechanism of Action

GLP-1 Agonists, also known as incretin mimetics, constitute a medication class primarily employed in type 2 diabetes mellitus treatment. These drugs emulate the actions of endogenous GLP-1, a hormone secreted by intestinal cells in response to food ingestion. GLP-1 plays a pivotal role in regulating blood glucose levels by stimulating insulin secretion, inhibiting glucagon release, retarding gastric emptying, and promoting satiety. Ozempic's primary mode of action centers on GLP-1 receptor activation, primarily located in pancreatic beta cells. By emulating endogenous GLP-1, Ozempic stimulates insulin secretion in a glucose-dependent manner, reducing postprandial hyperglycemia. Additionally, it curbs glucagon secretion, thereby slowing hepatic glucose production. Beyond glycemic control,

CLINICAL BENEFITS:

1. **Improved Glycemic Control:** GLP-1 Agonists consistently lower HbA1c levels, making them effective alternatives or complements to traditional antidiabetic medications and insulin.
2. **Weight Loss:** Addressing the common comorbidity of obesity in type 2 diabetes, GLP-1 Agonists facilitate weight loss, making them an attractive option for patients seeking both weight management and glycemic control.
3. **Cardiovascular Benefits:** Certain GLP-1 Agonists, including liraglutide and semaglutide, reduce the risk of major adverse cardiovascular events (MACE), offering improved cardiovascular outcomes for diabetes patients at elevated cardiovascular risk.
4. **Renoprotective Effects:** Emerging research suggests that GLP-1 Agonists may have renoprotective properties, potentially slowing kidney disease progression in diabetes patients.

Ozempic significantly influences appetite regulation and energy balance. Activation of GLP-1 receptors in the central nervous system triggers increased satiety and reduced food intake, contributing to the remarkable weight loss observed in clinical trials.

Clinical Efficacy

Numerous clinical trials consistently report Ozempic's efficacy in achieving weight loss among type 2 diabetes patients. Trials such as SUSTAIN and STEP consistently demonstrate substantial reductions in body weight among participants receiving Ozempic compared to placebo, ranging from 5% to 15% of initial body weight, contingent on dosage and trial duration. Notably, Ozempic's weight loss effects are durable over the long term, as evidenced by the SUSTAIN-6 trial, underpinning its role as a weight management strategy.

Safety Profile

Ozempic has exhibited general tolerability in clinical trials, with typically mild to moderate adverse events. Commonly reported side effects encompass gastrointestinal symptoms such as nausea, vomiting, and diarrhea, often diminishing with continued use and manageable through dose titration. Hypoglycemia rates with Ozempic are notably low, particularly when compared to some other antidiabetic medications. Nonetheless, caution is warranted when prescribing Ozempic to patients concurrently taking sulfonylureas or insulin.

FDA Approval and Global Adoption

Ozempic obtained FDA approval in December 2017 and has subsequently received approvals in numerous countries, a testament to its efficacy and safety profile.

Semaglutide for Obesity

Semaglutide, the active component of Ozempic, garnered attention for its potential in obesity treatment, with FDA approval in 2021 for long-term weight management in adults with obesity. This marked a milestone in combating obesity and expanded possibilities for healthcare professionals seeking effective treatments.

Cardiovascular Outcomes

Semaglutide, as evidenced in clinical trials, demonstrated cardiovascular benefits by reducing the risk of major adverse cardiovascular events (MACE) in patients with type 2 diabetes. This positions it favorably in guidelines for diabetes and cardiovascular risk management.

CONSIDERATIONS FOR HEALTHCARE PROFESSIONALS

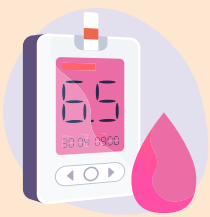
1. Patient Selection: Healthcare professionals should carefully assess patient characteristics, including glycemic control, weight, cardiovascular risk factors, and preferences when contemplating GLP-1 Agonists, ensuring individualized treatment plans.

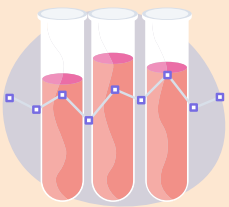
2. Injection Technique: Adequate patient education on injection technique is essential to ensure patient comfort with self-administering GLP-1 Agonists, impacting patient adherence.

3. Monitoring and Titration: Regular monitoring of blood glucose levels and patient follow-ups are imperative for evaluating treatment efficacy. Dose adjustments may be required for optimal results.

4. Potential Side Effects: Like any medication, GLP-1 Agonists carry potential side effects, notably gastrointestinal symptoms. Healthcare professionals should proactively discuss these issues with patients and manage them accordingly.

5. Cost Considerations: The cost of GLP-1 Agonists should be considered, with awareness of insurance coverage and patient affordability when prescribing these drugs. Ensuring access to innovative treatments like Ozempic for all individuals, regardless of their socioeconomic status, is a critical challenge that healthcare professionals must continue to address.





Healthcare professionals in the field of diabetes care are continuously seeking innovative therapies that efficiently control blood glucose levels and address the multifaceted challenges confronted by patients.

Ongoing Research and Innovation

Ozempic's story continues to evolve as ongoing research explores its applications in other conditions, such as non-alcoholic steatohepatitis (NASH) and Alzheimer's disease, showcasing the versatility of GLP-1 Agonists.

Conclusion

The journey of GLP-1 Agonists and Ozempic in diabetes management has been marked by remarkable advancements and promising developments. These drugs have redefined the way healthcare professionals approach the treatment of type 2 diabetes and obesity, offering a comprehensive and personalized approach that goes beyond glycemic control. As research continues to unveil new possibilities and applications for these drugs, the future of diabetes management looks brighter than ever. Healthcare professionals, armed with knowledge, dedication, and a patient-centered mindset, are poised to make a profound difference in the lives of individuals living with diabetes, ensuring that they receive the best care and the brightest future possible.

Original Study

The Role of 18 F-Fluorodeoxyglucose Positron Emission Tomography with Low Dose Computed Tomography for Evaluation of Fever of Unknown Origin

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Keywords:
18 F- Fluorodeoxyglucose, Computed Tomography, Positron Emission Tomography scan, Fever of Unknown Origin, Infection.

Abstract

Introduction: The use of 18F-Fluorodeoxyglucose Positron Emission Tomography (FDG PET) CT represents a non-invasive nuclear medicine modality utilized for the purpose of identifying the focal point(s) associated with fever of unknown origin (FUO). The study aims to assess both the clinical and diagnostic importance of 18F-FDG PET CT among patients presenting with FUO and to investigate the predictive value of PET CT in achieving a definitive diagnosis.

Materials and Methods: The study was done in a quaternary health care center in Kerala, including 38 adult patients fulfilling the criteria for FUO who underwent PET CT. Data was collected and statistical analysis was done for the prediction value of PET CT in diagnosing FUO.

Results: There were 77 eligible patients, 52 male and 25 female. Of these, eight have lost follow-up. FDG uptake was observed in 60 patients (86.9%) and 9 patients (11.7%) showed normal study. PET-CT as a diagnostic aid in FUO had 91.2% sensitivity, 33.3% specificity, and a Positive Predictive Value of 86.6%. Despite the PET CT results, among the 57 individuals with FUO, the final diagnosis revealed infections in 20 patients (30%), non-infectious inflammatory processes in 20 patients (30%), and malignancy in 17 patients (24.6%).

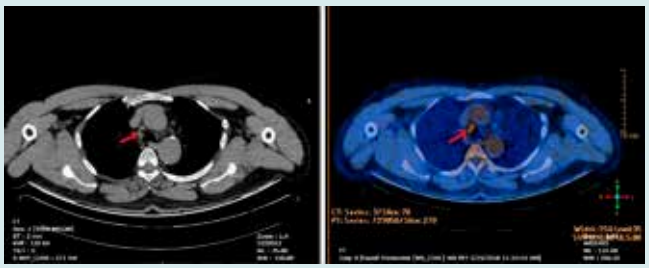
INTRODUCTION

Fever of Unknown Etiology (FUO) is referred to as body temperature more than 38.3oC/ 101oF on at least two occasions with an illness duration of more than 3 weeks and the patient is not in an immunocompromised state. Also, the diagnosis may be unknown even after a thorough history taking, physical examination, and intense inpatient investigations[1]. The etiologies for FUO can be classified into infections, non-infectious inflammatory disorders, and malignancies. The causes for FUO are influenced by the demographic characteristics, epidemiology, immune status of the patient, etc[2]. The use of 18Fluorodeoxyglucose Positron Emission Tomography with low-dose Computed Tomography (18FDG PET-CT) becomes important in these patients, who at this point of the workup, still remain undiagnosed[3].

Several studies like Ergul N et al. and Meller J et al. have reported the usefulness of PET-CT in FUO[4,5]. They have demonstrated that PET CT has aided 42% to 89% of patients with FUO in reaching a final diagnosis by PET-CT[6,7]. It is a non-invasive diagnostic technique widely employed in nuclear medicine, enabling the detection and localization of various foci throughout the body by assessing functional changes. The use of PET-CT in the diagnostic approach for patients with FUO is based on the metabolic characteristics of FDG. This imaging technique has the capability to offer early diagnosis, even in the absence of overt morphologic changes, define or confirm the degree of activity in equivocal structural abnormalities, and detect inflammatory processes that are poorly localized and are challenging to detect or are even missed by conventional imaging modalities[4]. Fluorodeoxyglucose (FDG) exhibits uptake in tissues characterized by high glycolytic activity. This metabolic characteristic is not exclusive to malignant cells but is also observed in activated leukocytes, enabling the visualization of both acute and chronic inflammatory processes through imaging techniques[8]. FDG PET-CT in the context of FUO demonstrates a high level of sensitivity and a relative non-specificity, making it a valuable tool for detecting malignancy, infection, and inflammation. In addition, FDG PET-CT has a relatively high negative predictive value[6,9].

The objectives of the study are to evaluate the clinical and diagnostic significance of FDG PET-CT in patients with FUO and to analyze the prediction value of PET-CT in arriving at a diagnosis or as a diagnostic pointer in FUO. The study also demonstrates the spectrum of etiologies of FUO in South India including its age and gender-wise distribution.

Figure 1. FDG AVID paratracheal node: CT guided lymph node biopsy: Tuberculosis

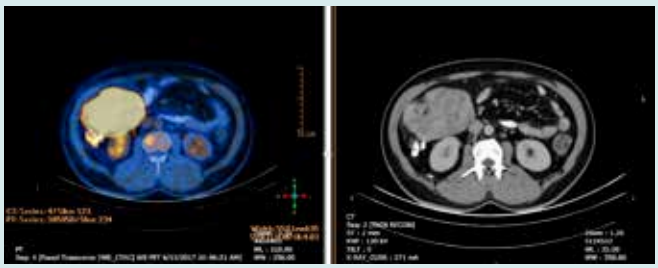


MATERIALS & METHODS

The study was a prospective observational cohort study conducted between September 2017 to December 2021 at Aster Medcity, Kochi - a quaternary care center in South India. The study was conducted after clearance from the institute ethics committee (Ref. no: AM/EC/10-2017 dated 05/07/2017). The primary objective of the study was to evaluate the clinical and diagnostic significance of FDG PET-CT in a patient with a Fever of Unknown origin. The secondary objective was to perform statistical analysis for the prediction value of PET-CT in arriving at a diagnosis or as a diagnostic pointer in FUO. The sample size was calculated to be 38 based on a previous study done by Ferda et al [6].

We included all patients above the age of 18 years fulfilling the criteria for FUO and who were willing for PET CT. Only those patients in whom, a PET-CT was ordered by the treating physician were included in the study. FUO was defined as a body temperature of more than 38.3 0C/101 0F on at least two occasions with an illness duration of more than 3 weeks and no known immunocompromised state. Moreover, the diagnosis remains unknown after thorough history taking, physical examination, and intense inpatient investigations. Patients below the age of 18 years, pregnant ladies, patients known to have malignancy, HIV infection, and patients who had undergone surgery in the past 3 months were excluded from the study. Patients already undergone a PET-CT

Figure 2. FDG avid mass in the transverse colon: Biopsy: Spindle cell neoplasm



from another center before admission were excluded. Patients who did not gave consent to include in the study and patients who were lost to follow-up before completion of the study were also excluded.

The basic demographic data like age, gender, comorbidities, socioeconomic status, and clinical details of the present condition were collected from electronic medical records of the hospital and patient interviews. Once the patient was identified as having a fever of unknown origin, their workup was followed up. A detailed history, clinical examination, appropriate initial lab tests, and initial imaging, to group the possible cause into a probable etiological group was done. Since there is no standardized diagnostic method for FUO, the diagnostic process is guided by the so-called "potential diagnostic clues" (PDC). PDC emerged from medical history, physical examination, and obligatory tests which potentially point toward a diagnosis. Finally, those patients in whom a PET-CT was ordered, were enrolled in this study. After the patients were identified and informed consent was taken, the PET-CT was taken. No extra tests or treatment was done as part of the study. Once the PET-CT was reported, the patient was further followed up and data on further investigations as well as a final diagnosis at discharge were obtained. A 4-week follow-up was done in patients who did not have a definitive diagnosis at the time of discharge.

Patients selected for PET-CT were instructed to fast, except for glucose-free oral hydration, for 4 to 6 hours before the injection of 296–444 MBq (8 to 12 mCi) of 18F-FDG. The patients were instructed to keep their regular drug schedule except for OHAs and insulin and was advised not to do physical overexertion. Blood glucose levels were measured before the injection and the target pre-procedure glucose level was <180 mg/dl with no additional use of glucose-control drugs. PET and CT images were acquired consecutively 50-60 min after the injection of 18 F-FDG, using a Philips Tru Flight Select 16-slice PET CT scanner. Standard Uptake Value (SUV) uptake up to 2.5 g/ml was taken as normal. Foci of increased FDG uptake were recorded.

STATISTICAL ANALYSIS

The descriptive variables were expressed as percentages and proportions, the continuous data was expressed using mean and standard deviation, and the Independent sample t-test was used to compare quantitative variables and the Chi-square test was used to compare discrete variables between groups. FDG PET-CT studies were evaluated for their clinical contribution. A PET-CT study showing normal findings was considered as contributory in excluding focal disease, a PET-CT study with no suggestive foci was defined as false-negative, and a PET-CT study demonstrating a focal, precisely localized disease process was considered as contributory for diagnosis. Abnormal findings in a patient with no final diagnosis of a focal disease process or with pathology identified in a location different from the site demonstrated on PET-CT were defined as noncontributory and false-positive (FP). The sensitivity, specificity, Positive predictive value (PPV), Negative predictive value (NPV), and accuracy were analyzed. All data were entered into a Microsoft Excel file and the Statistical Package for the Social Sciences (SPSS) version 16 for Windows was used for data analysis.

RESULTS

We had 77 eligible patients enrolled in the study after obtaining informed written consent. There were 52 males (67.5%) and 25 females (32.5%) (range 19-86 years) with a mean age of 50.1 years and a standard deviation of 16.45 years. Among them, 8 patients opted for no testing even though a PET CT was done and were lost to follow-up. Hence actual sample size was taken to be 69.

Of the 69 patients, 60 PET-CT studies (86.9%) showed an increase in FDG uptake whereas 9 patients (11.7%) had normal PET-CT studies. Among 52 of the 60 positive studies (86.6 %), PET-CT diagnosed the etiology of FUO and was therefore

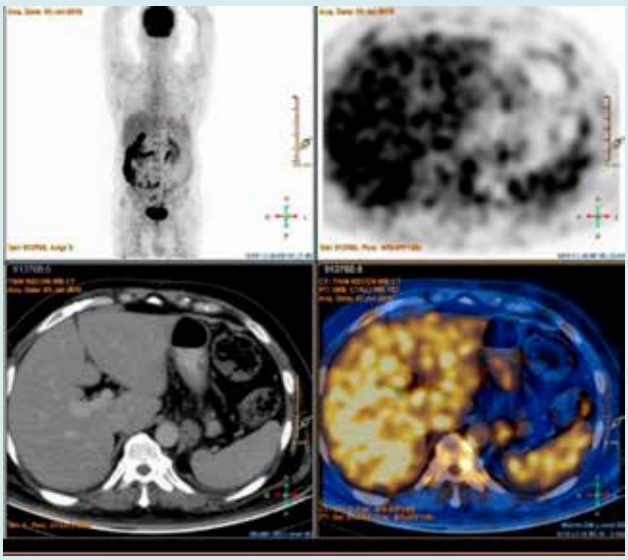
defined as true positive (TP). The remaining eight positive PET-CT study reports were non-contributory to the final diagnosis and were identified as false positives (FP).

Among the 52 patients who had the diagnosis made by PET CT, 17 (32.7%) had infections, 18 had (34.6%) inflammation and 17 patients (32.7%) had malignancies. The etiology of 17 patients who had infections were found: 10 patients had tuberculosis, 6 patients had Kikuchi's disease based on lymph node biopsy and 1 patient had an enteric fever which was diagnosed based on colonoscopy and biopsy with the culture of the biopsy sample. Out of the 17 patients who had malignancy, a biopsy of enlarged lymph nodes revealed various types of lymphoma in 7 patients, and a biopsy of FDG avid lesions in 10 patients revealed GIST (1 patient), carcinoma lung (2 patients), adrenal adenoma (2 patients), carcinoma colon (2 patients), and carcinoma thyroid (3 patients). Among the 17 patients who had an inflammatory process, 5 patients had thyroiditis confirmed by FNAC of thyroid, 2 patients had abnormal FDG uptake in the spinal cord with further tissue sampling showing meningitis, adult-onset Still's disease with Macrophage Activation Syndrome was diagnosed as per criteria in 2 patients based on PET-CT findings and bone marrow biopsy, 2 patients were diagnosed as SLE on subsequent retesting of autoimmune profiles, 2 patients were diagnosed to have Crohn's disease and Diverticulosis following colonoscopy and biopsy. Five patients out of the 17 who had inflammatory processes did not undergo further testing and were diagnosed based solely on the PET-CT findings, and these included 2 cases of pyelonephritis, 2 cases of abscesses, and a single case of inflammatory polyarthritis.

PET-CT showed no abnormal FDG uptake in 9 patients. Among 4 out of 9 patients, FUO resolved spontaneously, without any evidence of inflammatory, infectious, or malignant process for a clinical follow-up period of 4 weeks. These patients were defined as true negatives (TN). Five patients with negative PET/CT had a final diagnosis of focal infection, inflammation, or malignancy, and this was taken as false-negative (FN).

The PET-CT for the diagnosis of a disease process representing the etiology of FUO had a sensitivity of 91.2%, a specificity of 33.3%, a Positive Predictive Value (PPV) of 86.6%, a Negative Predictive Value (NPV) of 44.4 %, and accuracy of 81.1% as shown in table 1.

Figure 1. FDG AVID paratracheal node: CT guided lymph node biopsy: Tuberculosis



The final diagnosis obtained in 57 patients (82.6%) out of 69 who completed the study irrespective of PET-CT findings included an infectious process in 20 (30%) patients, inflammatory noninfectious processes in 20 (30%) patients, and malignancy in 17 (24.6%) patients. Among the 20 patients who had infections, 17 (85%) patients had focal infections, and 3 (15%) patients had disseminated infections.

In this study, infection as a cause of FUO was seen in 11 (55%) males and 9 (45%) females, while malignancy as a cause of FUO was seen in 14 males (82.4%) and 3 females (17.6%). Out of the 69 patients who completed the study 36 cases (52.2%), belonged to the age group of 50 to 69 years. Table 2 shows the distribution of the type of disease diagnosed in each age group.

DISCUSSION

Our study focused on the clinical utility of PET CT for FUO and analyzed the statistical significance of the same as a diagnostic tool. The study proved PET-CT to be a valuable tool in diagnosing or ruling out a focal cause in 81.2% of the cases within this prospective study involving 77 patients presenting with FUO. The study reported 52 true positive cases and 4 true negative cases,

Table 1. Table showing TP, FP, FN, TN, Sensitivity, Specificity, PPV, and NPV of PET-CT in FUO.

	Disease identified	No disease identified		TOTAL
PET Findings	52 (TP)	8 (FP)	PPV: 86.6%	60
No PET Findings	5 (FN)	4 (TN)	NPV: 44.4%	9
TOTAL	57	12		69
	Sensitivity : 91.2%	Specificity: 33.3%		

According to Fisher's Exact Test, P value obtained is 0.095.
TP – True positive, FP – False positive, FN – False negative, TN – True negative
PPV – Positive predictive value, NPV – Negative predictive value

indicating the clinical significance of PET-CT in providing relevant information for accurate diagnosis. In other words, positive PET-CT studies were found to be beneficial in 86.7% of the cases by either identifying the underlying cause of FUO or providing adequate guidance for subsequent management which could include invasive therapeutic procedures. This highlights the significant contribution of PET-CT imaging in improving diagnostic and treatment outcomes for patients with FUO.

As a whole, a positive PET-CT study contributed to the final diagnosis in 75.3% of the present study population. It is important to correlate positive PET-CT studies in patients with FUO with their clinical, biochemical, and immunologic status. When clinically deemed necessary, these positive findings should be further confirmed through other imaging techniques or invasive diagnostic modalities[9]. The present study showed that the ultimate diagnosis regarding the cause of FUO consisted of an infectious process in 30% of patients, an inflammatory process in 30%, and malignancy in 24.6% of cases. These findings highlight the diverse etiological factors contributing to FUO, including infections, inflammatory conditions, and malignant diseases, emphasizing the need for a comprehensive diagnostic approach in order to accurately identify and address the underlying cause. In 17.6% of patients, no specific cause could be identified for FUO, and the condition resolved spontaneously.

In a study conducted by Dong et al. in 2011, the combined sensitivity and specificity of 18F-FDG PET/CT in detecting FUO were 98.2% (95% CI: 93.6–99.8) and 85.9% (95% CI: 75–93.4) respectively. Based on these results, the researchers recommended considering this method as one of the primary diagnostic tools for patients with FUO, especially when conventional diagnostic approaches have been unsuccessful in identifying the cause(10). The sensitivity was somewhat similar to our study, but the specificity in our study was very low as compared to this study. Our study also showed similar sensitivity to the referenced study, indicating a comparable ability to detect positive cases. However, in contrast, the specificity observed in our study was notably lower compared to the findings reported by them.

Tateuchi et al. conducted a study in 2016 and showed that 18F-FDG PET/CT is valuable in identifying the fever source among patients with classic FUO, specifically focusing on those who were immunocompetent. The study reported summarized sensitivity, specificity, and diagnostic yield values of 86% (95% CI: 81–90), 52% (95% CI: 36–67), and 58% (95% CI: 51–64), respectively. However, it is important to consider that the contribution of this method may be limited in clinical settings where infectious and neoplastic causes are less prevalent or encountered less frequently. Comparisons of test performance showed that 18F-FDG PET/CT was better than 18F-FDG PET alone in detecting causes of FUO[11]. The results of this study more closely resembled those of ours with similar sensitivity and specificity profiles.

Comparing the age group presenting with FUO, out of the 77 patients presented with FUO, 46.1% of patients belonged between 50 and 69 years. Hence, the majority of the patients presenting with FUO in our center were the elderly population. Among them the cause of FUO were infections in 29.7%, non-infectious inflammatory processes in 21.6 %, and 27% malignancies. Our study revealed malignancies presenting as FUO were more common in males (82%) compared to

Table 2. Distribution of type of disease diagnosed in each age group

Age (in years)	18- 29	30 - 49	50 - 69	≥ 70	Total
Infection	1	8	11	0	20
Non-infectious inflammation	4	5	8	3	20
Malignancy	1	6	10	0	17
True negative PET CT	1	1	2	0	4
No PET CT findings	1	1	5	1	8
Lost to follow up	0	3	1	4	8
TOTAL	**8**	**24**	**37**	**8**	**77**

females (18%). Infection presenting as FUO seems to be slightly higher in males (55%) as opposed to 45% in females. Among infections, Tuberculosis is the main culprit and was the diagnosis in half of the infectious cases.

From our observation, one important advantage arising out of FDG PET CT investigation was the identification of metabolically active foci that is most likely to yield a positive result in biopsy or FNAC. This is an advantage over the conventional anatomic imaging where an enlarged lymph node that is picked up may not be the maximum metabolically active one with high FDG uptake and hence may not yield a positive result if sampled.

LIMITATIONS

Previous use of antibiotics, steroids, and anti-inflammatory drugs can lead to decreased uptake of 18F FDG in a pathological area due to transient suppressed activity. The sample size we got was around 77, out of which 8 were lost to follow-up, 9 were negative and 60 were PET-positive cases. The small sample size would have impacted the accuracy of the result obtained.

CONCLUSIONS

The study demonstrated that FDG PET-CT exhibited a good PPV and high sensitivity when assessing patients with FUO, aligning with previous findings reported in the literature. When evaluating the diagnostic yield of 18F-FDG PET/CT in FUO patients, it is essential to consider both positive and true negative cases, as individuals with a negative 18F-FDG PET/CT result tend to have a favorable clinical outcome. Given the absence of a reliable "gold standard" for diagnosing FUO, the early utilization of PET-CT in the diagnostic process of PUO offers the advantage of avoiding unnecessary multiple imaging procedures, ultimately leading to reduced hospital stays and decreased healthcare expenditure.

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Type 2 Diabetes

Advances in the Management of Type 2 Diabetes in Adults

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Abstract

Type 2 diabetes is a chronic and progressive cardiometabolic disorder that affects more than 10% of adults worldwide and is a major cause of morbidity, mortality, disability, and high costs. Over the past decade, the pattern of management of diabetes has shifted from a predominantly glucose centric approach, focused on lowering levels of haemoglobin A1c (HbA1c), to a directed complications centric approach, aimed at preventing short term and long term complications of diabetes, and a pathogenesis centric approach, which looks at the underlying metabolic dysfunction of excess adiposity that both causes and complicates the management of diabetes. In this review, we discuss the latest advances in patient centred care for type 2 diabetes, focusing on drug and non-drug approaches to reducing the risks of complications of diabetes in adults. We also discuss the effects of social determinants of health on the management of diabetes, particularly as they affect the treatment of hyperglycaemia in type 2 diabetes.

INTRODUCTION

Diabetes, a chronic and progressive cardiometabolic disorder, is a major cause of morbidity, disability, and mortality worldwide. Comprehensive person centred management of diabetes requires attention to glycaemic control and risk factors for cardiovascular disease (hyperlipidaemia, hypertension, and tobacco use), weight management, early detection and treatment of microvascular, macrovascular, and metabolic complications of diabetes and mental health concerns, mitigation of burden of treatment, addressing social determinants of health, and improving quality of life.[1] The past decade has seen multiple developments in each aspect of the management of diabetes. This review focuses specifically on recent advances in the management of hyperglycaemia in diabetes, including drug and non-drug treatments. People with diabetes,

caregivers, clinicians, health systems, payers, and policy makers need to appreciate the complexity and cost associated with optimal care of diabetes to meaningfully improve the health and well being of people living with diabetes.

EPIDEMIOLOGY

The current prevalence of diabetes among adults is 10.5% worldwide (536.6 million adults), with marked variation across regions and countries, and is estimated to reach 12.2% (783.2 million adults) by 2045.[2] Diabetes is more prevalent in high income (11.1%) and middle income (10.8%) countries than in low income countries (5.5%).

The prevalence of diabetes is rising everywhere, most rapidly in middle income countries where the prevalence is expected to reach 13.1% by 2045,[2] probably because of changing diet and lifestyle factors, rising rates of obesity, inadequate resources for early diagnosis and prevention, and potentially greater genetic or epigenetic susceptibility arising from inadequate fetal and childhood nutrition. Data for low and middle income countries are likely to be underestimated because of barriers to screening and timely diagnosis.

More than 90% of people with diabetes have type 2 diabetes,[3] characterised by insulin resistance and progressive beta cell failure, and commonly associated with other cardiometabolic disorders, including obesity, hypertension, cardiovascular disease, and hepatic steatosis. Diabetes contributed to 6.7 million deaths in 2021 alone,[4] highlighting the urgency of preventing diabetes and optimising its management to improve health outcomes and quality of life for all people at risk of or with the disease.[1]

SOURCES AND SELECTION CRITERIA

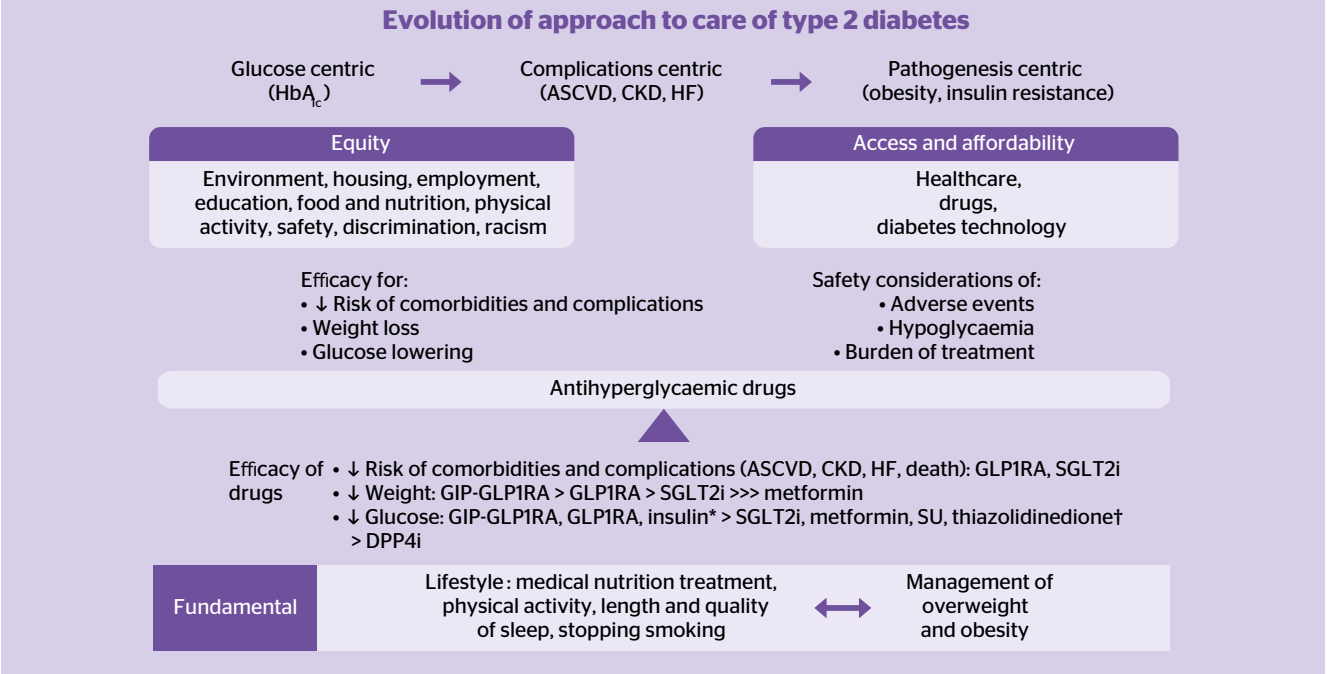
We searched PubMed for articles published in English. We prioritised randomised controlled trials, clinical guidelines, consensus statements, and systematic reviews. Search terms were: ((type 2 diabetes mellitus AND management (medical subject headings (MeSH) terms)) AND (type 2 diabetes mellitus (MeSH terms))) AND (care management, patient (MeSH terms)). Filters applied were: clinical trial, guideline, meta-analysis, practice guideline, randomised controlled trial, and systematic review, from 1 January 2013 to 1 January 2023. The reference lists of these articles were screened for relevant publications.

GOALS AND TARGETS OF MANAGEMENT OF TYPE 2 DIABETES

The primary objectives of the management of diabetes are to reduce the incidence and burden of complications and to improve quality of life (figure 1). Historically, these objectives were pursued through control of hyperglycaemia. In this glucose centric approach, clinical practice guidelines recommend targeting haemoglobin A_{1c} (HbA_{1c}) concentrations at <7% (53 mmol/mol) or <6.5% (47.5 mmol/mol) and, more recently, continuous glucose monitoring time in range >70% for most non-pregnant adults with type 2 diabetes, with lower or higher glycaemic thresholds individualised for each person.[5–7] These recommendations for levels of HbA1c come from data from randomised controlled trials showing a reduction in microvascular complications with more intensive glycaemic control,[8–12] although data for the association between time in range and risk of complications of chronic diabetes are limited but emerging.[13] Implementation of glycaemic targets based on continuous glucose monitoring has also been limited by gaps in insurance coverage and accessibility, although continuous glucose monitoring is increasingly recommended for and used by people with type 2 diabetes.[14 15]

Randomised controlled trials of older antihyperglycaemic treatments, such as sulfonylureas and insulins, however, have not shown a consistent association between intensive glycaemic control and reduction in macrovascular complications or mortality.[16] Nevertheless, longer term follow-up of intensively treated adults provides some evidence of a lower risk of macrovascular events and cardiovascular death.[8 17] Conversely, intensive glycaemic control in individuals with frailty, advanced age, and multimorbidity was associated with an increased risk of severe hypoglycaemia and death.[18–20] Therefore, future research is needed to examine the effect of intensive glycaemic control when achieved with newer glucose lowering drugs, which have a lower risk of hypoglycaemia and additional cardio-reno- metabolic benefits. Taken together, these data highlight the importance of individualised glycaemic management and the need to shift the emphasis away from the imperfect surrogate of levels of HbA1c towards reducing hard outcomes of the adverse health effects of diabetes, while lessening the burden of treatment.[21 22]

Figure 1. Shifting pattern of management of type 2 diabetes



HbA_{1c}=haemoglobin A_{1c}; ASCVD=atherosclerotic cardiovascular disease; CKD=chronic kidney disease; HF=heart failure; GIP=glucose dependent insulinotropic polypeptide; GLP1RA=glucagon-like peptide 1 receptor agonist; SGLT2i=sodium glucose cotransporter 2 inhibitor; SU=sulfonylurea; DPP4i=dipeptidyl peptidase 4 inhibitor. *Insulin is preferred for acute management of severe hyperglycaemia; †Thiazolidinediones improve insulin resistance.

Over the past decade, multiple randomised controlled trials have shown a reduction in cardiovascular disease, kidney disease, heart failure, and mortality with the use of glucagon-like peptide 1 receptor agonists (GLP1RAs) and sodium glucose cotransporter 2 inhibitors (SGLT2is), independent of a reduction in levels of HbA_{1c}.[23] These findings signalled a new complications centric era of the management of diabetes, focused directly on preventing or reducing macrovascular, microvascular, and other emerging complications of diabetes, such as heart failure. Many,[6,24,25] although not all,[26] clinical practice guidelines recommend treatment with GLP1RAs or SGLT2is, or both, for patients with cardiovascular or kidney disease, or both, or with risk factors for atherosclerotic cardiovascular disease, independent of glycaemic control, although all continue to stress the concurrent importance of achieving HbA_{1c} targets.

More recently, the pattern of management of diabetes has begun to shift further, with a renewed focus on looking at the causes of type 2 diabetes and its metabolic comorbidities and long term complications. This pathogenesis centric approach places the management of obesity at the centre of the prevention and treatment of the disease.[27] Even a relatively small amount (5-7%) of weight loss reduced the risk of incident diabetes and improved glycaemic control in people with type 2 diabetes.[28–31] Greater amounts of weight loss have been reported to have greater beneficial effects on glycaemic control (including remission of diabetes), metabolic dysfunction, and quality of life.[29 30 32–37] Weight loss achieved with metabolic surgery reduced the risks of microvascular and macrovascular complications of diabetes and reduced mortality.[38–41]

By contrast, intensive lifestyle treatments in the Look AHEAD (Action for Health in Diabetes) randomised controlled trial of 5145 adults with type 2 diabetes and overweight/obesity did not reduce the risk of cardiovascular events compared to usual care.[30] The likelihood of detecting differences between the intensive lifestyle and conventional treatment groups might have been reduced because the cardiovascular event rate in the Look AHEAD population was much lower than anticipated (0.7% per year v estimated 3.1% per year).[42] A post hoc analysis suggested that those who lost at least 10% of their body weight in the first year had

a significantly lower risk of the primary outcome, which was a composite of the first occurrence of death from cardiovascular causes, non-fatal acute myocardial infarction, stroke, and hospital admission for angina (adjusted hazard ratio 0.79, 95% confidence interval 0.64 to 0.98, P=0.034).[35] How weight loss achieved with drug treatment, particularly agents such as semaglutide and tirzepatide, compares with metabolic surgery for glycaemic control, microvascular and macrovascular complications, and mortality, should be examined.

Lifestyle treatments: medical nutrition treatment, physical activity, and sleep Successful management of type 2 diabetes must include consistent attention to behaviours that sustain a healthy lifestyle and are foundational for achieving glycaemic control, preventing complications, supporting quality of life, and preserving optimal health. Medical nutrition treatment for diabetes emphasises a balanced selection of nutrient dense foods while minimising or eliminating added sugar, refined grains, and highly processed foods.[6 7 43] Recommendations for optimal carbohydrate intake and composition vary, with the strongest evidence supporting an overall reduction in intake of carbohydrates. This principle can be applied to multiple dietary patterns, including a Mediterranean diet high in monounsaturated and polyunsaturated fats, low carbohydrate, vegetarian, or a plant based diets, and the Dietary Approaches to Stop Hypertension diet, with a focus on non-starchy vegetables, fruits, and legumes, and some dairy in those who are lactose tolerant.[6 43] Only the Mediterranean diet has been shown to reduce cardiovascular disease and mortality.[44] Also, evidence indicates the beneficial effects of involvement of community health workers to support education in self-management of diabetes and overall care, especially in rural or underserved communities, or both.[45] Because hypertension and cardiovascular disease are major causes of mortality in individuals with diabetes, more attention needs to be paid to overall sodium intake and limiting the content of saturated fat and trans fat in the diet.[6]

Stopping smoking and abstinence from tobacco products is also imperative for cardiovascular health in adults with diabetes, and robust evidence supports the benefit of stopping smoking despite the potential for weight gain.[6 46] Although nicotine replacement products and electronic cigarettes might facilitate stopping smoking, nicotine itself can impair glucose tolerance and adversely affect the cardiovascular system through increased sympathetic activation.[47]

Baseline levels of physical activity should be assessed to set reasonable and realistic behaviour oriented goals. Increasing the duration of physical activity and reducing sedentary time have been reported to improve cardiorespiratory fitness and HbA_{1c} levels.[48] Recommendations can be made to increase leisure time physical activity (walking, taking the stairs, and household chores), decrease sedentary time, and introduce physical activity on most days.[6 49] Physical activities include both aerobic and resistance training, as well as flexibility and balance training.[50]

The length and quality of sleep are increasingly recognised as essential components of the management of diabetes and individuals should be screened for sleep related disorders.[6 43] Referral for diagnosis and treatment of obstructive sleep apnoea and other sleep disorders should be considered if indicated. Screening for psychosocial factors and social determinants of health that might affect an individual's diabetes care and quality of life should also be performed, with engagement of or referral to relevant clinical team members for further evaluation and care, as appropriate.[43]

Lifestyle interventions in individuals with obesity or who are overweight are most successful when efforts are intensive and frequent follow-up is available, either in person or virtually.[6 49] Weight loss can be achieved in various ways, and is most effective when strategies are combined: caloric restriction, increased caloric expenditure, elimination or substitution of drugs that promote weight gain, use of weight reducing drugs and, in select individuals, metabolic or bariatric surgery. One dietary strategy that has received considerable attention in recent years is time restricted eating,[51] although data in adults with type 2 diabetes are limited to one randomised controlled trial[52 53] and a larger trial is ongoing (n=344; Using Early Time Restricted Feeding and Timed Light Therapy to Improve Glycemic Control in Adults With Type 2 Diabetes, NCT04155619). Weight management is discussed in more detail below.

DRUG TREATMENT OF TYPE 2 DIABETES

Initial management of type 2 diabetes has traditionally included metformin in most adults because of its glucose lowering effect, neutral

effects on weight, minimal risk of hypoglycaemia, safety profile, low cost, and ease of administration. Now, in the light of evidence from trials of cardiovascular and kidney outcomes, decisions on treatment of diabetes with drugs should be made based on cardiac comorbidities (established atherosclerotic cardiovascular disease and heart failure), risk factors for atherosclerotic cardiovascular disease and kidney disease, engaging adults in shared decision making, and prioritising the use of drugs shown to reduce the risk of cardiovascular or kidney adverse outcomes, or both, in adults with specific comorbidities.[7 24–26]

Adults with atherosclerotic cardiovascular disease or indicators of high risk

In people with established atherosclerotic cardiovascular disease or risk factors for atherosclerotic cardiovascular disease, a GLP1RA or SGLT2i with known cardiovascular benefit should be started, regardless of levels of HbA_{1c} or background glucose lowering treatments.[24] Drugs that have been shown to cause significant reductions in major adverse cardiovascular events in cardiovascular outcomes trials compared with placebo include the GLP1RAs dulaglutide (hazard ratio 0.88, 95% confidence interval 0.79 to 0.99), liraglutide (0.87, 0.78 to 0.97), and subcutaneous semaglutide (0.74, 0.58 to 0.95), and the SGLT2is canagliflozin (0.86, 0.75 to 0.97) and empagliflozin (0.85, 0.75 to 0.97).[54–58] None of the trials of cardiovascular outcomes involved head-to- head comparisons of GLP1RAs versus SGLT2is.[59]

Individual components of the composite major adverse cardiovascular events outcome as well as secondary outcomes in the cardiovascular outcomes trials vary between GLP1RAs and SGLT2is. A reduction in stroke was seen in meta-analyses of randomised controlled trials of GLP1RAs compared with placebo (hazard ratio 0.83, 95% confidence interval 0.76 to 0.92) but not with SGLT2is compared with placebo (0.95, 0.85 to 1.05).[59] The mechanisms and benefits of GLP1RAs and SGLT2is seem to be complementary, and evidence is emerging to support combination treatment, which might provide more benefit than each used alone.[60–62] Currently, guidelines from the American Diabetes Association/European Association for the Study of Diabetes recommend the addition of the alternative class when more glucose lowering is needed.[24 25]

Adults with heart failure

GLP1RAs have not shown benefit for heart failure outcomes in individual randomised controlled trials of cardiovascular outcomes,[55 56 58] although meta-analyses of these studies suggested a potential benefit.[59 63 64] SGLT2is, by contrast, have consistently shown significant benefit for heart failure outcomes.[54 57 65] Also, dapagliflozin and empagliflozin were beneficial in people with reduced or preserved ejection fraction without type 2 diabetes, and have an indication for improving heart failure outcomes.[66–69] Accordingly, in people with heart failure, an SGLT2i with known benefit should be started to reduce the risk of major adverse cardiovascular events and worsening heart failure.[24 26]

Adults with chronic kidney disease

GLP1RAs have shown benefit for secondary kidney related outcomes in large individual randomised controlled trials[55 56 70] and meta-analyses[59 63 64] of cardiovascular outcomes, but dedicated kidney outcome trials are ongoing.[71] Several SGLT2is, including canagliflozin, dapagliflozin, and empagliflozin, have shown benefit in adults with chronic kidney disease with or without type 2 diabetes and in dedicated kidney outcome trials, and have an indication for improving chronic kidney disease outcomes.[24 72] Therefore, SGLT2is with primary evidence are preferred for individuals with an estimated glomerular filtration rate <60 mL/min/1.73 m2 or albuminuria, or both, to reduce the progression of chronic kidney disease. If SGLT2is are not tolerated or cannot be used, GLP1RAs with demonstrated renal benefit are a reasonable alternative.[24 26 73] Current prescribing information allows SGLT2is to be started in adults with an estimated glomerular filtration rate of ≥20 mL/min/1.73 m2 for kidney benefit, although the glucose lowering effects are substantially reduced at an estimated glomerular filtration rate <45 mL/min/1.73 m^2.[74] A small reduction in the estimated glomerular filtration rate can be seen after starting treatment with SGLT2is because of reversal or correction of the previous hyperfiltration state in adults with diabetes, but it does not predict further reductions in estimated glomerular filtration rate or require discontinuation of treatment.

Role of metformin

Although metformin was a commonly used background drug in most large trials of cardio-

vascular and kidney outcomes,[75] several post hoc analyses have demonstrated benefit with GLP1RAs or SGLT2is regardless of background use of metformin.[76–82] Current guidelines from the American Diabetes Association/European Association for the Study of Diabetes and the American Association of Clinical Endocrinology no longer recommend metformin as the preferred first line agent for all individuals with type 2 diabetes, and instead suggest consideration of cardiac and kidney comorbidities when selecting first line treatment.[6 24 25] Cost is a major consideration in selecting the most appropriate treatment, however, probably contributing to differences in these recommendations from guidelines used in other countries. In the US, insurers have not caught up with the guidelines, and require that metformin is used before other agents. Guidance from the National Institute for Health and Care Excellence (NICE) still recommends metformin as the first line treatment for people with cardiac or kidney comorbidities, or both, with introduction of an SGLT2i in people who cannot tolerate metformin or need intensification of treatment.[26] Despite robust outcome data, GLP1RAs are not recommended ny NICE until failure of triple oral drug treatment and only in people with a high body mass index or in whom insulin treatment cannot be used.[26] Insurance formulary restrictions on prescribing GLP1RAs and SGLT2is, including the requirement of step treatment starting with metformin, still persist but should be reconsidered to better align with scientific evidence.

Other situations when a drug other than metformin can be considered as first line treatment include severe or symptomatic hyperglycaemia (HbA_{1c}>10%, ketosis, or weight loss), creatinine clearance or estimated glomerular filtration rate <30 mL/min/1.73 m², or when the person cannot tolerate metformin despite slow up titration of the dose or a trial of the extended release formulation, or both. Sulfonylureas and thiazolidinediones are now less commonly recommended because of their adverse effect profiles. Sulfonylureas can lead to weight gain and are associated with a high risk of hypoglycaemia, and thiazolidinediones can also cause weight gain, as well as fluid retention and osteoporosis. People treated with thiazolidinediones must be monitored for the development of heart failure; thiazolidinediones are not recommended for those with symptoms of heart failure and are contraindicated in class 3 or 4 heart failure. Because generic forms of sulfonylureas and thiazolidinediones are available, however, these drug classes are options when cost is a barrier to accessing other agents or the individual's clinical situation requires these drugs. Pioglitazone, a thiazolidinedione, has beneficial effects in hepatic steatosis and stroke, and can be considered in these contexts.[6 83]

Effect on weight and weight related comorbidities

Clinicians should also consider the effect of the glucose lowering regimen on weight and weight related comorbidities, including overweight or obesity and non-alcoholic fatty liver disease or non-alcoholic steatohepatitis. Weight loss is greatest with the dual glucose dependent insulinotropic polypeptide (GIP)-GLP1RA, tirzepatide, and subcutaneous semaglutide, followed by dulaglutide and liraglutide.[27] Moderate weight loss is seen with the other GLP1RAs and SGLT2is. Drugs with neutral effects on weight include the dipeptidyl peptidase 4 inhibitors (DPP4is) and metformin, whereas the sulfonylureas, thiazolidinediones, and insulin all increase the risk of weight gain (table 1).[24 27 84] Recent single centre and population based cross sectional studies in the US estimated that >70% of people with type 2 diabetes have non-alcoholic fatty liver disease and more than half of those with type 2 diabetes and non-alcoholic fatty liver disease have steatohepatitis.[85–88] Insulin resistance, impaired lipid and glucose metabolism, and altered insulin secretion play a part in non-alcoholic fatty liver disease and progression of type 2 diabetes, and might indicate why the two diseases are so closely linked.[89] Although limited evidence exists so far, current guidelines recommend the use of a GLP1RA or pioglitazone for the treatment of diabetes in people with non-alcoholic steatohepatitis.[90 91] Weight management, which is essential for the treatment of hepatic steatosis, is discussed below.

Glucose lowering efficacy

In addition to choosing a drug that targets cardiovascular, kidney, and metabolic outcomes, clinicians should also develop a treatment approach that has sufficient efficacy to achieve glycaemic targets.[24] Although some guidelines (most notably, the Australian Diabetes Society) cite a

Table 1. Choosing drug class for type 2 diabetes

Drug class	Glucose efficacy	Effect on weight	Risk of hypoglycaemia	Route of administration	Cost	Ideal candidates for use
Metformin	High	Neutral	No	Oral	Low	▸ Newly diagnosed, especially in the absence of atherosclerotic cardiovascular disease, heart failure, or chronic kidney disease
SGLT2i	Intermediate to high	Loss (intermediate)	No	Oral	High	▸ Established or high risk of atherosclerotic cardiovascular disease ▸ Heart failure ▸ Chronic kidney disease
GLP1RA	High	Loss (intermediate to very high)	No	Subcutaneous (oral semaglutide)	High	▸ Established or high risk of atherosclerotic cardiovascular disease ▸ Chronic kidney disease (after SGLT2is) ▸ Non-alcoholic steatohepatitis or non-alcoholic fatty liver disease ▸ Overweight or obesity
GIP-GLP1RA	High	Loss (very high)	No	Subcutaneous	High	▸ Overweight or obesity
DPP4i	Intermediate	Neutral	No	Oral	High	▸ Older adults or others that require easy administration and high tolerability
Sulfonylurea	High	Gain	Yes	Oral	Low	▸ Those with cost or access barriers, especially in the absence of atherosclerotic cardiovascular disease, heart failure, chronic kidney disease, or overweight or obesity
Thiazolidinedione	High	Gain	No	Oral	Low	▸ Those with cost or access barriers, especially in the absence of heart failure, chronic kidney disease, or overweight or obesity ▸ Non-alcoholic steatohepatitis or non-alcoholic fatty liver disease ▸ History of stroke/TIA

GIP=glucose dependent insulinotropic polypeptide; GLP1RA=glucagon-like peptide 1 receptor agonist; SGLT2i=sodium-glucose cotransporter 2 inhibitor; DPP4i=dipeptidyl peptidase 4 inhibitor

lack of evidence to support substantial differences in glucose lowering between antihyperglycaemic drug classes when used as monotherapy,[92] prior meta-analyses, including a meta-analysis of 453 trials assessing nine drug classes, and the recently completed Glycemia Reduction Approaches in Type 2 Diabetes: A Comparative Effectiveness (GRADE) pragmatic randomised clinical trial comparing insulin glargine U-100, the sulfonylurea glimepiride, the GLP1RA liraglutide, and the DPP4i sitagliptin in 5047 individuals with moderately uncontrolled type 2 diabetes found insulin and GLP1RA to be significantly more effective at lowering HbA1c than the other examined drugs.[93 94] The American Diabetes Association Standards of Care there categorise drug classes as having very high, high, or intermediate glucose lowering efficacy (table 1).[24] The greatest reductions in levels of HbA_{1c} are seen with the dual GIP-GLP1RAs, GLP1RAs, and insulin. In the GLP1RA class, subcutaneous semaglutide and dulaglutide had the highest efficacy for glucose lowering. The recently approved dual GIP-GLP1RA, tirzepatide, seems to have the greatest efficacy for reducing levels of glucose. SGLT2is and DPP4is have less robust HbA_{1c} lowering effects and are classified as intermediate to high (SGLT2is) and intermediate (DPP4is).[24 25 93]

GRADE, a large scale, comparative effectiveness study of four drugs in combination with metformin, found that insulin glargine and liraglutide achieved and maintained HbA_{1c} targets more effectively than glimepiride and sitagliptin. The study did not, however, include newer agents, such as the SGLT2is, or once weekly GLP1RAs.[95] The

GRADE study also highlighted the challenges of maintaining glucose targets over time, with 71% of study participants progressing to HbA_{1c} ≥7% within four years, regardless of the treatment option.[94] A meta-analysis of 229 randomised controlled trials comprising 121 914 participants suggested that glucose lowering efficacy was highest with GLP1RA and weakest with DPP4i, with other agents in between.[96] By contrast, a meta-analysis of 140 randomised trials and 26 observational studies showed that each new class of non-insulin drugs added to metformin monotherapy lowers levels of HbA1c by about 0.7-1%.[95] A shift towards earlier use of combination treatment, in contrast with a stepwise approach, to reach glucose targets and provide better glycaemic durability has been reported.[24 97] For people with marked hyperglycaemia (eg, HbA_{1c} >10% or with symptoms), clinicians should start insulin, or a combination of insulin with GLP1RAs.[98] When improved glycaemic control is achieved, many people with type 2 diabetes can be safely transitioned to non-insulin treatments with close monitoring to prevent hypoglycemia and hyperglycemia.

SAFETY CONSIDERATIONS

Other considerations in the selection of treatment for diabetes are the risks of hypoglycaemia, other adverse effects and safety considerations, as well as cost and administration requirements that often result in barriers to adherence. Therefore, individuals with diabetes, care partners, and clinicians need to engage in shared decision making to identify treatment strategies that are aligned with the individual's goals of care, treatment preferences, the clinical and psychosocial context, and risks and benefits associated with each treatment option. Tables 1 and 2 summarise this information. Some key and controversial safety considerations are discussed below.

Acute pancreatitis

Acute pancreatitis has been reported in individuals who received GLP1RAs, DPP4is, and the GIP-GLP1RA, tirzepatide. After early post-marketing reports, the US Food and Drug Administration warned of a potential link between acute pancreatitis and GLP1RAs and DPP4is.[99] Multiple preclinical, observational, and randomised controlled studies were inconsistent, with some showing positive associations and others showing no association.[100] Ultimately, the FDA concluded that a causal relation could not be established and insufficient evidence existed to modify treatment. Systematic reviews and meta-analyses of randomised controlled trials (eg, long term cardiovascular outcomes trials) concluded that treatment with GLP1RAs or DPP4is was not associated with an increased risk of pancreatitis or pancreatic cancer.[101–103]

Nonetheless, current prescribing information, FDA guidance, and treatment guidelines recommend cautious use of these drug classes in people with a history of pancreatitis, in part because these people were excluded from most trials.[24] If these drug classes are used, individuals should be monitored for signs and symptoms of pancreatitis and, if pancreatitis develops, treatment should be discontinued and not restarted.[24 99] We also suggest caution in starting these drugs in people with a previous history of pancreatitis, particularly when the cause of pancreatitis is unknown or persists. Monitoring of lipase levels in randomised controlled trials showed asymptomatic fluctuations in both groups (intervention and placebo). Hence no evidence exists to suggest ongoing monitoring during treatment.

Gallbladder or biliary disease

GLP1RAs, DPP4is, and GIP-GLP1RAs are also associated with an increased risk of gallbladder and biliary disease, including cholelithiasis and cholecystitis. [104–107] Although the absolute risk of biliary or gllbladder disease with GLP1RA therapy seems to be small, with a recent meta-analysis of 76 randomised controlled trials involving 103 371 103 371 participants reporting an additional 27 incidences per 10 000 patients per year,[104] this finding might under-represent the true risk, because many studies did not report biliary related events. The risk seems to be higher with higher doses of drugs, longer duration of use, and when used for weight loss rather than glycaemic control. We therefore advise caution with the use of GLP1RAs, DPP4is, and GIP-GLP1RAs in people at high risk of biliary complications.

Diabetic retinopathy

A significant increase in retinopathy complications (3% *v* 1.8%, P=0.02), including vitreous haemorrhage, blindness, or need for photocoagulation treatment or an intravitreal agent, was

Table 2. Safety and mitigation considerations for each drug class for type 2 diabetes

Drug class	Safety considerations	Strategies for successful initiation & use	Key education points
Metformin	Common adverse effects are gastrointestinal (diarrhoea, stomach upset), metallic taste, vitamin B12 deficiency (with long term use) **Use caution:** ▸ estimated glomerular filtration rate 30-45 mL/min/1.73 m2 ▸ increased risk of lactic acidosis **Do not use:** ▸ estimated glomerular filtration rate <30 mL/min/1.73 m2	▸ Start at low dose and titrate slowly to lessen gastrointestinal adverse events ▸ Consider extended release to lessen gastrointestinal adverse events ▸ Monitor vitamin B12 at regular intervals after five years of use ▸ Monitor kidney function and adjust dose accordingly based on prescribing information.	▸ Gastrointestinal adverse events are usually transient and lessen over time ▸ Take with food ▸ Do not crush or chew extended release products
SGLT2i	Common adverse effects are genital mycotic infections and urinary tract infections (less common) **Use caution:** ▸ recurrent yeast infections or urinary tract infections ▸ volume depletion ▸ diabetic ketoacidosis ▸ amputations ▸ necrotising fasciitis of perineum (exceeedingly rare)	▸ Use lowest dose for cardiorenal effects ▸ Recognise less glucose lowering effect if estimated glomerular filtration rate <45 mL/min/1.73 m2 ▸ Consider delaying start of treatment during severe hyperglycaemia ▸ Assess volume status, blood pressure, and adjust other drugs (eg, diuretics) if needed ▸ Hold during acute illness and before surgery (at least 72 hours) ▸ Identify those at high risk for adverse events and evaluate benefits and risks (eg, high amputation risk, recurrent yeast or urinary tract infections, diabetic ketoacidosis) ▸ Do not stop SGLT2i after initial drop in estimated glomerular filtration rate unless related to volume depletion. Initial drop is considered correction of previous hyperfil tration rates, not predictor of further estimated glomerular filtration rate trajectories ▸ Adjust background treatments as needed to avoid hypoglycaemia ▸ Monitor kidney function and adjust dose accordingly based on prescribing information ▸ Cross communicate with other healthcare providers	▸ You might notice an increase in urine output ▸ Stay well hydrated, stand up slowly, and note any dizziness ▸ Recognise signs and symptoms of genital mycotic infections, maintain good personal hygiene, call healthcare provider if yeast infection occurs because it can likely be treated without discontinuing SGLT2i ▸ Follow sick day plan when sick; do not stop taking your insulin ▸ Do not start a low or non-carbohydrate diet without consulting your healthcare provider ▸ Call your healthcare provider if you experience symptoms of diabetic ketoacidosis (nausea, vomiting, abdominal pain, tiredness, trouble breathing)
GLP1RA	Common adverse effects are gastrointestinal (nausea, vomiting, diarrhoea, constipation) **Use caution:** ▸ pancreatitis ▸ diabetic retinopathy ▸ gastroparesis ▸ gallbladder and biliary disease **Do not use:** ▸ thyroid C cell carcinoma (black box warning: contraindicated in personal or family history of medullary thyroid cancer or multiple endocrine neoplasia type 2)	▸ Start at low dose and titrate slowly to lessen gastrointestinal adverse events (for most agents) ▸ Consider slower dose titration if gastrointestinal adverse events persist ▸ Provide practical education on administration, storage, missed doses ▸ Use demonstration delivery pen devices and ask the patient to demonstrate administration technique with the teach back method ▸ Set expectations (eg, time to full effect, dose titration, timing of adverse effects, and how to lessen) ▸ Adjust background treatments as needed to avoid hypoglycaemia ▸ Follow-up within first few weeks to assess and reinforce ▸ Don't assume the patient is resistant to injections ▸ Proactive screening for diabetic retinopathy is recommended	▸ Gastrointestinal adverse events are usually mild to moderate, transient, and resolve in most individuals ▸ Eat smaller meals, eat slowly, stop eating once full, avoid eating when not hungry, avoid high fat or spicy food, and limit alcohol189–191
GIP-GLP1RA	Same as GLP1RA	Same as GLP1RA	Same as GLP1RA
DPP4i	Very well tolerated; few common adverse effects **Use caution:** ▸ pancreatitis ▸ gallbladder and biliary disease ▸ joint pain	▸ Monitor kidney function and adjust dose accordingly based on prescribing information	▸ Take once daily by mouth with or without food
Sulfonylurea	Common adverse effects are weight gain and hypoglycaemia	▸ Avoid in kidney dysfunction and older adults (especially glibenclamide and glyburide) ▸ Set expectations about adverse effects	▸ Prevention, detection, and treatment of hypoglycaemia ▸ Eat meals consistently to avoid hypoglycaemia
Thiazolidinedione	Common adverse effects are oedema and weight gain Use caution: ▸ heart failure ▸ risk of bone fractures ▸ bladder cancer	▸ Consider using lower dose, especially when used in combination with insulin to avoid side effects ▸ Set expectations about adverse effects	▸ Take once daily by mouth with or without food

GIP=glucose-dependent insulinotropic polypeptide; GLP1RA=glucagon-like peptide 1 receptor agonist; SGLT2i=sodium-glucose cotransporter 2 inhibitor; DPP4i=dipeptidyl peptidase 4 inhibitor.

seen in people receiving semaglutide during the SUSTAIN-6 (Trial to Evaluate Cardiovascular and Other Long term Outcomes With Semaglutide in Subjects With Type 2 Diabetes) randomised controlled trial with 3297 participants with type 2 diabetes.[56] Of those with retinopathy complications, 83.5% had a history of retinopathy at baseline. In a meta-analysis of four cardiovascular outcomes trials of dulaglutide, liraglutide, oral semaglutide, and subcutaneous semaglutide, use of GLP1RAs was associated with an increased risk of rapidly worsening retinopathy (odds ratio 1.23, 95% confidence interval 1.05 to 1.44).[108] In another meta-analysis, GLP1RAs were not independently associated with an increased risk of retinopathy, but an association between retinopathy and the magnitude of the reduction in levels of HbA1c was found.[109] Rapid glucose lowering has previously been associated with worsening diabetic retinopathy,[110] and the GLP1RA cardiovascular outcomes trials were not powered to detect differences in retinopathy complications. Thus whether worsening retinopathy is caused by the drug itself, a change or rate of change in glucose levels, or a combination of both is unclear. We advise caution when GLP1RAs are used, particularly semaglutide, in people with diabetic retinopathy, and individuals should be monitored closely for progression of retinopathy.[111]

Whether other GLP1RAs similarly increase the risk of progressive diabetic retinopathy is not known. Consultation with an ophthalmologist should be considered before starting GLP1RAs in people with pre-existing retinopathy.[111] A large randomised controlled trial (A Research Study to Look at How Semaglutide Compared to Placebo Affects Diabetic Eye Disease in People With Type 2 Diabetes (FOCUS), NCT03811561) evaluating the long term effects of subcutaneous semaglutide on eye disease in 1500 people with type 2 diabetes is ongoing and should provide more evidence.

Amputations

An increased risk of lower limb amputations was first reported in the cardiovascular outcomes trial for canagliflozin that included 10 142 participants with type 2 diabetes and high cardiovascular risk (6.3 *v* 3.4 participants per 1000 patient years; hazard ratio 1.97, 95% confidence interval 1.41 to 2.75)[57] and led to a warning added to the prescribing information for canagliflozin in 2017.[112] The FDA removed the warning in 2020 based on more clinical trial data that found that the risk was less than previously described.[113] Subsequent real world cohort studies, randomised controlled studies, and meta-analyses have reported conflicting results, with some suggesting an increased risk with all SGLT2is and others finding no increased risk.[114–121] Therefore, reasonable steps to take are to consider factors that increase the risk of amputations before starting an SGLT2i, closely monitor people for lower limb ulcers or infections, and discontinue the SGLT2i if these occur. Subgroup and exploratory analyses of the SGLT2i cardiovascular outcomes trials, however, suggest cardiovascular benefit in patients with peripheral arterial disease,[122–124] so clinicians should use shared decision making when assessing the benefits and risks of SGLT2is in those at high risk.

Diabetic ketoacidosis

SGLT2is are associated with an increased risk of diabetic ketoacidosis, particularly in people with type 1 diabetes and in the perioperative population.[125 126] Rates in adults with type 2 diabetes are low and range from 0.16 to 0.76 events per 1000 patient years.[127] In type 2 diabetes, the risk is increased in people who are insulin deficient, in older people, with prolonged use of SGLT2is, or in those with a combination of these factors.[128] Guidance on risk management of diabetic ketoacidosis is mainly from individuals with type 1 diabetes, with little guidance specific to type 2 diabetes, and recommendations are mostly extrapolated from the type 1 diabetes context.[126 129] People with diabetes should be informed of the importance of adherence to insulin treatment, avoiding very low carbohydrate diets (such as ketotic diets), and excessive intake of alcohol. Education on management of sick days should also be given, and insulin doses should be monitored carefully; basal insulin should not be discontinued completely during illness or planned activity, particularly in those receiving intensive insulin treatment.

Clinicians and people with diabetes should be aware of predisposing factors and the clinical presentation of diabetic ketoacidosis, which often occurs with lower serum glucose levels (so-called euglycaemic diabetic ketoacidosis), sometimes at glucose concentrations of ≤200 mg/dL (11.1 mmol/L). The SGLT2i should be discontinued and

treatment started promptly if diabetic ketoacidosis is suspected. SGLT2is should also be discontinued 3-4 days before scheduled surgery, during prolonged fasting or low carbohydrate intake, or during critical illness to lessen the risk of diabetic ketoacidosis.[24] Some have suggested that absence of ketosis (<0.6 mmol/L blood ketones, negative urine ketones) should be confirmed in people with type 1 diabetes before the start of treatment if SGLT2is are being used off label in this population,[126] but no evidence exists in support of this practice for people with type 2 diabetes.

Starting and titrating insulin treatment

Many people with type 2 diabetes will eventually require insulin because of the progressive nature of the disease. For most people, a GLP1RA should be considered as the first injectable agent before basal insulin, based on the strong evidence of similar efficacy, beneficial effect on weight, and less hypoglycaemia.[130 131] If more treatment is needed after a GLP1RA, basal insulin should be started first and titrated to a maximum effective dose in a safe and timely way.[7 98] Several steps are necessary to support optimisation of insulin treatment, including clear communication of expectations, adequacy of glucose monitoring (including continuous glucose monitoring for people with basal insulin or intensive insulin treatment, and remote telemonitoring), a feasible dose titration plan, clearly defined glycaemic targets, and education on proper administration of insulin and storage.[131–134] Whether the individual can self-titrate the dose or if more support is needed should be assessed. People who can self-titrate can be instructed to continue uptitrating the dose until fasting glucose levels are consistently between 80 and 130 mg/dL (4.4 to 7.2 mmol/L; or an individualised glycaemic target), an anticipated maximum basal dose is reached (eg, 0.5 units/kg/day), or have unexplained hypoglycaemia. Providing these endpoints is key to reducing the risk of being treated with an inappropriately high dose of basal insulin in an attempt to compensate for inadequate postprandial glycaemic control (ie, overbasalisation) while facilitating continued titration to an effective dose.[135] If the individual cannot self-titrate, consider providing weekly follow-up healthcare remotely (ie, telehealth) for timely dose titrations.

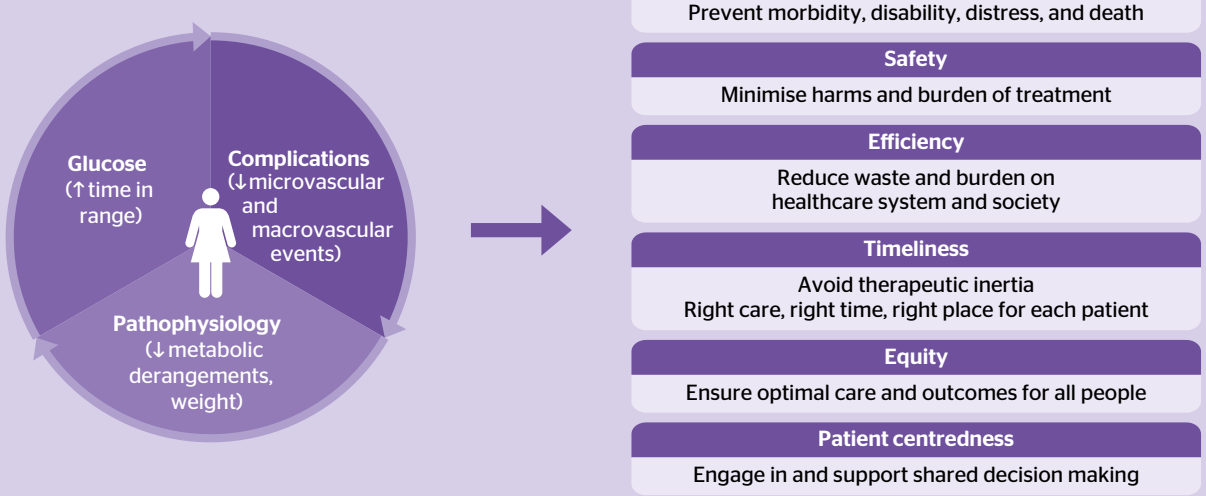
If the basal insulin dose has been sufficiently titrated but levels of HbA_{1c} remain above the person's individualised target or concern for overbasalisation exists, targeting postprandial glucose excursions is warranted. Initially, consider adding a GLP1RA or GIP-GLPRA if not already being used. The next step is to add prandial insulin as a separate injection or by switching to a fixed ratio combination. Basal bolus insulin treatment requires more injections, more glucose testing, more education, and carries a higher risk of hypoglycaemia and weight gain.[98] Metformin or complication centric drugs (GLP1RAs and SGLT2is), or both, should be continued. Sulfonylureas should be discontinued because of the risk of hypoglycaemia with concurrent insulin treatment.

Weight management in type 2 diabetes

Among adults with diabetes in the US, almost 28% are overweight (body mass index 25.0-29.9), 46% have obesity (body mass index 30.0-39.9), and 16% have severe obesity (body mass index ≥40.0).[136] Increasingly recognised as a chronic disease, obesity (termed adiposity based chronic disease)[137 138] is characterised by excessive, maldistributed, and dysfunctional adipose tissue, and is associated with increased risks of hyperglycaemia (ie, prediabetes and type 2 diabetes), cardiovascular disease, hyperlipidaemia, hypertension, chronic kidney disease, cancer, urinary incontinence, non-alcoholic fatty liver disease, osteoarthritis, infertility, obstructive sleep apnoea, and gastro-oesophageal reflux disease.[137]

Obesity is closely related to the pathogenesis and pathophysiology of type 2 diabetes and it also affects the management and outcomes of diabetes.[137 139] Strong evidence indicates that weight loss, particularly if >10% of body weight, can prevent, improve, and even reverse type 2 diabetes.[140] The Diabetes Prevention Programme showed that people with prediabetes who were randomised to receive an intensive lifestyle intervention had a 16% reduction in the risk of progressing from prediabetes to diabetes for every kilogram of weight loss.[37] In the Look AHEAD study of people with type 2 diabetes and overweight or obesity, improvement in fasting glucose and HbA1c levels was found with weight loss as little as ≥2 kg, and improvements were directly proportional to the amount of weight lost.[31] After initial weight loss from lifestyle

Figure 1. Shifting pattern of management of type 2 diabetes



interventions or pharmacotherapy, compensatory physiological responses often make efforts at further weight loss more difficult, less successful, or difficult to maintain, a biological phenomenon referred to as obesity protecting obesity.[141] Hence clinicians should provide a supportive approach, recognising personal biases, and avoiding stigma and judgment to facilitate weight management efforts.[141]

Despite years of commercial availability, obesity drugs are rarely used, with fewer than 5-10% of people with diabetes and obesity receiving obesity drugs in the US.[142] This finding could be driven by the relatively low efficacy of historically available drugs for weight loss, with most drugs causing <7% body weight loss.[141] Recent developments with incretin treatments have closed this gap, however, with up to 20% weight loss reported with tirzepatide.[107] Several studies in people with obesity, with or without type 2 diabetes, treated with semaglutide or tirzepatide have reported reductions in body weight of at least 5-10% in up to 80-90% of people, and reductions of 15-20% in up to 40-50% of people.[106 107 143 144] Efforts to lose weight in people with type 2 diabetes and obesity should be supported through preferential use of glucose lowering drugs that are associated with weight loss, avoiding glucose lowering and non-diabetes drugs associated with weight gain, and aiming for weight loss of 12-15% as appropriate, to achieve maximum benefits.[7 140]

Equity and affordability of diabetes care

Affordability, accessibility, and feasibility of implementing the diabetes care plan are major considerations in shared decision making. In the US, the high and rising costs of insulin and non-insulin drugs[145] have contributed to diabetes distress,[146] cost related non-adherence[147 148] with a detrimental effect on diabetes health outcomes[149] and rationing of other vital expenses.[150] Therefore, healthcare providers must discuss concerns about affordability with all people with diabetes, ensure that prescribed drugs are available and accessible, and leverage care team and community support systems to reduce the financial burden of the management of diabetes.[151 152]

To deal with the growing concerns about affordability of insulin in the US, out-of- pocket costs have been capped in 2023 by the Centers for Medicare and Medicaid Services (which oversee publicly funded insurance for seniors, low income individuals, and people with disabilities or end-stage kidney disease), several private insurance plans, and insulin manufacturers, and the effect of these changes on cost related non-adherence and rationing will need to be assessed. The cost of drugs is generally much lower outside of the US because of highly regulated policies on drug pricing and cost effectiveness in other high income countries,[153 154] but 80% of people with diabetes live in low and middle income countries[155] and half do not have access to recommended

diabetes treatments.[156] These findings call for multifaceted policy solutions to lower costs, increase supply, and improve accessibility of evidence based diabetes treatments and technologies in all settings and populations.[157]

Socioeconomic barriers to optimal management of diabetes are multifaceted and include not only the high costs of diabetes drugs, technology, and equipment, but also foundational social determinants of health, such as the home environment with access to healthy food choices and space for physical activity, environmental pollution and endocrine disrupting chemicals, stable housing with access to electricity and refrigeration, employment type and stability, and educational attainment.[152] Geographical differences in the quality of care and prevalence of type 2 diabetes and its complications exist across levels of rurality,[158 159] neighbourhood disadvantage,[158 160] and geopolitical environment.[161–163] Several interventions have been shown to be successful in improving the management of diabetes, including community health worker programmes, diabetes prevention and self-management programmes adapted specifically to the needs of underserved and disadvantaged populations, expansion of health insurance as part of the Affordable Care Act, food and housing support programmes, and others.[152]

We must also be cognisant of pervasive racial and ethnic inequalities in the quality of diabetes care and health outcomes. In the US, racial and ethnic minority populations are disproportionately affected by diabetes[164] and its complications. [152 165 166] Multiple studies have shown worse glycaemic control[165 167 168] and higher rates of acute complications (hypoglycaemia,[160 165 169–172] diabetic ketoacidosis, and hyperglycaemic hyperosmolar state),[160 165 170 173] chronic complications (kidney disease,[165 174–178] amputation,[165 175] cardiovascular disease,[165 175] and retinopathy),[176 179] and mortality[180 181] among black people with type 2 diabetes relative to other racial and ethnic groups. People with type 2 diabetes from racial and ethnic minority groups are also substantially less likely to be treated with GLP1RAs and SGLT2is than non-Hispanic white people.[182 183] Similar inequalities in the prevalence, management, and health outcomes of diabetes have been described in Europe[184 185] and around the world.[186 187] These inequalities highlight the need for structural solutions and multisector collaborations that deal with the barriers to optimal diabetes management and health at all levels to ensure that all people, regardless of race, ethnic group, socioeconomic status, or place of residence, receive high quality care.

CONCLUSIONS

The paradigm of diabetes management has shifted over the past decade from a predominantly glucose-centric approach to approaches that prioritise prevention of diabetes complications and addressing the underlying causes of diabetes and metabolic dysfunction, such as obesity (figure 2). High quality, evidence based management of diabetes therefore requires reducing glucose levels to a safe, patient centred range; using glucose lowering drugs with a strong evidence base for reduction of diabetes complications and excess adiposity, not just lowering levels of HbA1c; minimising burden of treatment and improving quality of life; and implementing care delivery models that support high quality (effective, efficient, safe, equitable, timely, and person centred) care.[188] Access and affordability remain major barriers, as is the sustainable implementation of effective lifestyle interventions.

Contributors
All authors designed the study, drafted sections of the manuscript, and reviewed or edited the manuscript. RGM secured funding and supervised the study. RGM is the guarantor of this work and, as such, had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. RGM affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

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Competing interests
We have read and understood the BMJ policy on declaration of interests and declare the following interests: in the past 36 months, RGM received support from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), National Institute on Aging of the National Institutes of Health (NIH), the Patient Centered Outcomes Research Institute (PCORI), the National Center for Advancing Translational Sciences, and AARP. RGM also served as a consultant to Emmi (Wolters Kluwer) on developing patient education materials related to prediabetes and diabetes. In the past 36 months, RJG has received unrestricted research support (to Emory University) from Novo Nordisk, Dexcom, and Eli Lilly, and consulting or personal fees from Sanofi, Eli Lilly, Novo Nordisk, Boehringer-Ingelheim, Bayer, Pfizer, and Weight Watchers, all outside the scope of this work.

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Feature

By **Jane Bracher**
Digital Content and Social Media Producer

Could a new tool stop a dengue outbreak before it even starts?

DENGUE IS A THREAT TO PEOPLE'S HEALTH IN VIETNAM, AND IT'S BEING EXACERBATED BY CLIMATE CHANGE. A NEW DIGITAL TOOL COULD PROTECT MORE PEOPLE BY PREDICTING WHERE POTENTIAL DENGUE OUTBREAKS MIGHT HAPPEN.

In 2022, Vietnam went through one of its worst dengue outbreaks. According to the World Health Organization (WHO), there were more than 360,000 reported cases of dengue and 140 deaths in Vietnam. By comparison, in 2021, Vietnam recorded 72,880 cases and 27 deaths.

Kien Quoc Do, a senior epidemiologist in the south of Vietnam working in dengue surveillance, intervention and response, remembers the outbreak vividly.

"Hospitals and medical centres at all administrative levels in Vietnam were crowded [with] the patients," said Do, who works at the Pasteur Institute directed by Vietnam's Ministry of Health and in charge of communicable disease surveillance and control.

"They even [had] to share beds due to a huge number of hospitalisations per day. Doctors [and] nurses were all exhausted."

A new digital tool, E-DENGUE, is being developed by public health researcher Dr Dung Phung at the University of Queensland in Brisbane, Australia, with funding through

our discretionary awards within our Digital Technologies Development Awards portfolio.

The tool will be used by Do and other local governmental health practitioners to predict outbreaks as early as two months in advance and try to prevent or mitigate them early..

Dengue in Vietnam

Vietnam is among the countries with the highest number of cases around the world, alongside Brazil, the Philippines, Indonesia and India.

Cases peak during the rainy season from June to November. From 2000 to 2020, Vietnam reported an average of 95,000 cases each year. Besides overwhelming the healthcare system and impacting people's health, dengue in Vietnam also has an annual economic burden of millions of dollars.

The Mekong Delta region in the south of Vietnam – with its many rivers, canals and streams stemming from the Mekong River – is among the most affected annually. It had the highest record of dengue cases from 2000 to 2016.

Phung has seen first-hand Vietnam's struggles dealing with dengue. He has worked

as a medical doctor in Hanoi and as a health expert and researcher developing policy with Vietnam's Ministry of Health.

One of the main challenges he's identified is being one step behind the disease, reacting to an outbreak once it has already spread instead of being more proactive through prevention.

A digital tool to predict dengue outbreaks

E-DENGUE is a software dashboard for desktop computers that will use various data sources to predict the incidence of dengue ahead of time, without relying on case reporting. If successful, Phung's team may look into creating a mobile app as well.

The tool, which will be developed with prediction models, will allow local health practitioners to accurately predict where an outbreak might occur as early as two months ahead of time. It could give them valuable time to mobilise resources and control the outbreak even before it has taken place, putting public health practitioners one step ahead of dengue.

"We expect E-DENGUE can help reduce about 25% of dengue incidence and outbreaks in comparison with the current reactive prevention practice," Phung said. "E-DENGUE can help facilitate proactive prevention rather than reactive prevention."

E-DENGUE will utilise data strongly associated with dengue transmission and the increased risk of dengue incidence in communities. This includes:

climatic data, such as

- temperature
- rainfall
- relative humidity

socio-demographic data, such as

- population density
- the proportion of urban area
- road transportation
- water supply
- socioeconomic status like poverty rate and average household income

preventive data, such as

- vector monitoring
- mosquito control interventions
- policy and regulations.

The tool will be tailored for the Mekong Delta region.

Phung has introduced the project to 13 provinces in the Delta, all of which have agreed to participate in the project.

"That means all provinces are aware of the strong benefit of the project to reduce the dengue incidence and the burden in the future," he said.

"If we cannot develop a cost-effective tool for the health department to afford and to use in the current routine practice, that tool will not be used."

— **Dr Dung Phung,** Public Health Researcher and Senior Lecturer, University of Queensland, Australia

Ensuring the tool's usability, cost-effectiveness

Advanced technology won't mean anything if it's not usable for the communities that need it most. Making sure the tool is cost-effective and easy to use is one of the top priorities – and challenges – for Phung and his team.

"If we cannot develop a cost-effective tool for the health department to afford and to use in the current routine practice, that tool will not be used," said Phung.

He intends for E-DENGUE to be integrated into the existing surveillance system, using already available data such as the weather station near the Mekong Delta region. Integrating the tool into systems already in use will help make it usable for local health practitioners like Do.

Credit: **Kien Quoc Do**

Kien Quoc Do, a senior epidemiologist in the south of Vietnam working for the Pasteur Institute directed by Vietnam's Ministry of Health, shared these images from field trips related to dengue surveillance and control. Here, his colleague inspects a container of water.

"Many projects before [would] have a forecasting tool but [would] require very high experience and knowledge and skilled staff to run the model and to interpret the model," said Do.

"But for E-DENGUE, I hope that it's suitable so that the district health staff can use the model and can understand the result in an easy way so they can decide when and where to conduct the intervention for dengue control."

Do also finds promising the possibility E-DENGUE can spot more precise locations for intervention – for example, at the district or community level.

"You can concentrate your intervention so it will save your resources – human resources and financial resources," he said.

Dengue and climate change

"Together with global mobility and urbanisation, climate change is a major driver of the increase of the number of dengue virus infections, which have doubled every decade since 1990," said Phung. Shifts in human behaviour because of extreme weather events brought on by climate change are a problem. For example, prolonged drought can lead to saltwater intrusion into mainland waters, which then causes a freshwater shortage. This leads to the informal storage of fresh water among communities like those in the Mekong Delta region.

Dr Dung Phung is a Public Health Researcher and Senior Lecturer at the University of Queensland in Brisbane, Australia. He worked as a medical doctor in Hanoi, Vietnam and as a health expert and researcher developing policy with Vietnam's Ministry of Health.

"When they store water, it [creates] a very beautiful and very wonderful breeding site for mosquitoes," said Do.

"The mosquito population will develop quickly in that situation so the dengue virus will be spread widely in communities, and we normally deal with a very big epidemic whenever there are climate change events like [intense] El Niño [or] the heavy rain in the dry season."

If successful, E-DENGUE could have a valuable impact on the communities in the Mekong Delta region that currently have to live with the threat of dengue at all times.

Phung hopes that, in an increasingly warmer world with a higher burden of vector-borne disease, E-DENGUE's usefulness could also extend beyond just Vietnam.

Surgical Management of Follicular Carcinoma of Thyroid with Spine Metastasis: A Case Report

We report an unusual case of 55-year-old female from Ethiopia with a Thyroid swelling for 25 years came to us with Right upper limb radiating pain and hand weakness for 7 months.

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ABSTRACT

We report an unusual case of 55-year-old female from Ethiopia with a Thyroid swelling for 25 years, came to us with Right upper limb radiating pain and hand weakness for 7 months. MRI showed thyroid swelling–suspicious for carcinoma with metastatic involvement of C6, C7 and T1 vertebral bodies. After appropriate evaluation, she underwent Total Thyroidectomy and combined anterior-posterior approach in a single stage with complete excision of spinal lesion with spinal cord decompression and stabilization. The histopathological result was compatible to the metastasis of follicular thyroid carcinoma. Post-operative recovery was uneventful.

INTRODUCTION

Differentiated thyroid cancer (DTC) account for the vast majority (90%) of all thyroid cancers and includes papillary (70–75%) and follicular (15–20%) cancers[1]. Follicular type thyroid cancer (FTC) is the second most frequent type of DTCs, and is more inclined to metastasize to the bone than papillary type. This characteristic is probably due to the fact that FTC usually spreads via blood, whereas papillary type prefers lymphatic route for dissemination[2]. The treatment of DTC with bone metastasis is still controversial. Surgery or radioiodine therapy alone is usually unsatisfactory, and thus the management needs multidisciplinary collaboration.

Here, we describe a case of FTC in which we provided a comprehensive treatment plan for the patient through preoperative evaluation and multidisciplinary consultation, which significantly improved the patient's quality of life and prognosis.

CASE REPORT

A fifty-five-year-old female patient from Ethiopia, presented with complaints of Thyroid swelling for 25 years with a rapid increase in size since few years. She developed right shoulder pain for 8 months which settled with medications. Also, there was progressive weakness in right

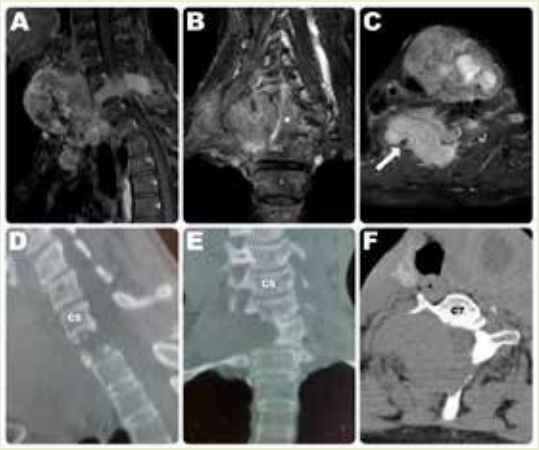

Figure 1. Post contrast cervical MRI images obtained before surgery (a—c). a) Sagittal image. b) Coronal image with star representing spinal cord compressed by spinal tumor. c) Axial image, white arrow showing vertebral artery encased by spine tumor. CT images (d–f) Osteolytic destruction of C6 & C7 vertebral body.

hand for 7 months, associated with burning sensation in inner aspect of right upper limb. She was initially evaluated in Addis Ababa (Ethiopia) with a spine MRI that revealed a thyroid swelling – suspicious for carcinoma with metastatic involvement of C6 & C7 vertebral bodies with compression of spinal cord and right C7 & C8 nerve roots (Figure.1 A- C). CT scan of spine showed osteolytic destruction of C6, C7 & T1 vertebral bodies along with involvement of Right C6, C7 & T1 pedicles (Figure.1 D-F). PET scan of whole body revealed primary thyroid malignancy with skeletal metastasis (Figure 2).

A multidisciplinary team involving surgical, medical oncology & nuclear medicine was involved. FNAC of the thyroid swelling was done which suggested possibility of follicular neoplasm. In view of long-standing history, better prognosis and significant spinal cord compression with neurological deficits, a decision was then made to go ahead with the surgery for Thyroid tumor and spine metastasis along with spinal cord decompression and stabilization. She underwent a combined anterior-posterior single-stage surgery with complete excision of spinal lesion with spinal cord decompression and stabilisation – a combined effort involving the surgical oncology and spine surgery team.

First an anterior cervical approach was planned and horizontal skin incision was taken (Figure 3A). Total thyroidectomy was performed by surgical oncology team. Using same incision C6 & C7 corpectomy and tumour involving the anterior and middle columns of the spine was resected. The vertebral body defect was reconstructed with an expandable cage filled with allograft and anchored to the vertebral body with inbuilt locking screws (Figure 3B). Then patient was then turned prone, a midline skin incision was deepened in layers to expose the spinous process, lamina and facet joints along with removal of the metastatic component involving the posterior column. Once tumour resection was completed, supplemental posterior stabilisation was done with consecutive C5-D2 on left side with Right C5 and D2 pedicle screws using 3D real time navigation using intraoperative O-arm® system (Figure 4). The right C6, C7 and D1 pedicles were destroyed by the tumour and screw could not be inserted. The total duration of surgery was 12 hours and blood loss was around 500ml. Post-surgery she recovered very well and her radicular pain decreased (Figure 5). The histopathological result was compatible to the metastasis of follicular thyroid carcinoma (Figure 6).

After the surgery, the patient took thyroid hormone replacement therapy (L-T4 200 µg/d) and the TSH concentration was controlled under 0.1 mU/L. The radioactive iodine scan showed iodine accumulation in cervical lymph nodes and left femur. Hence the patient took I-131 adjuvant therapy, with a dose of 200 mCi and nine months later for the second time with the same dose. She remained asymptomatic at 12 months telephonic consultation and follow-up as was able to do daily routine and household work. She was advised to do a repeat imaging study in her country.

DISCUSSION

Follicular thyroid carcinomas (FTC) are subtypes of thyroid cancers which are slow growing tumors and are associated with a favourable prognosis except when they present with distant metastasis[3]. Lung and bone are the two most favoured sites of metastases[4]. Bone metastases from FTC tend to be multiple and more often to the ribs, vertebra and sternum5. Spinal metastases usually affect the thoracic (60%-80%), lumbar (15%-30%), and cervical vertebrae (< 10%). While the 10-year survival rate is 80-95% for patient with differentiated thyroid carcinoma, survival rate decreases approximately 40% for patients with distant metastasis[3].

The management of Differentiated thyroid carcinoma with bone metastasis is challenging: a careful evaluation and a personalised approach are essential to improve patients' outcomes[6]. Multimodal and multidisciplinary management strategy can achieve disease control and symptom relief in these tumours.

Thorough pre-operative examinations are the basic foundation for accurate diagnosis and favourable prognosis. CT of the neck and chest and MRI of the spine, pelvis, and femurs can be useful to visualize metastatic foci[7]. PET-CT can be applied to investigate further skeletal metastases for tumor staging[8]. Patients with Bone metastasis(BM) from thyroid carcinoma generally have

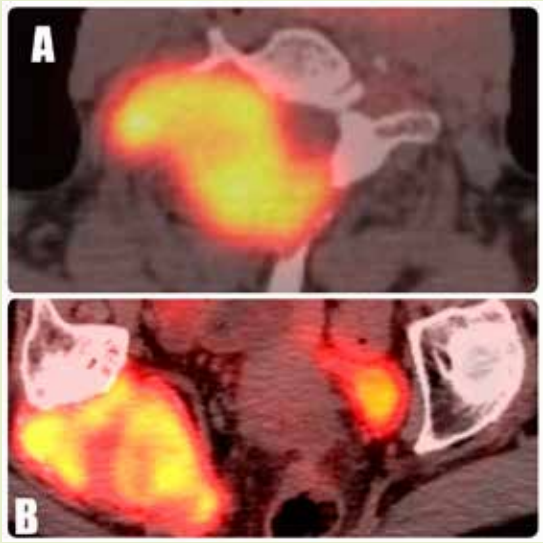

Figure 2. PET—CT a) Expansile Lytic lesion at C6 involving the Right transverse process & lamina. b) Expansile lytic lesion with soft tissue involving right acetabulum.

Figure 3. Intra operative images a) Showing incision taken for anterior approach(after thyroidectomy). b) After C7 & T1 corpectomy with Expandable cage in-situ. Star representing recurrent laryngeal nerve.

better survival than some other carcinomas that frequently metastasise to bone, such as lung and renal cell carcinoma[6].

Surgical resection has remained the first choice for the treatment of DTC.Total/near-total thyroidectomy and thyroid lobectomy are the two most accepted options[9]. Our patient underwent Total thyroidectomy. Resection of solitary bone metastasis, together with total thyroidectomy, could increase survival rate[10]. Wu et al[11], who analyzed 44 patients of thyroid carcinoma with bone metastasis, showed that proper operations aiming at preventing or treating complications of metastatic bone disease appear to be useful in improving morbidity in patients with skeletal disease. Bernier et al[12] retrospectively studied 109 DTC with bone metastasis, in which 24 (22%) patients were treated by complete excision of the metastasis, 60 (55%) patients were treated by partial removal, while others did not receive any surgery, with the median survival time being 6.2, 4.2, and 2.5 years, respectively (P<0.05).

The indications for the surgical intervention on bone metastasis are as follows: (a) continuous pain; (b) solitary bone metastasis;(c)insensitivity to other treatment; (d) existence or high risk factors of pathologic fracture and paraplegia;(e)obvious manifestation of neurodeficits[13]. Meanwhile, multiple organ metastasis and poor general condition are regarded as the contraindications for surgery.

Our patient successfully underwent combined anterior & posterior single stage complete excision of spinal lesion with spinal cord decompression and stabilisation.

Adjuvant therapy can prolong survival and improve quality of life by elimination of microscopic residual or metastatic disease after surgery[14]. In a study of 106 cases, Qiu et al[15] pointed out that radioiodine therapy could significantly decrease or at least stabilize serum Thyroglobulin level as well as alleviate pain on the bone. It could also help shrink or stabilize lesions for most DTC patients with bone metastasis. Petrich et al[16] also conducted a retrospective study of 107 patients, with the conclusion that bone metastases from DTC could be treated by radioiodine therapy, despite the contrary opinion that bone metastases had general resistance to I131 therapy [17]. The dose of I-131 should be 3.7–5.5 GBq for an adult and 37 MBq/kg for a child[18]. However, the optimal doses are still under investigation.

Thyroid hormone replacement therapy should be given in order to rectify the resulting hypothyroidism and increase the survival rate. It is indicated that with high doses of replacement therapy, the recurrence of the cancer decreased [15]. When TSH is >2 mU/L, the mortality and recurrence increase [19]. However, long-term usage of thyroid hormone above physical dosage will lead to sub-clinical hyperthyroidism. The ideal aim of thyroid hormone replacement therapy is reducing the mortality and recurrence, simultaneously avoiding side effects. It is mandatory to evaluate the thyroid function periodically. Our patient took L-T4 200 µg/d and received the appropriate effect.

CONCLUSIONS

Differentiated Thyroid carcinomas with spinal metastases can be managed safely and effectively with a multidisciplinary team involving Surgical oncologists, Spine surgeons, medical oncologists and nuclear medi-

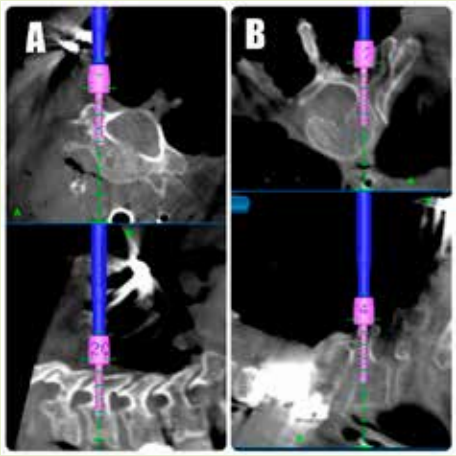

Figure 4. A & B Illustrative images showing insertion of Pedicle screws using real time 3D navigation

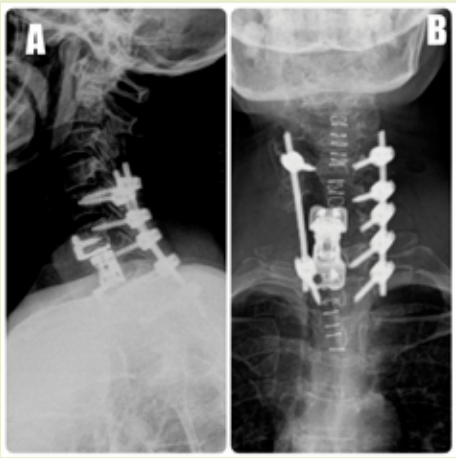

Figure 5. Post op X-ray. A & B - Lateral & Antero posterior X-ray of Cervical spine.

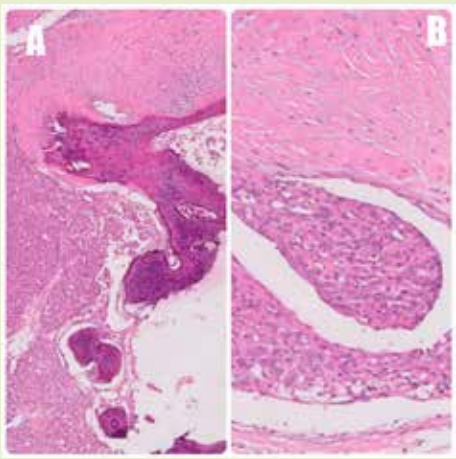

Figure 6. a) 10x, HPE image showing closely packed thyroid follicles infiltrating bone & cartilage. b) 40X, HPE image showing Lymphovascular spaces with presence of thyroid follicular cells

cine specialists. Our case outlines the result of such team effort to treat a unique and large thyroid carcinoma with cervical spine metastasis causing vertebral destruction and spinal compression, through a single stage surgery and post-operative adjuvant therapy, to achieve good outcomes.

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A Two-Layer Prolene Mesh Coupled with Bone Cement and Local Myofascial Flap Reconstruction for a Chest Wall Tumor

We present a case of 70 years old female who presented to us with painless hard swelling involving left chest, at inner aspect of left breast. It gradually increased in size and was mildly painful.

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Keywords:

Chest wall reconstruction, Malignant chest wall tumors, Bone cement.

INTRODUCTION

Chest wall neoplasms are a heterogenous group of tumors that are challenging to both diagnose and treat. They can arise from any soft tissue or bony structures around thoracic cavity. They can be either primary or metastatic, and either symptomatic or asymptomatic. Malignant rib tumors include multiple myeloma, chondrosarcoma, osteosarcoma and Ewing's sarcoma which typically manifest as painful, rapidly growing large palpable masses. Desmoid tumors and neurogenic tumors are benign but locally aggressive rare tumors of chest wall. Incorrect diagnosis, incomplete resection and unsuccessful reconstruction of large thoracic wall defects have resulted in high rates of perioperative morbidity and mortality. Chest wall resection and reconstruction is the primary surgical option for chest wall tumors. This surgery involves the removal of one or more ribs to extract the tumor, followed by reconstruction to recreate a normal appearance after invasive surgery. This involves prosthetic materials, 3D printing- Titanium Powder light weight implants and/or rotation of muscle flaps.

CASE REPORT

We present a case of 70 years old female who presented to us with painless hard swelling involving left chest, at inner aspect of left breast. It gradually increased in size and was mildly painful. On examination hard lump was palpable in inner aspect of left breast, which was involving 5th and 6th rib and encroaching over the costochondral junction and was immobile, the overlying breast was mobile over the lump. Core Biopsy was reported as low grade spindle cell tumor and immunohistochemistry was suggestive of low grade spindle cell proliferation probable mediastinal fibrosis – spindle cell express SMA focally and negative for Desmin, CD34, Beta catenin, STAT-6 and S-100 protein. She defaulted for the advised surgery, and presented to us after 7-8 months with huge painful enlargement of swelling.

CECT thorax was done which showed well-defined mild heterogeneously enhancing lobulated soft tissue density lesion of approximate size 10 x 9.3 x 7.1 cms seen epicentred in chest wall on left side paramedian anterior aspect of lower chest causing erosion of adjacent 4th to 6th ribs costo-chondral junction, intrathoracicextrapleural component lesion indenting over adjacent right atrium of heart with distinct interface between lesion and pericardium and adjacent volume loss of lung. Anteriorly lesion was seen up to subcutaneous plane. After preanaesthetic evaluation, patient underwent surgery. Incision was taken along the left inframammary crease and breast was lifted to expose the tumor. Then wide excision

of tumor along with full thickness resection of 4th to6th ribs along with part of serratus anterior with adequate margins. In view of low grade spindle cell proliferation and probable mediastinal fibrosis (benign) as reported on IHC, sternal bony margin of 2 cm was not considered. The chest was full thickness defect was reconstructed by bone cement wrapped in the prolene mesh which was secured to the cut margins of resected ribs with no.1 prolene sutures. Pectoralis major local rotation flap was mobilized to buttress the reconstructed area. Left intercostal drain was placed and suction drain was placed at the reconstructed site below the pectoralis muscle. Duration of surgery was 150 minutes with total blood loss of 150 ml. Final histopathology reported as Low grade spindle cell tumor with wide and adequate soft tissue and bony margins microscopically free of tumor. Patient was discharged in stable condition on post operative day 5, with all drains removed and no complications. Although 3D-Printing with Titanium implant is the standard of care, we performed local modification with Prolene mesh coupled with bone cement, as second tier cities like us are financially challenged and also lack local expertise for 3D titanium implants. On follow up, patient was stable and asymptomatic, without any mesh and bone cement related complications. Patient is disease free till date on latest follow-up 1 month back.

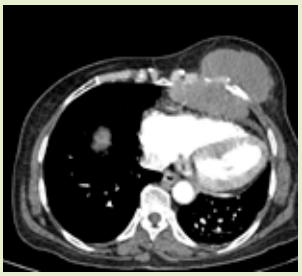

Figure: CT scan showing tumor eroding ribs (4th to 6th rib).

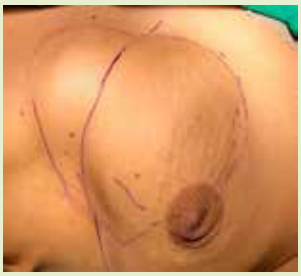

Figure: Outline of the swelling involving the chest wall, with inframammary crease incision marked En

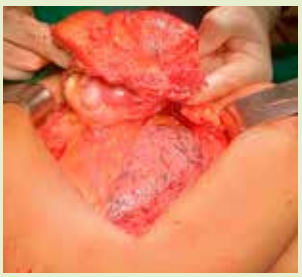

Figure: En bloc resection of tumor along with the tumor bearing ribs

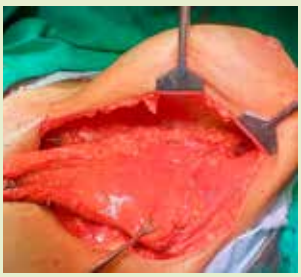

Figure: Pectoralis major myo-fascial flap mobilized to cover the defect

Figure: Bone cement prosthesis shapenedto reconstruct bony defect

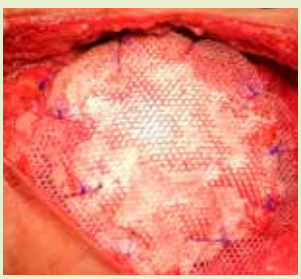

Figure: Prolene mesh wrapped around the cement prosthesis, and fixed to surrounding ribs, to cover the defect Pectoralis

DISCUSSION

Muscular, vascular, fibrous and fibrohistiocytic, peripheral nerve, osseous and cartilaginous, adipose, hematologic, and cutaneous are the eight fundamental diagnostic categories for malignant chest wall tumours. But some cancerous tumours that grow in the chest wall don't necessarily fall into any of these categories (eg, Ewing sarcoma and synovial sarcoma). Malignant chest wall tumours are characterised by large, painful, palpable masses. Chest radiography, the modality most usually used for initial evaluation, can detect cortical damage. Chest radiography is less effective than computed tomography at detecting calcified tumour matrix and cortical damage. Magnetic resonance imaging is frequently helpful in more precisely identifying and localising the tumour when determining the presence and extent of tumour invasion. Due to considerable morbidity and mortality considerations, chest wall resection and reconstruction surgery is a challenging therapy option for

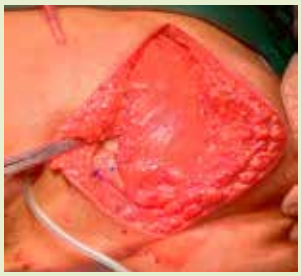

Figure: Pectoralis major myofascial flap inset to cover the prosthesis

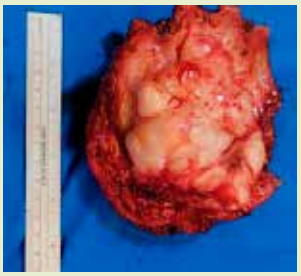

Figure: Wide excision Tumor specimen

thoracic surgeons. Extensive chest wall resections now have more tolerable morbidity and fatality rates thanks to advancements in anaesthesia, ICU care, thoracic surgery, and reconstructive procedures. Defects smaller than 5 cm in size in any location and defects up to 10 cm in size located posteriorly do not generally require reconstruction, while larger defects and most defects in the anterior region do require reconstruction. For the majority of chest wall cancers, wide surgical excision is the most beneficial course of action. Less morbidity and mortality rates have been observed following chest wall excision due to advancements in reconstructive procedures and postoperative patient care [1]. Accurate diagnosis, extensive surgical removal, and suitable restoration of significant chest wall abnormalities are essential for successful therapy [1]. The reconstruction of chest wall deformities must take into account a variety of parameters [2]. Even if the defect's size and location are crucial, a reconstruction may be significantly changed by the patient's medical history and the specifics of the wound. If a full-thickness reconstruction is necessary, both the thorax's structural stability and the soft tissue coverage must be taken into account [2,5,6]. After resection, stability and integrity are required to prevent chest wall collapse. Silicone, Teflon, acrylic materials, or a sandwich of Prolene mesh and bone cement have all been used to achieve structural integrity [1,3]. To buttress the deficiency if necessary, we frequently use a bone cement sandwich with prolene mesh and myocutaneous flap. According to Daigeler and colleagues [7], neither the size nor the site of the resection appreciably impaired pulmonary function, which was only mildly diminished. They came to the conclusion that thoracic wall reconstruction offers great stability to sustain pulmonary function, although there are significant postoperative pain and sensory abnormalities [4]. In surgical procedure, the skeletal chest wall defect is fixed using a bone cement-prolene prosthesis after the resection is complete. The defect's vertical and horizontal dimensions are measured after the chest wall has been resected. To avoid heat damage to nearby structures during hardening, bone cement is combined with solution in a receiver outside the body. In order to simulate the bone cement to the resection borders of the chest wall defect, it is then spread over the two-layer Prolene mesh. Use a sterile ruler to gauge the size of the defect or excision. Nonresorbable interrupted sutures are used to firmly attach the edge of the two-layer Prolene mesh to the defect in the chest wall. To return the chest wall's natural form, the underlying lung is ventilated using normal tidal volumes and positive end-expiratory pressure. After covering the soft tissue with soft tissue, a two-layer Prolene mesh is used to reconstruct the chest wall, giving it an aesthetic aspect. Chest wall resection complications are frequent, ranging from 46 to 69% [5]. The most frequent issues are respiratory ones, which account for 24% of all reported cases and include pneumonia, acute respiratory distress syndrome, and atelectasia. 8 to 20% of the patient group is said to experience wound complications like infection, dehiscence, and hematoma [7].

CONCLUSION

Broad resection with tumor-free margins is essential for the long-term survival of patients with malignant chest wall tumours. Numerous medical developments have made it possible to successfully repair the chest wall, particularly by using prosthetic materials like the Prolene mesh and bone cement sandwich.

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Case Report

Nodular Pulmonary Ossification

Diffuse Pulmonary Ossification is a rare disease, patients are usually asymptomatic and often discovered on autopsy specimens. In one study, the prevalence of diffuse pulmonary ossification was 0.5% with an incidence of 0.28 cases per year.

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INTRODUCTION

Diffuse Pulmonary Ossification is a rare disease, patients are usually asymptomatic and often discovered on autopsy specimens. In one study, the prevalence of diffuse pulmonary ossification was 0.5% with an incidence of 0.28 cases per year. [(1)] Another study showed the incidence to be 1.63 cases per 1000 autopsies. [(2)] It is commonly seen in elderly men above the age of 65, [(1)] however it can occur in women as well. [(3)] With the increased utility of high-resolution CT, more cases are being discovered.

High-resolution CT of the chest showed multiple bilateral lung nodules, some demonstrating speculated margins.

A biopsy was taken via Video-Assisted Thoracoscopic Surgery (VATS) from the left lower lobe of the lung. Sample sent for histopathology.

The histopathology report showed no malignancy. However, Pulmonary Ossification, the nodular type is identified.

Cardiology consultation is done to rule out cardiac causes. Echocardiography was ordered and showed the following:

- Normal Left ventricular size with preserved systolic function.
- Ejection fraction of 60%.
- Mitral annular calcification.
- Mild aortic valve sclerosis without stenosis.
- Mild Aortic regurgitation.
- Grade one diastolic dysfunction with an elevated mean left atrial pressure.
- Trace tricuspid regurgitation.

COURSE AND TREATMENT

The patient was continued on his Asthma treatment including Long Acting B2 Agonist/Inhaled corticosteroids and Leukotriene antagonists. He was not initiated on systemic steroids or any immune modulation therapy, because he was very stable clinically. However on this approach he showed improvement, and clearing of the nodules subsequently and on follow up. This suggest strongly that this diagnosis was discovered incidentally as part of investigations of lung nodules.

DISCUSSION

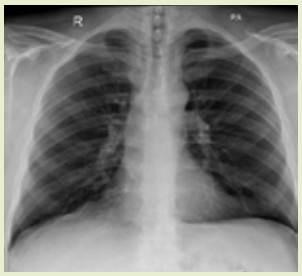
Pulmonary ossification is an uncommon entity and is usually

discovered incidentally on autopsy specimens. Patients are usually asymptomatic or present with symptoms of the predisposing condition. Pulmonary ossification in essence is the presence of mature bone tissue — bone marrow may or may not be present — in the lungs. It can occur secondary to an underlying condition or could be idiopathic and is classified histologically as either nodular or dendriform. The nodular form is usually seen within the alveolar spaces and is commonly associated with cardiac disorders that cause pulmonary venous congestion, particularly mitral stenosis.[4, 5, 6] The dendriform type, as opposed to the nodular, is usually seen in the interstitium and as the name implies, it resembles a "tree" in appearance. It is commonly idiopathic or seen with pulmonary fibrosis.[7] Other etiologies such as Acute Respiratory Distress Syndrome,[8] and Silica exposure[9] have also been reported (Table 1). The pathogenesis of pulmonary ossification is not fully understood. It requires the presence of calcifications in the lungs along with other factors such as an alkaline environment which promotes the deposition of calcium. The liberation of calcium from bone and reaching the lungs via circulation are essential. Interestingly, calcium is not necessarily elevated for calcification to occur — calcium levels may be normal or even low. Alkaline phosphatase levels are usually normal. For ossification to occur, additional factors come into

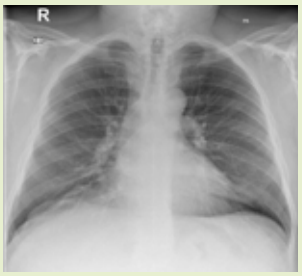
Laboratory Investigations

Investigation	Reference range
c-ANCA: < 1:2	Titer < 1:2
p-ANCA: < 1:10	Titer < 1:10
C3: 2.08	0.82 - 1.85 g/L
C4: 0.43	0.15 - 0.53 g/L
Rheumatoid factor: < 15	< 30
Lupus anticoagulant: absent	-
Angiotensin converting enzyme (ACE): 17 U/L	20 - 70 U/L
NA: 2.9 CU	Negative < 20
Anti-Beta 2 Glycoprotein Abs (IgG): < 6.4 CU	Negative < 20
Anti-Beta 2 Glycoprotein Abs (IgM): 1.4 SMU	Negative < 20
Anti-Cardiolipin IgG: 3.8 CU	Negative < 20
Anti-Cardiolipin IgM: < 1.0 CU	Negative < 20

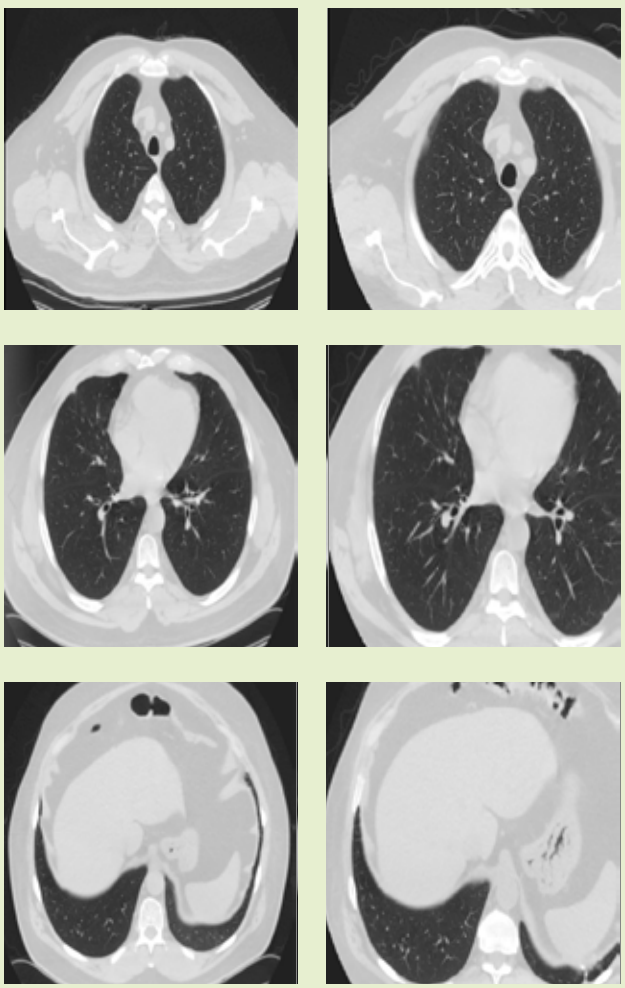
Initial X-ray

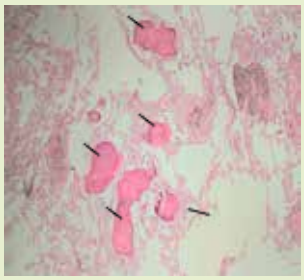


Follow-up X-ray

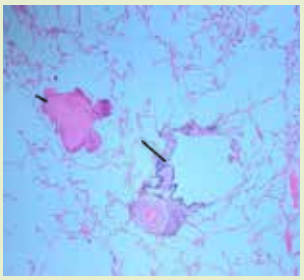


Initial (left side) and follow-up (right side) CT scans showing bilateral nodules

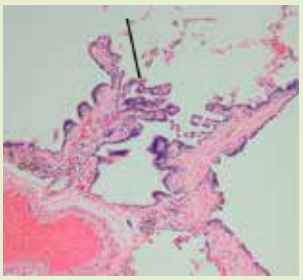




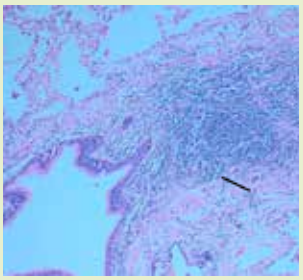
Slide 1: Small, lobulated, mature, lamellar bone nodules of calcified osteoid material deposited within the alveolar spaces and are devoid of fat or marrow elements - Hematoxylin and Eosin stain.



Slide 2: Pulmonary Ossification (short arrow) and bronchiolar metaplasia near a blood vessel (long arrow) - Hematoxylin and Eosin stain.



Slide 3: Bronchiolar metaplasia - Hematoxylin and Eosin stain.



Slide 4: Peri-bronchiolar inflammation (chronic bronchiolitis) - Hematoxylin and Eosin stain.

play such as lung injury, fibrosis, congestion, and angiogenesis. One important growth factor implicated in Pulmonary Ossification is the Transforming growth factor-beta.[4]

On imaging, the nodular type can be mistaken for granulomatous conditions or infections because of its heavy calcifications. The dendriform type is usually seen at the bases of the lungs, bilaterally.[10] It is worth mentioning that the extent of calcifications on radiography doesn't correlate with symptomatology, i.e., patients with minor calcifications can have severe presentations and vice versa.[4]

Table 1: **Causes of Pulmonary Ossification.**

I.	**Idiopathic pulmonary ossification.**
II.	**Preexisting pulmonary disorder:**
A.	Idiopathic pulmonary fibrosis
B.	Pulmonary amyloidosis
C.	Chronic busulfan therapy
D.	Acute respiratory distress syndrome
E.	Hamman-Rich syndrome
F.	Sarcoidosis
G.	Histoplasmosis
H.	Tuberculosis
I.	Metastatic breast cancer
J.	Pulmonary metastases of osteogenic sarcoma
K.	Metastatic melanoma
III.	**Preexisting cardiac disorder:**
A.	Mitral stenosis
B.	Chronic left ventricular failure
C.	Idiopathic hypertrophic subaortic stenosis
IV.	**Preexisting extra-cardiopulmonary disorder:**
A.	Primary and secondary hyperparathyroidism
B.	Hypervitaminosis D
C.	Pyloric stenosis with alkalosis

Reference: Calcium deposition with or without bone formation in the lung. Chan ED, Morales DV, Welsh CH, McDermott MT, Schwarz MI Am J Respir Crit Care Med. 2002;165(12):1654.

CONCLUSION

Pulmonary ossification is an uncommon condition to be encountered and is usually diagnosed on autopsy as most patients are asymptomatic. Here we present the case of a living patient with biopsy-proven pulmonary ossification.

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Post Covid Rhabdomyolysis with Rare Cutaneous Manifesta

Here is the case of a 46 year old male who presented with rhabdomyolysis with dermatological manifestation and complicated by Acute Kidney Injury (8-20% incidence) following an unknown etiology.

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Keywords:

Rhabdomyolysis, covid19, creatine kinase (CK), myoglobinuria, post infectious myositis, myocardial infarction

ABSTRACT

Rhabdomyolysis may result from trauma, extreme physical exertion, prolonged immobilization, temperature induced states such as neuroleptic malignant syndrome, malignant hyperthermia.

Massive necrosis manifested as limb weakness, myalgia, swelling and commonly gross pigmenturia without hematuria is the common denominator of both traumatic and non-traumatic rhabdomyolysis. Here is the case of a 46 year old male who presented with rhabdomyolysis with dermatological manifestation and complicated by Acute Kidney Injury (8-20% incidence) following an unknown etiology. A multidisciplinary approach for search of etiology, early initiation of treatment and full-fledged therapy has served in bringing him back to normal life.

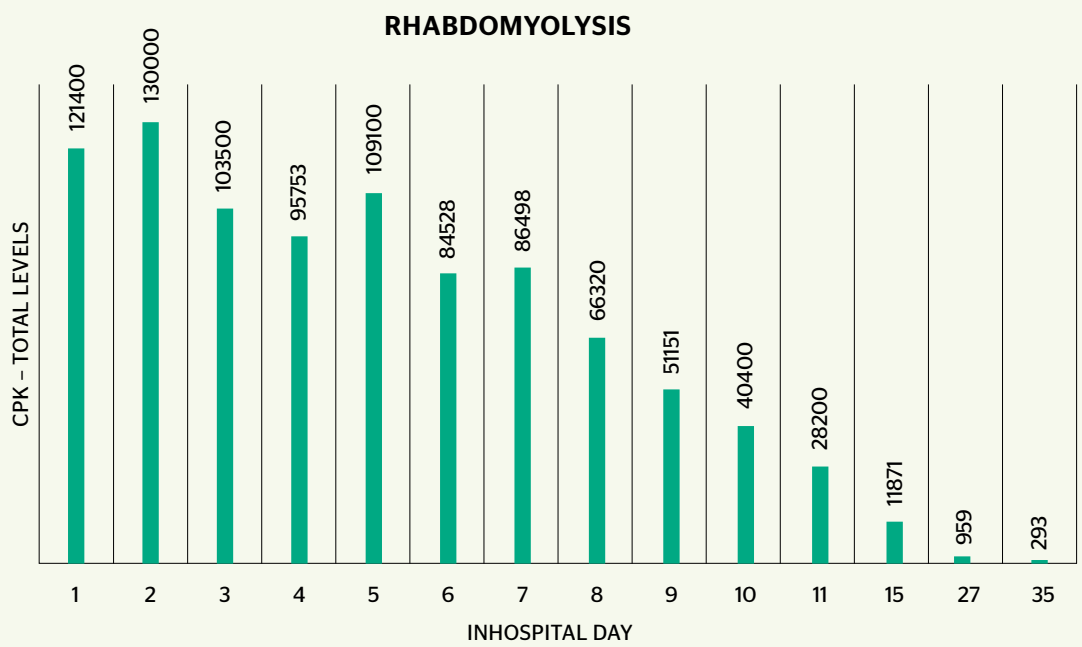
INTRODUCTION

Rhabdomyolysis is a complex clinical condition with rapid dissolution of injured skeletal muscle. It ranges from an asymptomatic illness with elevation in Creatinine Kinase level to a life threatening condition associated with extreme elevations in CK, electrolyte imbalances, acute renal failure and disseminated intravascular coagulation. Our patient, a 46 year old male was diagnosed with rhabdomyolysis with symptoms ranging from severe muscle spasm to severe oliguric renal failure and multisystem involvement. He had typical cutaneous manifestations and features of sepsis which account to less than 10% of the total cases of rhabdomyolysis reported so far.

CASE PRESENTATION

A 46 year old male, a goldsmith by profession, presented to our Emergency Department with severe muscle spasm, typically prominent in proximal muscle groups, such as the thighs, shoulders, lower back and calves. He also had other symptoms like muscle stiffness and cramping which progressed to extreme difficulty in walking over a span of 2 weeks. He had prodromal

Figure 1: **-Descending trend of Creatine Phosphokinase (CPK) level treatment.**

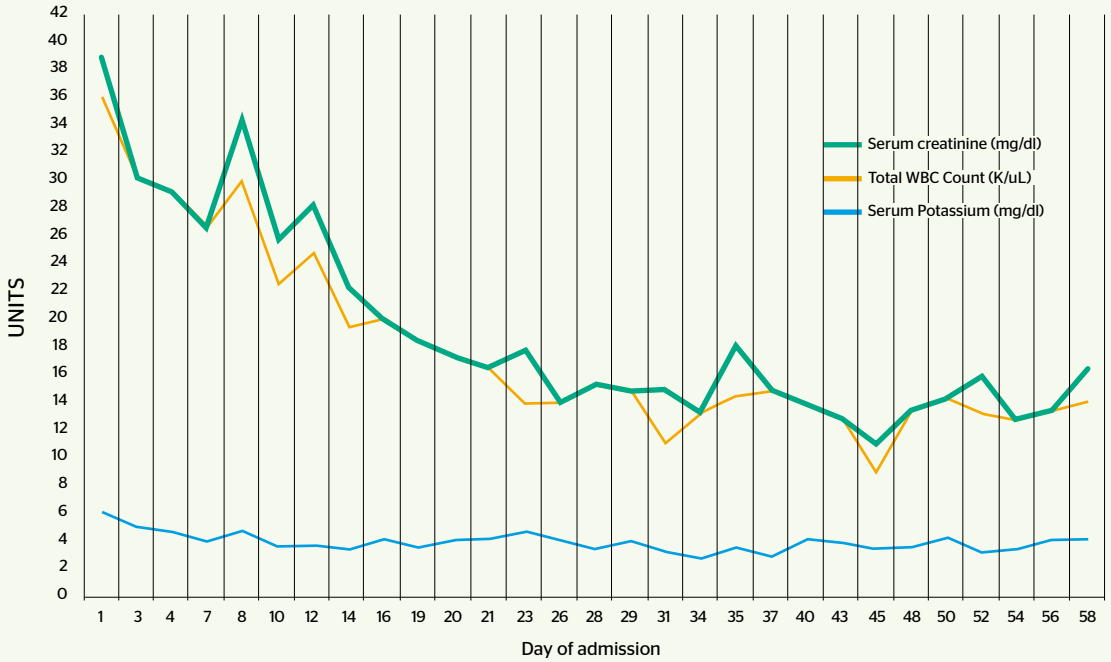


flu like symptoms, loose stools and respiratory distress and was tested Covid19 positive .He initially consulted in a local hospital and sought symptomatic management as an outpatient and was temporarily relieved of symptoms after which he went in home isolation. Three days later, he again developed a sudden onset of high grade fever with evening rise of temperature and took homeopathic medications for the same. But with worsening of existing symptoms and severe Acute gastroenteritis, he was admitted in Covid ward. Inflammatory markers were initially normal. Routine blood investigations showed hyperkalemia and elevated transaminases. All tropical and viral markers were sent but reported negative. His serum Creatinine kinase levels were checked in view of persisting myalgia and showed>24000 U/L(fig-1).

As the symptoms persisted, a CT Chest with Abdomen was taken which showed mild bulky bilateral kidneys with perinephric stranding likely to be pyelonephritis but there were no further spikes of fever or any evidence of urosepsis substantiating CT findings. On the second day of hospital stay, he developed tachypnea and was oliguric. He was shifted to Covid ICU and was started on Lasix infusion. On day 2 of ICU stay, respiratory symptoms worsened, became hypotensive and was initiated on Bipap and inotropes. Possibility of post infectious myositis/autoimmune myositis was considered and was started on low dose steroids. On day 3 of ICU stay oliguric renal failure set in and he was brought to our center for further management. On arrival, he was drowsy and tachypneic, and had generalized anasarca and myoglobinuria. There was no history of drugs or alcohol intake. Bullous eruptions with local heating sensation were noted extensively over both upper and lower limbs. Well demarcated erythematous swollen plaques were noted on the right side of cheek and chest wall. Blood investigations done was suggestive of neutrophilic leukocytosis (TC 29000), raised inflammatory markers (D dimer- 5870mg/L,LDH- 3622 mg/L, ferritin-3005mg/L), impaired renal functions (S.creatinine-2.87 mg/dl) (fig-2) elevated transaminases (SGOT-1392U/L, SGPT-290 U/L) and alarmingly elevated creatinine kinase of 1,21,400U/L. ABG revealed severe metabolic acidosis and hyperkalemia.

Tropical fever work up was repeated which turned out to be negative. A provisional diagnosis of Rhabdomyolysis with oliguric Acute Kidney Injury, metabolic acidosis with secondary hepatitis was made post Covid was made. He was started on empirical intravenous antibiotic therapy, intravenous furosemide, Bipap ventilation, NAC infusion and other supportive medications. An intense interdepartmental approach comprising dermatology, neurology, nephrology and gastro medicine was involved. Hemodialysis was initiated in

Figure 2: **Decreasing trend of serum creatinine, Total white blood cell count and serum potassium levels during treatment.**



view of oliguric renal failure and metabolic acidosis. in view of the cutaneous manifestations secondary to Rhabdomyolysis, skin biopsy was advised. With the existence of a scaly facial rash with accompanying muscle tenderness, possibility of an autoimmune condition was also considered. ANA profile was sent which turned out to be negative. Skin and muscle biopsy showed mild muscle inflammation, however had no features to explain myositis. He gradually developed foot drop and a nerve conduction study was done to elucidate the findings which showed bilateral axonal motor neuropathy. During the course of hospital stay, he again developed spiking fever and cultures yielded growth of Staph haemolyticus and antibiotics were optimized. Meanwhile, he was tested negative for Covid19.

Few days later he developed acute abdominal pain with 2 episodes of hematemesis and melena. A CECT Abdomen was done which revealed retroperitoneal and intraperitoneal hematoma near duodenum. He was hence kept in continuous RT ryle's tube aspiration. Multiple blood transfusions were done to combat hemoglobin drop and stabilized. Patient showed improvement and was shifted out to the ward where he was keeping well for nearly two days. During the ward stay, he developed aspiration pneumonitis and was shifted back to ICU. Adding to the gruesome situation, he also developed respiratory acidosis, was intubated and put on a mechanical ventilator. Bronchoalveolar lavage was sent which grew Pseudomonas and Klebsiella species. Culture sensitivity reports were sensitive to Colistin and hence antibiotics were escalated. Tracheostomy was done in view of prolonged need of mechanical ventilation. He tremendously improved during the subsequent days, became hemodynamically stable and was switched over to rental Bipap. After continuous sessions of hemodialysis and adequate tracheostomy tube care, his general condition improved, renal functions stabilized and urine output improved. Hence was discharged on supportive measures.

Three months later, he was decannulated out of the tracheostomy tube by seeking optimal aseptic measures and nephrology consultation was sought to nullify any further indications for hemodialysis. Post decannulation period was uneventful. Regular OPD reviews were done following that, repeat blood investigations were normal and was back to his normal self.

DISCUSSION

Rhabdomyolysis is a potentially life threatening syndrome. In severe form it is characterized by muscle necrosis and the release of intracellular muscle constituents into circulation. It's characterized by markedly elevated creatinine kinase levels along with muscle pain and myoglobinuria. The disease can vary from asymp-

tomatic elevation in serum enzymes to life threatening disease associated with renal involvement and dyselectrolytemia. This is due to skeletal muscle death caused by reactive oxygen species from mitochondrial dysfunction, which has occurred in response to rise in intracellular free ionized calcium and resultant skeletal muscle contractility.

From studies done by Gearoid et al[1] and Giorgia et al[2], the most frequently associated clinical conditions include exogenous toxins (46%), trauma (26%), immobilization (18%) and sepsis (10%). The characteristic triad of rhabdomyolysis include dark urine (due to myoglobinuria), muscle pain and weakness[3][4][5][6]. Muscle pain here will be prominent in proximal muscle groups. The hallmark of the disease is an elevation in CK and other serum muscle enzymes. When the aetiology is a crush injury or infection, there will be marked elevation of acute phase reactants and peripheral WBC count, while these will be normal or minimally raised in other aetiologies like toxin induced or electrolyte derangements[7]. Aspartate aminotransferase was elevated in 93.1% and alanine aminotransferase in 75% of rhabdomyolysis cases in which CK was greater than or equal to 1000units/L[7]. Skin changes of ischemic tissue injury, such as discoloration or blisters, may also be seen but are present in less than 10 percent of patients[5][6].

Three main differential diagnoses were considered in this case in view of presence of myalgia, elevated CK and dark urine. The first one is Myocardial infarction where the cardiac troponin and CK-MM will be elevated and there will be ischaemic chest pain or specific ECG signs. The next differential is Immune-mediated necrotizing myopathy, where there will be a history of use of statins[15] along with markedly elevated CK with generalized weakness which improves on immunosuppressant therapy[6][8][9][10]. The third differential considered here was Inflammatory myopathy where the patient exhibits myalgias, elevated CK and myoglobinuria[11] along with a chronic clinical progression. The systemic features associated with inflammatory myopathies such as dermatomyositis will be present here and there will be relatively stable laboratory abnormalities compared to rhabdomyolysis. Electromyographic or histopathological changes suggestive of myositis are usually absent in rhabdomyolysis cases[12][13][14].

In this case, the aetiology is idiopathic, probably an unnoticed COVID19 disease. The role of homeopathic drug use and heavy metal exposure (gold) does not seem to have caused the disease here, as these were not during the acute timeline of the current presentation. The use of statins, immunosuppressant drugs, alcohol or other toxins were ruled out[6][8][9][10]. Skin and muscle biopsy samples were taken and histopathologically ruled out myositis, dermatomyositis and other immune mediated necrotizing myopathy or inflammatory myopathy. His cardiac troponin and CK-MM were within normal limits and there were no clinical features pointing to cardiac involvement in this case. This case is hence a very rare presentation of Rhabdomyolysis, as the presence of dermatological complications[5][6] and associated sepsis is found in less than 10% of total rhabdomyolysis presentations. The mortality of this case was calculated by Gearoid et al[1] and it was more than 61.2%.

CONCLUSION

Rhabdomyolysis is caused by a triad of symptoms including myalgia, weakness and myoglobinuria, with an elevation in CK level ceiling the most sensitive test for muscle injury-induced rhabdomyolysis. A correlation between flu-like illness and elevated CK levels may exist further supporting the hypothesis that direct myocyte invasion by the virus may be a key component in pathogenesis. Additionally, with the peak incidence of Covid19 pandemic, it should remain in the differential for unexplained rhabdomyolysis.

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Staged Diabetes Management

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Roger Mazze, Richard M. Bergenstal, Robert Cuddihy, Ellie S. Strock, Amy Criego, Oded Langer, Gregg Simonson, Margaret A. Powers

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