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Study Design: This double-blind study (18-week A and 26-week B) randomized 1296 drug-naive patients (defined as no AHA therapy within the 4 months for longest) to receive the screening visit with T2DM (mean baseline hemoglobin A1c (HbA1c) 9.3%) in sitagliptin/metformin 50/1500 mg bid or metformin 1500 mg bid (up titrated over 4 weeks to achieve maximum doses of sitagliptin/metformin 50/1800 mg bid or metformin 1500 mg bid). Results of the primary efficacy endpoint (mean HbA1c reductions from baseline at the end of Phase A1 were reported in the study.³

³HbA1c mean baseline was 9.3%.

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**The Cover Shot**

### Twilight at Civil Dawn

Twilight is a kind of light produced by sunlight scattering in the upper atmosphere when the Sun is still below the horizon. It illuminates the lower atmosphere and the Earth’s surface. Morning twilight appears between dawn and sunrise when the Sun is between 18 degrees to 0 degrees below the horizon. It can be divided into three categories, namely astronomical dawn (when the Sun is between 18 degrees to 12 degrees below the horizon), nautical dawn (when the Sun is between 12 degrees to 6 degrees below the horizon) and civil dawn (when the Sun is between 6 degrees to 0 degrees below the horizon). Most objects are distinguishable at civil dawn. The sky is blue if it is clear. However, we can see different colours in the sky (bronze, orange, yellow, etc) when there is a cloud or haze.

This photo was taken at civil dawn on 28 August 2023, a few days before Super Typhoon Saola slammed Hong Kong. The sky was so attractive that it was filled with pink and purple light.

---

**Dr WONG Hin-keung**

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With improved management of dyslipidaemia in diabetes, the incidence of cardiovascular complications has decreased over the last two decades among people with diabetes. On the other hand, the burden of diabetic kidney disease remains high, with diabetes now accounting for more than half of the cases entering dialysis programmes annually. Wilson Fung has provided an overview of the latest developments in the management of diabetic kidney disease, including the 4 pillars of 1) renin-angiotensin-aldosterone system inhibitors; 2) sodium-glucose cotransporter-2 inhibitors (SGLT2i); 3) non-steroidal mineralocorticoid receptor antagonists (MRAs); 4) glucagon-like peptide-1 receptor agonists (GLP-1RA). The exciting beneficial data on the renin-angiotensin system, which has transformed the landscape of glucose monitoring, providing a welcomed alternative to traditional self-monitoring of blood glucose using strips and glucometers. In particular, they have provided an updated review of the use of CGM in different settings to help guide clinicians and healthcare professionals on the use of CGM. Ron Yau has provided an update on diabetes emergencies and their management, including the emerging complications of euglycaemic diabetic ketoacidosis. Brian Tomlinson has provided an update on non-HDL cholesterol as a target for the treatment of hyperlipidaemia, and also provided expert comments regarding the use of non-fasting lipid profiles.

All healthcare professionals are likely to encounter people affected by diabetes. According to the Centre for Health Protection of the Department of Health, diabetes affects 8.5% of the population in Hong Kong and ranks among the top 10 causes of death locally. The burden of diabetes and related complications has highlighted the need for enhanced surveillance and services to combat diabetes and other chronic diseases in the community, as highlighted by the recent launch of the Primary Healthcare Blueprint and the Chronic Disease Co-Care Scheme.
Hong Kong International
HEAD AND NECK
Conference
SATURDAY 13 JULY 2024
Venue: Lecture Theatre, Cheung Kung Hai Conference Centre,
LKS Faculty of Medicine

WILLIAM I. WEI LECTURE
Orator: Jatin Shah
Memorial Sloan-Kettering Cancer Center, USA

INVITED FACULTY
Pierre Delaere, Belgium
Marco Ferrari, Italy
Xiao-Ming Huang, China
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Precision Medicine in Diabetes - What Is It and Why Do We Need It?

Prof Ronald Ching-wan MA
Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, New Territories, Hong Kong

ABSTRACT
Diabetes is a major public health problem associated with a significant healthcare burden. Advances in our understanding of the genetic basis of diabetes and the pathophysiological processes contributing to diabetes have given us new insights into the complexity and heterogeneity underlying diabetes. We are now at the dawn of a new era of precision medicine in diabetes, whereby treatment can be truly individualised in order to aim for the best outcome. A recent international effort was initiated to review the current landscape, identify knowledge gaps, and accelerate the development and implementation of precision medicine in diabetes. In this article, the principles underlying precision medicine in diabetes are described. Furthermore, some early exemplars addressing the different aspects of precision medicine in diabetes have been described. The successful implementation of precision medicine in diabetes has the potential to provide patient-centric care, enhance the quality of care in diabetes and improve outcomes for all affected by the disease.

INTRODUCTION
Diabetes currently affects an estimated 422 million people worldwide, according to the World Health Organization, with an estimated 110 million or more people with diabetes in China1. It is estimated that there are more than 0.6 million people with diabetes in Hong Kong. The burden of diabetes is significant, with the majority of the healthcare burden related to hospitalisation for the management of diabetes-related complications and co-morbidities, including cardiovascular disease, kidney disease, retinopathy, and other vascular complications. Increasingly, it is also appreciated that diabetes is associated with an increased risk of infections, a variety of malignant tumours, and an increased risk of dementia2.

A recent analysis of trends in diabetes complications over the last two decades has indicated that diabetes control has improved significantly over recent years, and that the incidence rates of cardiovascular disease have declined3,4. Whilst this is encouraging news, the emergence of other diabetes-related co-morbidities, increasing young-onset diabetes and the increasing life expectancy of people with diabetes have meant new challenges have emerged regarding the management of this large population of people with diabetes.

Whilst Asia has the largest number of people with diabetes compared to other regions of the world, patients with diabetes in Asia are also characterised by some features that appear to be somewhat different to other populations5,6. For example, there appear to be lower rates of type 1 diabetes in most parts of Asia compared to Europe, Australia and North America. For patients diagnosed with type 2 diabetes, the mean BMI appear to be substantially lower than people with type 2 diabetes in the other regions7. Asia is also notable for having a high proportion of patients with young-onset type 2 diabetes, with more than 20 % of patients being diagnosed with diabetes by the age of 40 in several studies8,9. The patterns of diabetes complications also appear different, highlighting the unique phenotype of people with diabetes in Asia, and the potential need for slightly different treatment strategies1,2.

THE NEED FOR PRECISION APPROACH TO DIABETES AND MANAGEMENT
Although the practice of clinical medicine is much influenced by clinical guidelines, which summarises the best evidence with regard to a suggested overall approach to a clinical disease, in reality clinical practice centres on the individual with the disease, and hence, the approach to each patient needs to be individualised. This has been highlighted in classical medical teaching from different regions and through the philosophy of greater clinical teachers. This emphasis had gained increasing recognition in diabetes as well, notably when the clinical treatment algorithm from the American Diabetes Association and European Association for the Study of Diabetes (EASD) moved from a "one-size-fit-all" approach to one that is more individualised, and takes into account the fundamental differences between different patients in guiding treatment selection and decisions10. This evolution has coincided with the explosive advances in molecular diagnostics, genetics, sequencing, system biology and artificial intelligence, which has allowed clinicians and scientists to have a deeper understanding of the underlying pathophysiology of each patient with diabetes, and hence provided opportunities to better tailor treatment strategies to each patient’s need11. This concept of being able to deliver precision medicine, based on the
The principle of providing the right therapy for the right patient at the right time, encapsulates the very essence of good clinical practice, and has been demonstrated to be of great clinical utility in different disciplines, notably in oncology. For example, the demonstration that carriers of certain mutations affecting genes such as the epidermal growth factor receptor (EGFR) in some lung tumours could help with treatment selection has dramatically altered the landscape in terms of diagnostic algorithms and treatment recommendations for people with lung cancer11. This has spurred the development of precision medicine in other medical disciplines, and it is exciting that some of these developments are beginning to impact clinical practice in diabetes12.

CURRENT UPDATES ON PRECISION MEDICINE IN DIABETES

As highlighted earlier, the evolution towards precision medicine in diabetes has been evident in the changing recommendations and guidelines from professional organisations, with a greater emphasis on the individual characteristics of each patient with diabetes for consideration of choices of treatment and management strategies. Recent decades have witnessed revolutionary advances in molecular biology, genetics, and many biomarkers have been investigated for the diagnosis and prediction of diabetes and diabetes related complications. There has also been a rapidly expanding armamentarium of glucose-lowering agents. Given these advances, an international consortium, led by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD), supported by leading experts around the world, was launched in 2018, with the objective of reviewing the landscape and current state of knowledge with regard to precision medicine in diabetes, map some of the current knowledge gaps, and to formulate some recommendations based on current evidence, as well as point out directions for future research. Under this initiative, efforts to advance precision medicine in diabetes can be grouped under four main categories: precision prevention, precision diagnosis, precision treatment, and precision prognosis13, 14. Some examples of each of these, and how they may impact clinical care, are covered in the following discussion (Fig. 1).

Precision Prevention

Whilst it is well recognised that type 2 diabetes can be prevented, that is also true for gestational diabetes, and, to a lesser extent, type 1 diabetes. Precision prevention, hence, addresses the use of risk factors or biomarkers to identify those at risk of different types of diabetes, and to deliver intervention strategies to these individuals, aiming at reducing the progression towards diabetes. Lifestyle intervention has been shown to be highly effective in reducing progression to type 2 diabetes from prediabetes, though individuals may have variable risk, based on their underlying biology and composition of risk factors. A large number of studies have examined the utility of genetic factors, or polygenic risk scores constructed based on genetic markers of diabetes, for the prediction of diabetes risk15. Likewise, other biomarkers have been identified to identify those at-risk of diabetes for early intervention. Ongoing studies are working to establish whether there are differences towards individual responses to exercise and lifestyle intervention in order to provide more tailored approaches in preventive strategies13, 14.

Precision Diagnosis

It is increasingly recognised that diabetes is a heterogeneous disease, and precision diagnosis refers to approaches to apply tests and strategies to obtain better subclassification of patients with diabetes, with the aim to provide treatment that is most appropriate according to the underlying pathophysiology16. As demonstrated in some scenarios, the use of biomarkers or other tests that facilitate a more “precise” diagnosis can help improve treatment response and patient outcomes.

One important example of precision diagnosis relates to the increasing recognition that type 1 diabetes is not only a disease with onset in childhood, but that a significant proportion of type 1 diabetes is present in adulthood. However, given the less abrupt presentation of type 1 diabetes in adults, identifying individuals newly diagnosed with diabetes as having autoimmune type 1 diabetes can be more challenging than often appreciated. In the United Kingdom Prospective Diabetes Study (UKPDS), out of 3,672 patients with type 2 diabetes presenting to their general practitioners, retrospective testing of baseline samples revealed that 12 % were positive for at least one islet autoantibodies, suggesting underlying autoimmune diabetes17. Importantly, the individuals with anti-GAD or other islet antibodies progressed much more rapidly to insulin requirement compared to those who are antibody negative, highlighting islet autoantibodies is an important class of biomarker to identify those with rapid disease progression17. Subsequent studies in China have likewise highlighted that around 6 % of adults presenting with diabetes, in fact, have positive autoantibodies, and may actually have type 1 diabetes18. These results are supported by recent data, which suggests that type 1 incidence remains high after age 30. For example, an analysis in Hong Kong showed that among individuals diagnosed with type 1 diabetes, around 1/3 were diagnosed before the age of 20, 1/3 were diagnosed between ages 20 - 40, and 1/3 were diagnosed after age 4019. This is in line with global
data reviewed in a systematic review, suggesting that the incidence rate of type 1 diabetes in adults does not decline with increasing age, though new cases of type 1 diabetes among older adults may become more difficult to detect due to the much larger proportion of people with type 2 diabetes. In the latest edition of the International Diabetes Federation Diabetes Atlas, it was highlighted that a high index of suspicion is required to identify individuals presenting with type 1 diabetes in adults. Indeed, and the need for access to readily available biomarkers to facilitate the diagnosis. This is in line with other international recommendations regarding the use of C-peptide and islet autoantibodies for early detection of adult-onset type 1 diabetes. Even among individuals with type 1 diabetes, it was found that the number of positive autoantibodies, type and titre also identify different subphenotypes within type 1 diabetes and provide additional information on disease prognosis.

Another example of precision diagnosis in diabetes would be the correct identification of monogenic diabetes. This is particularly important in neonates presenting with neonatal diabetes, though this remains rare. In other instances, including in children and young adults with diabetes, recognising and establishing the correct molecular diagnosis of monogenic diabetes has important implications on treatment strategy and prognosis. In an early study, it was estimated that around 10% of those with young-onset diabetes with a positive family history may harbour mutations in genes implicated in monogenic diabetes. The different types of monogenic diabetes have been well described, and are beyond the scope of the current review. Nevertheless, the identification of monogenic diabetes would have important implications on treatment selection. For example, a diagnosis of monogenic diabetes due to glucokinase mutation may be associated with chronic elevation of fasting glucose due to an altered set-point of the glucose sensor, has a generally benign clinical course, and may not require glucose-lowering treatments outside of the pregnancy period. On the other hand, a diagnosis of monogenic diabetes due to HNF1A or HNF4A mutations may point towards the need for careful titration of medications given their acute sensitivity to the sulphonylurea class of agents (Table 1).

Precision Treatment

The preceding section has already highlighted how establishing the correct diagnosis through precision medicine has important implications for treatment selection. In addition to the choice of treatment following the diagnosis of monogenic diabetes, establishing a diagnosis of adult-onset type 1 diabetes should facilitate appropriate early use of insulin to address the underlying pathophysiology to achieve better glucose control and prevent ketosis. In the management of type 2 diabetes, assessment of underlying pathophysiology can facilitate the selection of the most appropriate treatment. In simplistic terms, the stratification of patients according to the degree of insulin resistance and impaired beta-cell function has been shown to be associated with disease progression and the need for insulin. In an analysis of 609 young patients with type 2 diabetes aged 20 - 50 who were free of insulin use at baseline, it was found that 48% progressed to glycaemic progression and insulin use over 8.6 years. Those classified as being both insulin deficient and insulin resistant had the highest rate of progression to insulin use compared to those with either defect alone, and were started on insulin approximately four years earlier.

Another major ongoing effort aims to identify underlying pathophysiology in people with diabetes, which can unravel the hidden heterogeneity in diabetes and facilitate treatment selection. In support of this approach, a variety of clinical factors have been identified which can affect individual responses to different glucose-lowering drugs. For example, it has been consistently shown that lean individuals have a greater glucose-lowering effect on sulphonylurea and DPP4i compared to individuals who are overweight, whilst conversely, those with higher BMI or markers of insulin resistance seem to have a greater glucose-lowering effect on TZD and reduced response to DPP4i. Incorporation of these factors and future biomarkers would facilitate more individualised choices of treatment selection in clinical practice for a more effective glucose-lowering effect to expedite glycaemic control.

Precision Prognosis

As mentioned earlier, much of the burden of diabetes relates to the burden of diabetes complications. With better control of hyperlipidaemia and other cardiovascular risk factors, there is a change in the overall pattern of complications, with a reduced burden of cardiovascular disease, but increasing concerns towards infection, kidney failure, cancers and cognitive decline. The ability to identify those at high risk of diabetes complications can facilitate early intensive intervention to control risk factors, as well as early initiation of agents that can confer beneficial effects on organ-protection. Different studies have highlighted the potential to use risk engines to identify those at risk of diabetes complications.

A recent systematic review has examined the current state of knowledge on the role of risk factors, risk engines and biomarkers for the prediction of cardiovascular complications in diabetes. Whilst a large number of studies have been undertaken, only a few of the risk engines have been compared systematically in different populations. Likewise, few of the biomarkers that have been investigated have been examined in multiple cohorts, or demonstrated incremental benefit above prediction provided by clinical risk factors. Machine learning methods and artificial intelligence have further enhanced the ability to incorporate these factors to better predict different complications and outcomes in diabetes. Whilst these advances can now provide better tools to improve patient risk stratification, the main challenge will be how best to incorporate these strategies into clinical practice to implement precision medicine in diabetes to reduce the burden arising from diabetes complications.

CONCLUSIONS

Advances in our understanding of the genetic basis
of diabetes and the pathophysiological processes contributing to diabetes have given us new insights into the complexity and heterogeneity underlying diabetes. This has heralded the dawn of a new era of precision medicine in diabetes, where treatment can be truly individualised in order to aim for the best outcome. In this article, some early exemplars addressing the different aspects of precision medicine in diabetes have been described. The implementation of precision medicine in diabetes will require capacity building across different disciplines ranging from genomic literacy, biomarker testing, sequencing and bioinformatics, as well as re-engineered workflows. Central to this inevitable move towards precision medicine requires the establishment of mechanisms to decide what advances are ready for clinical translation, a framework for evaluating cost-effectiveness, and measures to ensure the principles of health equity and equitable access. The successful implementation of precision medicine in diabetes has the potential to improve the quality of care in diabetes to improve outcomes for all affected by the disease.

Acknowledgement

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Disclosures

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Table 1. Comparison among various types of diabetes and their pathophysiology and implications for precision medicine in diabetes.

<table>
<thead>
<tr>
<th>Diabetes Subtypes</th>
<th>Multifactorial Diabetes</th>
<th>Monogenic forms of diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of onset</td>
<td>Children or adulthood</td>
<td>Typically after 40 years old</td>
</tr>
<tr>
<td>Mode of Inheritance</td>
<td>Non-Mendelian, sporadic</td>
<td>Non-Mendelian, familial</td>
</tr>
<tr>
<td>Genetic aetiology/Causal Genes</td>
<td>Polygenic, &gt;100 known associated genomic regions (e.g. HLA region, INS, etc.)</td>
<td>Polygenic, &gt;1,200 genomic regions (e.g. TCF7L2)</td>
</tr>
<tr>
<td>Clinical Feature</td>
<td>Islet autoimmunity*</td>
<td>Insulin resistance, progressive beta-cell dysfunction</td>
</tr>
<tr>
<td>Preferred Treatment</td>
<td>Lifelong insulin</td>
<td>Metformin, sulfonylureas, glitazones, DPP4 inhibitors, SGLT2 inhibitors, GLP-1 agonists or insulin</td>
</tr>
<tr>
<td>Clinical implications in precision medicine</td>
<td>Use of autoantibodies and C-peptide to identify adults with type 1 diabetes</td>
<td>A diagnosis by excluding, after consideration of other causes of diabetes. Heterogeneity in diabetes and the need for biomarkers to separate subtypes</td>
</tr>
</tbody>
</table>

References

Questions
1. What is the abnormality on the radiograph?
2. What is the most likely differential diagnosis?
3. What is the next step of the investigation?

(See P.33 for answers)
MCHK CME Programme Self-assessment Questions

Please read the article entitled "Precision Medicine in Diabetes - What Is It and Why Do We Need It?" by Prof Ronald Ching-wan MA and complete the following self-assessment questions. Participants in the MCHK CME Programme will be awarded CME credit under the Programme for returning completed answer sheets via fax (2865 0345) or answer link: https://forms.gle/Tjpq1g3Z4RQKxYh9 or by mail to the Federation Secretariat on or before 30 June 2024. Answers to questions will be provided in the next issue of The Hong Kong Medical Diary. (Address: Duke of Windsor Social Service Bldg., 4/F., 15 Hennessy Rd., Wan Chai. Enquiry: 2527 8898)

Questions 1 - 10: Please answer T (true) or F (false)

1. There has been a decrease over recent years in the incidence rates of cardiovascular complications due to diabetes, though hospitalisations due to infections related to diabetes have increased over recent years.
2. Precision medicine always requires the use of genetic or genomic information to guide treatment.
4. The presence of islet autoantibodies in patients with diabetes identifies individuals with underlying autoimmunity and rapid progression towards the need for insulin.
5. Patients with young-onset diabetes are more likely to have monogenic forms of diabetes compared to someone with older age of onset.
6. Type 1 diabetes is a condition predominantly affecting children and adolescents and adults who present with diabetes rarely have type 1 diabetes.
7. Patients with type 2 diabetes all share similar underlying pathophysiology and hence have similar treatment responses to the glucose-lowering agents.
8. Monogenic diabetes is a rare condition and is usually inherited in an autosomal recessive manner.
9. The glucose-lowering effect of DPP4 inhibitors is in general greater among lean individuals with diabetes compared to those who are overweight.
10. The prediction of the risk of diabetes complications is futile as there are no effective strategies to prevent diabetes complications.

ANSWER SHEET FOR JUNE 2024

Please return the completed answer sheet to the Federation Secretariat on or before 30 June 2024 for documentation. 1 CME point will be awarded for answering the MCHK CME programme (for non-specialists) self-assessment questions.

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Precision Medicine in Diabetes - What Is It and Why Do We Need It?

Prof Ronald Ching-wan MA

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Answers to May 2024 Issue

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Abbreviations: T2DM, type 2 diabetes mellitus; CV, cardiovascular; HF, heart failure

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DS-2024-JUN-001
INTRODUCTION

Low-density lipoprotein (LDL) cholesterol is well established as a cause of atherosclerotic cardiovascular disease (ASCVD) based on evidence from genetic, epidemiologic, and clinical studies, and it is considered the primary target for lipid-lowering treatment to reduce cardiovascular events in most lipid guidelines. However, triglyceride-rich lipoproteins (TRLs) also contribute to atherosclerosis from the cholesterol that they carry, and lipolysis of triglycerides may result in inflammatory or thrombotic effects. TRLs can enter the arterial intima more slowly than the smaller LDL particles and are trapped there as they have difficulty leaving the intima due to their larger size. It is generally thought that chylomicrons and large very low-density lipoprotein (VLDL) with diameters greater than 75 nm are not able to enter the intima. However, it has been shown that endothelial cells can take up chylomicrons via the scavenger receptor-BI (SR-BI) in some circumstances, and this might be responsible for the development of eruptive xanthomas in severe hypertriglyceridaemia with lipoprotein lipase (LPL) deficiency, as well as contributing to ASCVD.

NON-HDL CHOLESTEROL

Non-high-density lipoprotein (non-HDL) cholesterol includes the cholesterol carried in TRLs in addition to that in LDL particles and is considered an alternative or secondary target for treatment. The term, remnant cholesterol, can specifically refer to the cholesterol carried by chylomicron remnants and VLDL remnants, but it is commonly used to include all the cholesterol carried in particles other than LDL and high density lipoprotein (HDL) particles. If not reported with the lipid profile, non-HDL cholesterol can be easily calculated by subtracting the HDL cholesterol from total cholesterol values. Accurate non-HDL cholesterol calculation does not require the triglyceride concentration to be < 4.5 mmol/L (400 mg/dL), unlike LDL cholesterol, where the use of the Friedewald formula becomes inaccurate with such high triglyceride levels.

The targets for non-HDL cholesterol are based on the targets for LDL cholesterol with the addition of 0.8 mmol/L (30 mg/dL) to account for the cholesterol related to triglyceride levels of < 1.7 mmol/L (150 mg/dL), which are considered to indicate lower cardiovascular risk (Table 1). The latest UK National Institute for Health and Care Excellence (NICE) guidelines recommend a slightly lower target level for non-HDL cholesterol of 2.6 mmol/L in combination with the LDL cholesterol target of 2.0 mmol/L for secondary prevention of ASCVD.

### Table 1. Corresponding non-high-density lipoprotein cholesterol and apolipoprotein B levels for commonly used low-density lipoprotein cholesterol goals.

<table>
<thead>
<tr>
<th>Cardiovascular risk level</th>
<th>LDL cholesterol target</th>
<th>Non-HDL cholesterol target</th>
<th>Apolipoprotein B target</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate</td>
<td>2.6 mmol/L (100 mg/dL)</td>
<td>3.4 mmol/L (131 mg/dL)</td>
<td>100 mg/dL</td>
</tr>
<tr>
<td>High</td>
<td>1.8 mmol/L (70 mg/dL)</td>
<td>2.6 mmol/L (100 mg/dL)</td>
<td>80 mg/dL</td>
</tr>
<tr>
<td>Very high</td>
<td>1.4 mmol/L (55 mg/dL)</td>
<td>2.2 mmol/L (85 mg/dL)</td>
<td>65 mg/dL</td>
</tr>
</tbody>
</table>

Non-HDL = non-high-density lipoprotein; LDL = low-density lipoprotein.

Apolipoprotein B (apoB) levels provide an alternative treatment target for treatment, but apoB is not measured routinely, and the measurement is associated with increased cost. Non-HDL cholesterol and apoB levels are usually closely correlated.

Some studies have shown that non-HDL cholesterol is better than LDL cholesterol at predicting ASCVD risk in patients on statin therapy, and/or in those with obesity, diabetes, and metabolic disorders, as was reviewed recently. A Mendelian randomisation study comparing the effects of triglyceride-lowering variants in the LPL gene and LDL cholesterol-lowering variants in the LDL receptor gene (LDLR) gene, found that they were associated with similar lower risk of CHD per unit difference in apoB. Therefore, the clinical benefit of lowering triglyceride and LDL-C levels may be proportional to the absolute change in apoB.

HOW TO TREAT NON-HDL CHOLESTEROL?

The treatment of LDL cholesterol to appropriate goals involves the use of statins with the addition of ezetimibe and/or PCSK 9 inhibitors, as required. Bempedoic acid is available in some countries to use as an alternative to statins in those patients who may be statin intolerant. It could also be used in combination with statins if a small additional reduction in LDL cholesterol is required. These treatments will reduce triglyceride levels to a certain extent, and they could be intensified if triglycerides remain above 1.7 mmol/L after achieving the LDL cholesterol goal. These LDL cholesterol targeting treatments may be sufficient to achieve the non-HDL cholesterol target, but if triglycerides are >
The use of fibrates has become more controversial after the PROMINENT (Pemafibrate to Reduce Cardiovascular Outcomes by Reducing Triglycerides in Patients with Diabetes) study. In that study, pemafibrate 0.2 mg twice daily did not reduce cardiovascular events in patients with type 2 diabetes and moderately elevated triglyceride levels of 2.26 - 5.64 mmol/L (200 - 499 mg/dL) with LDL cholesterol levels at target on moderate or high intensity statin therapy. Pemafibrate lowered triglycerides and VLDL cholesterol by about 26 %, but there were unexpected increases in LDL cholesterol of 12.3 %, and apoB of 4.8 % and there was no change in non-HDL cholesterol. It might be predicted from these lipid changes that there would be no overall cardiovascular benefit. The reason for these effects is not clear, but it would not be appropriate to extrapolate these results to the use of other fibrates. Pemafibrate was developed to be more selective than the earlier fibrates, and its effects differ in various ways.

An earlier study showed that the combination of fenofibrate (160 mg/day) with simvastatin (20 mg/day) had greater effects on all lipid parameters, including LDL and non-HDL cholesterol compared to simvastatin alone, in patients with combined hyperlipidaemia and fasting triglyceride levels 150 - 500 mg/dL and there was no increase in any adverse effects with the combination. The response to fibrates does vary between patients according to the baseline lipid phenotype and perhaps other factors such as additional treatments, and it is important to monitor the change in all lipid parameters as LDL cholesterol may increase with fibrates particularly in those patients with higher baseline triglycerides. Gemfibrozil should not be combined with statins because of the pharmacokinetic interaction, which increases the risk of severe myopathy.

Several formulations of omega-3 fatty acids are approved to treat patients with severe hypertriglyceridaemia (triglycerides >10 mmol/L) to reduce the risk of acute pancreatitis but only highly purified eicosapentaenoic acid (EPA) ethyl ester (icosapent ethyl 2 x 2 g daily) is recommended to reduce cardiovascular events in patients with moderate hypertriglyceridaemia based on the results of the REDUCE-IT (Reduction of Cardiovascular Events With Icosapent Ethyl-Intervention Trial) study. In that study involving patients with established ASCVD or with diabetes and other risk factors receiving statin therapy with a fasting triglyceride level of 135 - 499 mg/dL (1.52 - 5.63 mmol/L) and LDL cholesterol level of 41 - 100 mg/dL (1.06 - 2.59 mmol/L) there was a 25% reduction in the primary composite end point of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularisation, or unstable angina with icosapent ethyl compared to the placebo group. The placebo was mineral oil and there were some adverse effects in that group which may have contributed to the apparent benefit of icosapent ethyl. There was also a small increase in hospitalisation for atrial fibrillation or flutter and a small increase in serious bleeding events in the active treatment group.

Similar benefits were seen with 1800 mg of EPA daily combined with statin in the open label Japan EPA lipid intervention study (JELIS). It has been shown that the triglyceride lowering effect of icosapent ethyl is related to the achieved concentrations of EPA in plasma and red blood cells. This may explain why lower doses of EPA are needed in Japanese patients, as they may have higher baseline EPA concentrations. A systematic review and meta-regression analysis concluded that the benefits of high-dose EPA appear to exceed the lipid-lowering effects, so other mechanisms are likely to be involved.

TO FAST OR NOT TO FAST?

The lipid profile is traditionally measured after fasting for at least eight hours. The requirement for fasting has become ingrained in laboratory practice and the assessment of lipid disorders, but is it really necessary? The work of Nordestgaard and colleagues in Copenhagen clearly shows that it is not necessary to fast before measuring the lipid profile. There are several arguments which show the benefit of measuring the non-fasting lipid profile (Fig. 1). There is a common misconception that lipid levels change dramatically after eating a meal. Triglyceride levels usually increase in proportion to the fat content of the meal, and the baseline plasma triglyceride concentration and other lipids show minimal changes. With a normal meal, the increase in triglycerides is generally quite small. In an analysis from four large prospective studies, the maximal mean changes for triglycerides were + 0.3 mmol/L (26 mg/dL), for total cholesterol -0.2 mmol/L (8 mg/dL), for LDL cholesterol -0.2 mmol/L (8 mg/dL), and for HDL cholesterol -0.1 mmol/L (4 mg/dL). The decrease in concentrations of the cholesterol fractions is thought to be related to the increase in plasma volume resulting from the fluid intake with the meal.
Many laboratories consider that the fasting lipid profile is more standardised and leads to less variation in the measured lipids, especially triglycerides. This consideration is not supported by large studies, even in patients with relatively high triglyceride levels. Another argument often voiced to support the use of fasting lipid profiles is that other measurements in the blood may also require fasting before blood sampling. However, diabetes control is usually monitored by the glycosylated haemoglobin (HbA1c), which does not require fasting and fasting glucose can usually be measured at home with home glucose monitoring. Avoiding fasting for the blood sample may also prevent hypoglycaemia in some diabetic patients.

Non-fasting lipid profiles have been endorsed by several national and international societies since 2009. In 2014, the UK NICE guidelines supported the use of non-fasting samples and the latest update to these guidelines in December 2023 recommended that a non-fasting sample need only be repeated with a fasting test in people with a triglyceride level between 10 - 20 mmol/L, which is quite uncommon. Postprandial hyperlipidaemia appears to contribute to the cardiovascular risk, particularly in patients with diabetes. Non-fasting triglyceride levels provide a surrogate marker of postprandial hyperlipidaemia and may provide a better estimate of cardiovascular risk in some patients.

CONCLUSIONS

Non-HDL cholesterol levels provide an alternative or potentially better target than LDL cholesterol for lipid therapy to reduce cardiovascular risk. Non-HDL cholesterol levels are easy to calculate and include the cholesterol carried inTRLs which contributes to the cardiovascular risk. It is not necessary to have a fasting sample to obtain accurate non-HDL cholesterol levels.

Non fasting lipid profiles are equally acceptable as those from fasting samples and may even provide a better estimate of cardiovascular risk. Laboratories should be aware that it is not necessary to require patients to fast overnight for the lipid sample unless the requesting doctor has specified that. Adopting such an approach is convenient for patients and is supported by current lipid guidelines.

References

Review of Acute Diabetic Emergencies in Adults

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INTRODUCTION

Diabetic ketoacidosis (DKA), hyperosmolar hyperglycaemic state (HHS), and hypoglycaemia are life-threatening complications that can occur in people with diabetes. This review covers the epidemiology, pathophysiology, precipitating causes, clinical presentation, management, complications and prevention of these acute diabetic emergencies.

ACUTE HYPERGLYCAEMIC CRISIS

Epidemiology

The frequency of DKA has increased during the past decade. Although DKA occurs predominantly in people with type 1 diabetes mellitus (T1DM), every one in five DKA admissions was attributed to type 2 diabetes mellitus (T2DM). Potential explanations for the observed increase in hospital admissions for diabetic emergencies include the rising prevalence of diabetes, as well as psychosocial, cultural, and economic factors which may limit access to insulin and outpatient medical care. Mortality related to DKA has progressively declined to less than 1 % since the discovery of insulin in the last millennium. HHS, which occurs more commonly in older adults with T2DM and underlying comorbidities, has a higher mortality rate of 15 - 20 %.

Pathophysiology

Both DKA and HHS result from an absolute or relative insulin deficiency together with an increase in circulating concentrations of counterregulatory hormones (primarily glucagon). A rise in counterregulatory hormones accelerates gluconeogenesis, glycogenolysis, ketonemia and impaired glucose utilisation by peripheral tissues. Due to insulin deficiency, lipolysis increases circulating free fatty acids, where excess free fatty acids are oxidised to acetoacetate and β-hydroxybutyrate in the liver, leading to ketonemia and metabolic acidosis. Both hyperglycaemia and high circulating concentrations of ketone bodies result in an osmotic diuresis, leading to volume depletion and electrolyte abnormalities. Hypovolemia leads to decreased glomerular filtration rate, further decreasing the clearance of glucose and ketone bodies.

The pathogenesis of HHS differs from DKA in that a more severe degree of dehydration is present due to osmotic diuresis in the absence of significant ketosis and ketonemia. This difference may be explained by a higher concentration of hepatic and circulating insulin, and a lower concentration of free fatty acids, cortisol, growth hormone and glucagon than that in DKA. The insulin levels are adequate to prevent ketogenesis but fail to counteract hyperglycaemia. Patients with HHS may still have a mild metabolic acidosis due to renal failure, dehydration, or severe sepsis.

Precipitating Causes

The most common precipitating factors in DKA and HHS are infection and inadequate insulin therapy (including insulin omission), followed by newly diagnosed diabetes, acute medical conditions or metabolic stressors, or alcohol/drug related problems. Insulin omission is more commonly seen in people with eating disorders, psychological distress, fear of hypoglycaemia or weight gain. Other factors include the inability to pay for insulin, the idea that insulin should be withheld when illness interferes with eating, accidental omission of an insulin dose, and rarely, pump malfunction. Insulin therapy has been wrongly withheld in patients admitted to hospital with T1DM who are fasted for surgical or other procedures, or in those on an insulin pump device owing to a lack of familiarity with these devices. Drugs, including glucocorticoids, diuretics, antipsychotics, and others, can predispose to DKA or HHS.

Clinical Presentation and Diagnosis

DKA is defined by a triad of hyperglycaemia, metabolic acidosis, and ketonemia (Table 1). HHS is defined by severe hyperglycaemia, high serum osmolality, and dehydration (Table 2).

The process of HHS usually evolves over days to weeks, whereas the evolution of DKA tends to be much shorter. The presentation of DKA and HHS often overlaps. People with DKA or HHS can present with symptoms including polyuria, polydipsia, vomiting, abdominal pain, lethargy, mental status change, tachycardia, tachypnea, Kussmaul breathing, and orthostatic hypotension, etc.

Management

People with DKA or HHS require immediate referral for emergency evaluation and treatment. Management principles include restoring circulatory volume and tissue perfusion, resolving ketoacidosis in DKA or plasma hyperosmolality in HHS, correcting electrolyte...
The first step in the acute management of DKA and HHS is to halt lipolysis and ketogenesis. The recommended starting dose of intravenous regular insulin is at a fixed weight-based dose of 0.1 - 0.14 units/kg/h, after initiation of fluid resuscitation and correction of any hypokalemia. As glucose levels improve, dextrose should be added to the intravenous fluids, with or without down-adjustment of insulin infusion rates, to allow continued insulin infusion sufficient to resolve ketonemia while avoiding hypoglycaemia. The JBDS guideline suggests that patients can continue their usual subcutaneous basal insulin while on intravenous insulin infusion for the treatment of DKA. Patients with mild to moderate DKA who are alert and able to tolerate oral fluids may be treated with subcutaneous rapid-acting insulin analogues every 1 or 2 hours with aggressive fluid management and frequent point-of-care blood glucose monitoring in the emergency department or step-down units. The timing of starting intravenous insulin is more variable in managing HHS. The ADA guideline recommends starting intravenous regular insulin similar to the management of DKA, while the JBDS guideline suggests delaying intravenous insulin therapy (and with an infusion rate usually lower than that in DKA) unless the patient has a raised β-hydroxybutyrate concentration, or the blood glucose fails to decline despite adequate fluid replacement.

After resolution of DKA and HHS and the patient is eating and drinking normally, patients can be transitioned from intravenous to subcutaneous insulin. Basal insulin should be administered around 2 hours before stopping the intravenous insulin to prevent recurrence of ketoadosis and rebound hyperglycaemia, due to a short half-life of intravenous regular insulin of approximately 10 minutes.

The use of bicarbonate in patients with DKA is generally not recommended for patients with pH above 6.9, as the acidosis will resolve when DKA is adequately treated with fluid replacement and insulin therapy.

Complications can arise either from the diabetic crisis or from the treatment. More commonly observed complications include hypo- or hyperkalemia, and hypoglycaemia. These abnormalities may arise from insufficient or over-aggressive potassium replacement, aggressive insulin infusion, inadequate monitoring frequency of glucose and electrolytes, or failure to appropriately add dextrose to intravenous fluids when glucose levels lower. Metabolic complications can arise from DKA or HHS, including myocardial infarction, stroke, and peripheral arterial or venous thrombosis. Cerebral oedema, although severe, is rare in adults.

### Table 1. Diagnostic criteria for diabetic ketoacidosis in adults (Summarised by author)

<table>
<thead>
<tr>
<th></th>
<th>ADA6</th>
<th>JBDS7</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Plasma glucose concentration (mmol/L)</strong></td>
<td>&gt; 13.9</td>
<td>&gt; 11 or known diabetes</td>
</tr>
<tr>
<td><strong>pH</strong></td>
<td>Mild: 7.25 - 7.30</td>
<td>&lt; 7.3 (Severe: &lt; 7.0)</td>
</tr>
<tr>
<td></td>
<td>Moderate: 7.00 - 7.24</td>
<td>&lt; 7.3 (Severe: &lt; 7.0)</td>
</tr>
<tr>
<td></td>
<td>Severe: &lt; 7.0</td>
<td>&lt; 7.3 (Severe: &lt; 7.0)</td>
</tr>
<tr>
<td><strong>Bicarbonate concentration (mmol/L or mEq/L)</strong></td>
<td>Mild: 15 - 18</td>
<td>&lt; 15 (Severe: &lt; 5)</td>
</tr>
<tr>
<td></td>
<td>Moderate: 10 - 14.9</td>
<td>&lt; 15 (Severe: &lt; 5)</td>
</tr>
<tr>
<td></td>
<td>Severe: &lt; 10</td>
<td>&lt; 15 (Severe: &lt; 5)</td>
</tr>
<tr>
<td><strong>Anion gap</strong></td>
<td>Mild: &gt; 10</td>
<td>NA (Severe: &gt; 16)</td>
</tr>
<tr>
<td></td>
<td>Moderate / severe: &gt; 12</td>
<td>NA (Severe: &gt; 16)</td>
</tr>
<tr>
<td><strong>Urine ketone</strong></td>
<td>Positive</td>
<td>Positive</td>
</tr>
<tr>
<td><strong>Blood β-hydroxybutyrate (mmol/L)</strong></td>
<td>&gt; 3</td>
<td>&gt; 3 (Severe: &gt; 6)</td>
</tr>
<tr>
<td><strong>Mental status</strong></td>
<td>Mild: alert</td>
<td>Severe: GCS ≤ 12 or abnormal AVPU scale</td>
</tr>
<tr>
<td></td>
<td>Moderate: alert or drowsy</td>
<td>Severe: stupor or coma</td>
</tr>
<tr>
<td></td>
<td>Severe: stupor or coma</td>
<td>Severe: stupor or coma</td>
</tr>
</tbody>
</table>

ADA = American Diabetes Associations
JBDS = Joint British Diabetes Societies
NA = Not included in guideline document

### Table 2. Diagnostic criteria for hyperosmolar hyperglycaemic state in adults (Summarised by author)

<table>
<thead>
<tr>
<th></th>
<th>ADA6</th>
<th>JBDS7</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Plasma glucose concentration (mmol/L)</strong></td>
<td>&gt; 33.3</td>
<td>≥ 30</td>
</tr>
<tr>
<td><strong>pH</strong></td>
<td>&gt; 7.30</td>
<td>≥ 7.30</td>
</tr>
<tr>
<td><strong>Bicarbonate concentration (mmol/L or mEq/L)</strong></td>
<td>&gt; 18</td>
<td>≥ 15</td>
</tr>
<tr>
<td><strong>Urine ketone</strong></td>
<td>Negative or low positive</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Blood β-hydroxybutyrate (mmol/L)</strong></td>
<td>NA</td>
<td>&lt; 3</td>
</tr>
<tr>
<td><strong>Plasma osmolality (mOsm/kg)</strong></td>
<td>&gt; 320</td>
<td>≥ 320</td>
</tr>
<tr>
<td><strong>Presentation</strong></td>
<td>Stupor or coma</td>
<td>Severe dehydration and feeling unwell</td>
</tr>
</tbody>
</table>

ADA = American Diabetes Associations
JBDS = Joint British Diabetes Societies
NA = Not included in guideline document

Identifying and treating the precipitating cause, and preventing complications and recurrence. The frequently cited guidelines on managing DKA and HHS include the American Diabetes Association (ADA) guideline and the Joint British Diabetes Societies (JBDS) for Inpatient Care guideline. The use of bicarbonate in patients with DKA is generally not recommended for patients with pH above 6.9, as the acidosis will resolve when DKA is adequately treated with fluid replacement and insulin therapy.
Identifying the precipitating cause of DKA or HHS is important but should not cause a delay in treatment. The cause of every episode of DKA and HHS should be determined, especially in those with recurrent episodes, to tailor education and intervention to prevent further recurrences. Appropriate education should be provided to the patient and their family members in accordance to individual patient’s needs. Appropriate education includes a review of the causes, signs and symptoms of impending DKA or HHS and provides sick day management or preventive measures.

Euglycaemic Diabetic Ketoacidosis

Since the introduction of sodium-glucose cotransporter-2 (SGLT2) inhibitors and their widespread use in diabetes treatment, interest has been renewed in the entity of euglycaemic DKA, where DKA occurs at a lower than anticipated blood glucose level. SGLT2 inhibitor use has been identified as a causal agent of euglycaemic DKA. However, euglycaemic DKA is not limited to people using SGLT2 inhibitors and has also been described in alcohol use disorders, starvation, pregnancy, and chronic liver diseases. Risk factors for euglycaemic DKA with SGLT2 inhibitors include latent autoimmune diabetes of adulthood, surgery, low carbohydrate diet, insulin withdrawal or dose reduction, and acute medical illness. Euglycaemic DKA can result in delayed diagnosis and treatment as well as the potential for adverse metabolic consequences.

Individuals should be educated to stop SGLT2 inhibitors for at least 24 hours to 5 days before scheduled surgical procedures or during periods of acute illness. Although the half-life of SGLT2 inhibitor is approximately 13 hours, the clinical effect can last several days after discontinuation. Individuals should be educated to check urine or blood ketones in the presence of early warning symptoms of DKA, even when the blood glucose concentrations are below 11.1 mmol/L. Treatment is similar to usual DKA except direct dextrose infusion can be given as the glucose level is not high.

HYPOGLYCAEMIA

Epidemiology

Hypoglycaemia is common, affecting almost two-thirds of people with diabetes, with an additional 7.5% reporting severe hypoglycaemia in one study. Hypoglycaemia is often the major limiting factor in the glycaemic management of diabetes. Avoiding hypoglycaemia is a priority, as hypoglycaemia increases the risk of repeated hypoglycaemia and severe hypoglycaemia, and is associated with worsened glycaemic control, reduced quality-of-life, diabetes distress and anxiety, reduction in medication adherence, potentially serious injury due to falls or when driving or operating hazardous machinery, damage to the brain and heart, and rarely, death. Hypoglycaemia increases hospitalisations, and health care usage. In-hospital hypoglycaemia mostly occurs in people admitted to hospital for other reasons but can be associated with significant adverse outcomes, increased hospital length-of-stay, and increased mortality.

Clinical Presentation and Risk Factors

Recommendations regarding the classification of hypoglycaemia are outlined in Table 3.

Symptoms of hypoglycaemia include autonomic symptoms such as shakiness, sweating, and palpitations; as well as neuroglycopenic manifestations such as irritability, confusion, drowsiness, and even coma, hemiparesis or seizures. Many people with diabetes demonstrate impaired counterregulatory responses to hypoglycaemia and experience impaired hypoglycaemia awareness, with the warning symptoms of hypoglycaemia becoming diminished in intensity, altered in nature or lost altogether. Hypoglycaemia unawareness increases the risk of progression to severe hypoglycaemia.

The major risk factors for hypoglycaemia include people treated with insulin (especially on intensive insulin therapy) or sulfonylureas, history of severe hypoglycaemia, impaired hypoglycaemia awareness, long duration of diabetes, renal and/or hepatic dysfunction, older age, cognitive impairment or dementia.

Management

The immediate management of hypoglycaemia would depend on the person’s consciousness level, clinical urgency, ability to swallow, and availability of intravenous access. People who are safe to swallow should be given 10-20g of fast-acting carbohydrates. Those who cannot swallow or are unstable should be given an intravenous infusion of 100 ml of 20% dextrose or 200 ml of 10% dextrose, or an intramuscular injection of glucagon if intravenous access is not available. The use of 50% intravenous dextrose has reduced substantially, given the concern about extravasation injuries with the use of hyperosmolar solutions, and a potentially higher chance of post-treatment hyperglycaemia. Glucagon mobilises glycogen from the liver, thus will be less effective in those with chronic liver disease. The glucose level should be rechecked after 10-15 minutes. Repeated carbohydrate ingestion or intravenous dextrose administration should be given for ongoing hypoglycaemia with an assessment on the need to seek further care. Once the glucose level is above 4.0 mmol/L, a long-acting carbohydrate snack or, the person’s planned meal, or an intravenous infusion of 10% dextrose should be followed. If the hypoglycaemia was caused by long-acting insulin therapy or sulfonylurea, the risk of hypoglycaemia may persist for up to 24-36 hours following the last dose, especially if there is concurrent renal impairment.

<table>
<thead>
<tr>
<th>Glycaemic criteria / description</th>
<th>Level 1</th>
<th>Level 2</th>
<th>Level 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose &lt; 3.9 mmol/L and ≥ 3.0 mmol/L</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucose &lt; 3.0 mmol/L</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A severe event characterised by altered mental and/or physical status requiring assistance</td>
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</table>
Severe or recurrent hypoglycaemia warrants adjustment of treatment regimen, behavioural intervention, self-management education and support, and the use of technology to assist with hypoglycaemia prevention and identification⁴. Continuous glucose monitoring (CGM) systems have become much more commonly used in people with diabetes and are recommended for all T1DM and some insulin-treated T2DM in the outpatient setting, especially for those with impaired hypoglycaemia awareness or fear of hypoglycaemia, using multiple daily insulin injections, or on continuous subcutaneous insulin infusion. CGM can reveal asymptomatic hypoglycaemia and help identify patterns and precipitants of hypoglycaemic events⁵, ¹², ¹⁷ - ¹⁸. Real-asymptomatic hypoglycaemia and help identify patterns of treatment regimen, behavioural intervention, self-management education for physicians, patients, and their caretakers. Appropriate education includes early recognition and treatment of diabetes emergencies, when to inform their diabetes healthcare provider and strategies for prevention. The management of diabetic emergencies, how to manage glucose during periods of illness, when to inform their diabetes healthcare provider and strategies for prevention. The availability of management guidelines, hospital care pathways, or electronic order sets can also assist in the optimal management of various diabetic emergencies.

CONCLUSION

Acute diabetic emergencies have the potential for adverse outcomes when not promptly recognised and treated. Greater focus is needed on diabetes education for physicians, patients, and their caretakers. Appropriate education includes early recognition and treatment of diabetes emergencies, how to manage glucose during periods of illness, when to inform their diabetes healthcare provider and strategies for prevention. The availability of management guidelines, hospital care pathways, or electronic order sets can also assist in the optimal management of various diabetic emergencies.

References

In the treatment of patients with type 2 diabetes and established CV disease receiving standard of care,

CV death can strike at any time

**BATTLE CV DEATH NOW MORE THAN EVER**

**JARDIANCE demonstrated 38% RRR in CV death**

- Established HbA1c efficacy
- Demonstrated safety profile
- Convenient, once-daily oral dosing

**ADA & EASD** recognize JARDIANCE as the SGLT2 inhibitor with stronger evidence of CV benefits

---

1 Standard care included CV medications and questionnaires specific to the disease of interest.
2 Results are based on 38% reduction in CV death compared to placebo in the JARDIANCE study.
3 Demonstrated safety profile compared to placebo in the JARDIANCE study.
4 Established, once-daily oral dosing compared to placebo in the JARDIANCE study.
5 Established CV disease included coronary artery disease, peripheral artery disease, history of myocardial infarction, or history of stroke.
6 Standard care included CV medications and questionnaires specific to the disease of interest.
Latest Update on the Management of Diabetic Kidney Disease: the Four Pillars of Cardiorenal Protection

Dr Winston WS FUNG

MA (Cantab), MBBS (Cantab), FHKCP, FHKAM (Medicine), FRCP (Lond), FISN
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INTRODUCTION

Diabetic kidney disease is a common and serious condition, owing to the high prevalence of diabetes globally1. This burden has been increasing and the global prevalence is now estimated to be 10.5 % (536.6 million people), rising to 12.2 % (783.2 million) in 2045.1 This is also true locally, with the majority of kidney failure presented to the Hospital Authority now being attributed to diabetes (about 50 % in 2021). Not only is it important to detect these cases early, it is equally important to instigate treatments once identified, as we now have effective therapeutic agents in delaying the progression of diabetic kidney diseases. As highlighted in the World Kidney Day 2024 editorial, there is an unmet need for equitable access and optimisation of effective medications for the benefit of our patients2. This article will discuss the latest update on using the "four pillars" of cardiorenal protection in diabetic kidney diseases.

PILLAR 1: RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM INHIBITOR

Renin-angiotensin-aldosterone system (RAAS) inhibitor has long been considered a cornerstone for treating diabetic kidney diseases. There have been a plethora of major clinical trials demonstrating its efficacy in cardiorenal protection. Two notable trials are the Reduction of Endpoints in Non-Insulin-Dependent Diabetes Mellitus with the Angiotensin II Antagonist Losartan (RENAAL) trial and the Irbesartan Diabetic Nephropathy Trial (IDNT)3,4. The relative risk reduction of reaching primary outcome (a composite of doubling baseline serum creatinine, end stage kidney failure or death) was 16 % in RENAAL and 20 % in IDNT3,4. Furthermore, both studies demonstrated a reduction in the risk of hospitalisation for heart failure. These major trials have convincingly transformed practices, as RAAS inhibitor became the standard of care for patients with diabetes and chronic kidney disease (CKD).

Yet, twenty years on, one may wonder why we are still talking about this relatively established class of medication? Even though there is overwhelming evidence of its efficacy, the usage of these medications has remained suboptimal. One of the barriers to optimising RAAS inhibitor is the fear of hyperkalaemia following the use of these agents. Epstein et al. examined the usage of RAAS inhibitor and the association between dose levels and clinical outcomes in a US patient population of about 200,0005. Their retrospective study showed that only 19 % to 26 % of patients were prescribed a maximum dose of RAAS inhibitor as recommended by international guidelines. In comparison, 58 % to 65 % of patients were given suboptimal dose irrespective of patients’ comorbidity status (CKD, heart failure, or diabetes). Furthermore, 14 % to 16 % of patients had their RAAS inhibitors discontinued, often following an event of hyperkalaemia.

When they looked at the association of the dose level with cardiorenal adverse events and mortality, there was a dose dependent effect6. Cardiorenal adverse event and all-cause mortality occurred in 34.3 % and 11.0 % of patients who discontinued RAAS inhibitor, 24.9 % and 8.2 % of patients on suboptimal doses, and 24.9 % and 4.1 % of patients on maximum doses, respectively7. Their study highlighted the importance of optimising RAAS inhibitor dosage for maximising cardiorenal protection, as this outweighs the effect of hyperkalaemia. Furthermore, we now have effective novel agents in reducing hyperkalaemia8.

Another concern is whether one should discontinue RAAS inhibitor in patients with advanced CKD, as stopping the drugs may increase the estimated glomerular filtration rate (eGFR) or slow its decline among these patients. The recent STOP-ACEI trial disproved this9. The investigators examined the impact of the continuation of RAAS inhibitors on the eGFR in advanced CKD in a multi-centre, randomised, open-label trial. They showed that discontinuation of RAAS inhibitor in patients with advanced CKD does not provide meaningful improvement of kidney function, as there was no difference in kidney decline between the two groups (the least-squares mean eGFR in the continuation group was 12.6 ± 0.7 and was 13.3 ± 0.6 in the discontinuation group (p = 0.42)).

All things considered, the international guidelines now advocate to optimise RAAS inhibitor as maximally as tolerated and only to reduce or stop these agents as a last resort if mitigation strategies are ineffective9.

PILLAR 2: SODIUM-GLUCOSE COTRANSPORTER 2 INHIBITOR

Another pillar is the sodium-glucose cotransporter 2 (SGLT2) inhibitor. It was initially developed as a medication to improve glucose control by promoting glucosuria. However, the mechanism of action goes beyond simply glucosuria as it also confers
cardiorenal protection, due to a concomitant reduction in tubular sodium reabsorption and increased sodium delivery to the macula densa, which leads to a reduction in intra-glomerular pressure via afferent arteriolar vasoconstriction by the tubuloglomerular feedback. Indeed, the use of SGLT2 inhibitors has already extended far beyond diabetes and includes cardiovascular protection in non-diabetic patients.10-12.

As for the efficacy in kidney protection, this was elegantly demonstrated by three notable phase III clinical trials with primary kidney outcome: The Canagliflozin and RenalEndpoints in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial13 enrolled patients with type II diabetes and CKD and showed a 30% relative reduction in the primary outcome (a composite of kidney failure, doubling of serum creatinine, or death from kidney or cardiovascular causes)14 by canagliflozin (Hazard ratio (HR): 0.70; 95% Confidence Interval (CI): 0.59 to 0.82)15. Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD) also showed a significant benefit, with dapagliflozin reduced the primary outcome (sustained decline in the eGFR of at least 50%, kidney failure, or death from kidney or cardiovascular causes) by 39% (HR: 0.61; 95% CI: 0.51 to 0.72)16. Study of Heart and Kidney Protection with Empagliflozin (EMPA-Kidney) also showed a similar result to DAPA-CKD (a 28% risk reduction in primary outcome (sustained decline in the eGFR of at least 40%, kidney failure, or death from kidney or cardiovascular causes) with empagliflozin, HR: 0.72, 95% CI: 0.64 to 0.82)17. Of note, both DAPA-CKD and EMPA-Kidney trials included patients with and without type II diabetes, paving the way for SGLT2 inhibitors to be used as a kidney protective drug in patients with non-diabetic CKD.

As such, the Kidney Disease: Improving Global Outcomes (KDIGO) guideline recommends starting a SGLT2 inhibitor to treat patients with type II diabetes and CKD with an eGFR >20 ml/min per 1.73 m² (1A). One should be mindful of the possible risks of urinary tract infection and ketoacidosis with the use of SGLT2 inhibitors. Patients should be educated to be watchful of warning flags and ways to mitigate these risks (e.g. sick day rule).8

PILLAR 3: NONSTEROIDAL MINERALOCORTICOID RECEPTOR ANTAGONISTS

Despite the addition of SGLT2 inhibitors to RAAS inhibitors, there is still residual risk in the progression of diabetic kidney disease, and efforts to develop more therapeutic agents continued. Finerenone is a highly selective nonsteroidal mineralocorticoid antagonist (MRA), which works similarly to conventional steroidal MRA, such as spironolactone, but without the steroid induced side effects such as gynaeomastia. In contrast to other agents, finerenone may have additional benefits in directly reducing inflammation and fibrosis.

Two major phase III clinical trials were recently published: Effect of Finerenone on Chronic Kidney Disease Outcomes in Type II Diabetes (FIDELIO-

DKD) and Cardiovascular Events with Finerenone in Kidney Disease and Type II Diabetes (FIGARO-DKD).18-19 Patients with type II diabetes and less advanced CKD (mean eGFR: 67.8 ± 21.7 ml/min/1.73 m²; median urinary albumin creatinine ratio (UACR): 308 mg/g) were enrolled in the FIGARO-DKD trial. Apart from a significant benefit in the primary composite cardiovascular outcome with finerenone, there was also a significant 23% reduction in a secondary kidney-specific composite endpoint that included a sustained >57% decline in eGFR from baseline (HR: 0.77; 95% CI: 0.60 to 0.99)18. Although similar to the FIGARO-DKD trial, FIDELIO-DKD was a primary kidney outcome trial and patients with type II diabetes and more advanced CKD (mean eGFR: 44.3 ± 12.6 ml/min/1.73 m²; median UACR: 852 mg/g) were enrolled. Compared with placebo, finerenone reduced the occurrence of the primary composite kidney endpoint by 18% (HR: 0.82; 95% CI: 0.73 to 0.93)19.

Both trials showed that finerenone has a slightly higher incidence of hyperkalaemia-related adverse events leading to discontinuation of the trial regimen. Still, hospitalisation for hyperkalaemia was rare, and there were no hyperkalaemia related deaths. Nevertheless, these trials demonstrated the convincing cardiorenal protective effect of finerenone in patients with type II diabetes. Indeed, the KDIGO guideline suggests the use of a nonsteroidal MRA for patients with type II diabetes, an eGFR > 25 ml/min per 1.73 m², normal serum potassium, and albuminuria (> 30 mg/g) despite the maximum tolerated dose of RAAS inhibitor (2A). Trial to assess whether these cardiorenal protective effects extend beyond diabetic kidney diseases are also being conducted currently (A Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Phase 3 Study to Investigate the Efficacy and Safety of Finerenone, in Addition to Standard of Care, on the Progression of Kidney Disease in Patients With Non-Diabetic Chronic Kidney Disease (FIND-CKD), ClinicalTrials.gov NCT05047263).

PILLAR 4: GLUCAGON-LIKE PEPTIDE-1 RECEPTOR AGONISTS

Glucagon-like peptide-1 receptor agonists (GLP-1 RA) are the final pillar as an emerging agent in the cardiorenal protection for diabetic kidney diseases. GLP-1 RA mimics the action of incretin hormone, which exerts a myriad of effects: reducing blood glucose by potentiating insulin release and by reducing glucagon secretion, suppressing appetite and promoting weight loss, increasing natriuresis and diuresis, decreasing oxidative stress and inflammation, and improving blood pressure and lipid control.20 Given its effect on reducing appetite, GLP-1 RAs have already been approved for obesity and weight management in individuals with or without diabetes.

This class of drugs have also demonstrated cardiovascular benefits in several large cardiovascular outcome trials, particularly death from a cardiovascular cause, nonfatal stroke, or nonfatal myocardial infarction.21 Although these trials are mainly designed for assessing primary cardiovascular outcomes, they also evaluated secondary kidney outcomes and showed...
some benefits\(^{21}\). Pivotal trial primarily assessing kidney outcomes in patients with type II diabetes and CKD is being done with the GLP-1 RA Semaglutide (Effect of Semaglutide Versus Placebo on the Progression of Renal Impairment in Subjects With Type II Diabetes and Chronic Kidney Disease (FLOW), Clinicaltrials.gov NCT03819153). This trial was stopped early in October 2023 due to the efficacy of kidney protection in the interim analysis.

Given these emerging benefits, KDIGO guideline recommends starting a long-acting GLP-1 RA in patients with diabetic kidney disease who have not achieved sIndividalised glycemic targets despite the use of metformin and SGLT2 inhibitor treatment, or who are unable to use those medications (1B). Furthermore, the American Diabetes Association has also recommended prescribing GLP-1 RA as one of two possible first line therapies to reach appropriate glycemic targets in patients with type II diabetes who have or are at high risk for atherosclerotic cardiovascular disease (ASCVD)\(^{22}\). Apart from semaglutide, which has an oral preparation, all the other GLP-1 RAs are currently administered via subcutaneous injections on a daily or, for the newer-generation GLP-1 RAs, weekly basis. One major precaution is that GLP-1 RA should not be used in patients with a history of pancreatitis, as cases of acute pancreatitis have been reported in association with the initiation of GLP-1 RA in post-marketing reports.

CONCLUSION

Diabetic kidney disease remains a huge burden in healthcare, with significant cardioenal morbidity and mortality. While prevention and early detection are key, prompt and optimal treatments are equally important in delaying the disease progression, especially given the availability of increasingly effective therapeutic agents nowadays. Future research with novel therapeutics, such as selective endothelin antagonists, is on the way, which may add to the current armamentarium and further improve the prognosis of diabetic kidney disease. Implementation science should also be done concurrently to identify barriers to prescribing these agents and to reduce clinical inertia, ultimately facilitating the translation of "what we know" into "what we do"\(^{2}\).

References


Certificate Course in

Allergy 2024
(Video Lectures)

Jointly organised by

The Federation of Medical Societies of Hong Kong
The Hong Kong Institute of Allergy

Objectives:
To provide an updated understanding in hot topics of allergy.

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| 3 Jul 2024 | Common Misconceptions in Allergy Prevention      | Dr. Alson W. M. CHAN
Specialist in Paediatric Immunology, Allergy & Infectious Diseases     |
| 10 Jul 2024| The New Perspectives of Seafood Allergy          | Dr. Agnes S. Y. LEUNG
Assistant Professor
Department of Paediatrics
The Chinese University of Hong Kong                                   |
| 17 Jul 2024| The Use of Biologics in Allergic Diseases        | Dr. Marco H. K. HO
Specialist in Paediatric Immunology, Allergy & Infectious Diseases     |
| 24 Jul 2024| Updates on the Management of Food Allergy        | Dr. Gilbert T. CHUA
Specialist in Paediatric Immunology, Allergy & Infectious Diseases     |
| 31 Jul 2024| Food Challenge & Food Desensitization: the Practical Approach | Ms. Sabrina W. S. MOK
Registered Dietitian                                                     |
| 7 Aug 2024 | Management and Referrals of Urticaria & Angioedema for the Greater Bay Area | Dr. Jane C. Y. WONG
Associate Consultant
Department of Medicine
Queen Mary Hospital                                                      |

Date: 3, 10, 17, 24, 31 July and 7 Aug 2024 (Wednesday)
Duration of session: 1.5 hours (6 sessions)
Time: 7:00 pm – 8:30 pm
Course Feature: Video lectures (with Q&A platform for participants to post the questions)
Quiz for doctors: DOCTORS are required to complete a quiz after the completion of each lecture
Language Media: Cantonese (Supplemented with English)
Course Fee: HK$1,000
Certificate: Awarded to participants with a minimum attendance of 70% (4 out of 6 sessions)
Deadline: 26 June 2024
Enquiry: The Secretariat of The Federation of Medical Societies of Hong Kong
Tel.: 2527 8898 Fax: 2865 0345 Email: toto.chan@fmshk.org

CME / CNE / CDE (Dietitians) Accreditation in application
Online Application from website: http://www.fmshk.org
Continuous Glucose Monitoring

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The Chinese University of Hong Kong

INTRODUCTION

There has been a rapid growth in the use of continuous glucose monitoring (CGM) technologies, which allows minute-by-minute glucose measurements without the inconvenience of finger pricking. Most commercially available CGMs are minimally-invasive, enzyme-based, and detect changes in interstitial glucose via an electrochemical reaction, which is then transmitted to a mobile reader via Bluetooth or near field connection. CGM sensors typically last 7 - 15 days and can be placed on the arm or the abdomen. Most latest versions of sensors are approved for non-adjunctive use and do not require compulsory user calibration. CGMs can be further classed by their functionality. Professional or blinded CGMs do not reveal glucose readings to the users and are used in research settings to evaluate the drug efficacy or intervention. The key difference between intermittently-scanned (is-CGM) versus real-time (rt-CGM) is how glucose readings are captured and revealed to the user. For is-CGM, glucose values are only revealed and transferred upon scanning of the reader by the user, whereas for rt-CGM, sensor readings are transmitted continuously via a blue-tooth connection. Both allow the generation of ambulatory glucose reports (AGPs) and remote data sharing by healthcare professionals or carers. However, only rt-CGM have real-time hypo- or hyperglycaemic alerts and can be integrated into automated insulin delivery systems (AIDs). These differences are summarised in Table 1.

People with type 1, type 2 diabetes (T2D) on insulin or non-insulin treatments have very different clinical needs. The choice of type of CGM, frequency of use and appropriate CGM targets will differ by population as well as patient preference. People with type 1 diabetes (T1D) span the pediatric to adult age range, are usually intensively-treated with multiple daily injections, are prone to hypoglycaemia and have high glucose variability. Conversely, a newly diagnosed patient with T2D on diet control may be at a very low risk of hypoglycaemia but need glucose data to inform lifestyle choices. Randomised controlled trials (RCTs) remain the gold standard for the evaluation of the efficacy of an intervention. Minimising the risk of bias is challenging as device studies are open-labelled and participants often receive additional attention in the operation of the study device. On the other hand, a substantial amount of real-world CGM data have been collected via registries and databases, which can inform effectiveness, but are subject to other biases. In the following sections, we shall review clinical evidence for the use of CGM in different diabetes populations and appropriate clinical targets.

TYPE 1 DIABETES

In many countries, CGM for continuous personal use is now reimbursed for children and adults with T1D. CGM has been shown to improve HbA1c in suboptimally controlled persons with T1D, reduce hypoglycaemia and improve quality of life in clinical studies. The DIAMOND trial was a 24-week, RCT evaluating the use of rt-CGM (Dexcom G4) vs conventional blood glucose monitoring (BGM) in 158 adults with type 1 diabetes in the United States. The baseline HbA1c was 8.6 %. At 24 weeks, the CGM group (n = 105) experienced a mean(SD) -1.0 (0.8) % reduction in HbA1c versus -0.4 (0.7) % improvement in the control group (mean adjusted difference -0.6 [95 % CI -0.8 to -0.3, p < 0.001]. There was a reduction in time-in-hypoglycaemia in the rtCGM group. The Flash UK study was an academically-funded, multicentered study in the United Kingdom.
that included 156 patients with T1D (mean age 44 years) with baseline HbA1c levels between 7.5 and 11 %. They were randomised to is-CGM (Abbott Freestyle Libre 2 with optional hypoglycaemic or hyperglycaemic alerts) versus standard BGM for 24 weeks. In the intervention group, HbA1c decreased from 8.7 to 7.9 %, with a between group difference of -0.5 % (95 % CI -0.7 to -0.3) at 24 weeks in favour of CGM. Time spent in hypoglycaemic state (< 3.9 mmol/l) was also 3.0 % (95 % CI, 1.4 to 4.5) lower in the intervention group 4. Though most RCTs were not sufficiently powered to demonstrate reductions in diabetic ketoacidosis (DKA) or severe hypoglycaemia (SH), given the rarity of events, real-world data from several large registries have shown consistent reductions in diabetic emergencies following the introduction of CGM. In a retrospective study of 74,011 individuals with T1D or T2D in France, there was a significant decrease in hospitalisations for DKA by 56 % and diabetes-related coma by 39 % following initiation of is-CGM (Freestyle Libre 1) among those with T1D, with a similar magnitude of reduction seen in those with T2D 5. Johnson and colleagues reported a significant reduction in risk of DKA in young people with T1D who were using CGM > 75 % of the time following introduction of universal subsidised CGM in Australia (incidence rate ratio 0.49, 95 % CI 0.33 to 0.74, p < 0.001) 6. Thus, there is substantial evidence that CGM can improve HbA1c and reduce hypoglycaemia in children and adults with T1D, and reduce diabetes-related acute admissions, but prospective long term studies on the use of CGM on reduction of microvascular complications and death are still lacking.

**TYPE 2 DIABETES**

T2D account for 90 % of the population with diabetes spanning a wide spectrum from insulin-treated (on multiple daily injections (MDI) or basal insulin), to those on oral glucose lowering drugs only or diet control. A patient with advanced T2D on intensive insulin therapy might experience frequent hypoglycaemia, whereas this might be unusual in a diet-controlled patient who instead requires postprandial glucose information to guide dietary decisions. Currently, there is good evidence supporting the use of CGM in insulin-treated T2D patients. One RCT compared rtCGM (Dexcom G4) vs BGM in 158 adults with T2D on MDI of insulin 7. In this study, the median duration of diabetes was 17 years, with a mean baseline HbA1c 8.5 % 8. After 24 weeks, HbA1c significantly decreased to 7.7 % in the CGM group versus 8 % in the control group (adjusted difference 0.3 %, 95 % CI -0.5 % to 0.0 %, p = 0.022). However, there were no meaningful differences in CGM-measured hypoglycaemia or quality-of-life outcomes. An MOBILE study of 175 patients with T2D on basal insulin were randomised to rtCGM (n = 116) vs BGM (n = 59) in primary care practices in the United States 9. HbA1c decreased from 9.1 to 8.0 % in the CGM group with an adjusted difference of -0.4 % (95 % CI -0.8 % to -0.1 %) in favour of the CGM group. Interestingly, there was no change in total or basal insulin daily dose in the CGM group, suggesting that glycaemic improvements were primarily driven by behavioural change. This lack of change in total insulin dose despite observed glycemic improvement has consistently been observed in other CGM clinical trials. In a follow-up of the MOBILE study, a rebound in HbA1c was observed six months post trial in those who discontinued rtCGM use, with a loss of approximately half of the initial glycaemic improvements gained with rtCGM use 10.

With respect to periodic CGM use in non-insulin treated T2D patients, there is currently very limited RCT evidence. One pilot RCT investigated periodic CGM use in non-insulin treated T2D patients with HbA1c 7.8 % - 10.5 % (n = 68, 45 in rtCGM and 23 BGM). The rtCGM group used unblinded rtCGM at 0, 4 and 8 weeks (3 sessions), whereas the SMBG group only wore a blinded CGM at eight weeks. At month 3, HbA1c was -0.5 (1.3 %) in CGM vs -0.2 (1.1 %) in BGM group with non-significant between group differences (p = 0.74). Further, these improvements were not sustained in month 9. At present, periodic CGM use may be considered for non-insulin treated T2D to support treatment titration and reinforce self management behaviours. Though there is good reason to assume non-insulin CGM patients with suboptimal control may also benefit from CGM use, this is pending formal evaluation in clinical trial settings.

**SPECIAL POPULATIONS**

**Pregnancy**

Optimal glucose control before and during pregnancy improves maternal and neonatal outcomes, but is often challenging in patients with pre-existing diabetes. The Continuous glucose monitoring in pregnant women with type 1 diabetes (CONCEPTT) trial evaluated 325 women with T1D who were planning pregnancy or pregnancy. The intervention group received rtCGM (Guardian REAL-time or MiniMed Minilink system) vs BGM (7 times a day). The primary outcome was a change in HbA1c from randomisation to 34 weeks gestation in pregnant women and to 24 weeks of conception in women planning pregnancy. There was a small difference in HbA1c in pregnant women using CGM (mean difference -0.19 %, 95 % CI -0.34 to -0.03; p = 0.0207). Pregnant CGM users spent more time in target (68 % vs 61 %; p = 0.0034) with no increase in hypoglycaemia. Notably, neonatal health outcomes were improved with lower incidence of large for gestational age babies (odds ratio OR 0.51, 95 % CI 0.28 to 0.90; p = 0.021), neonatal intensive care admission (OR 0.48; 0.26 to 0.86; p = 0.0157) and neonatal hypoglycaemia (OR 0.45, 0.22 to 0.89; p = 0.025) 11. Regarding use of CGM in pregestational T2D or gestational diabetes (GDM) who may or may not require insulin treatment, there are very few published RCTs, mostly with small patient numbers and no hard pregnancy outcomes. A 2023 Asia-Pacific consensus recently reviewed the use of CGM in different patient groups, concluding although evidence for the use of CGM in pregnant T1D is strong, there is limited evidence to support any recommendation for the use of CGM in pregnant women with T2D or GDM 12.

**Advanced Chronic Kidney Disease (CKD)**

In advanced CKD, HbA1c may be affected by altered red cell survival use of iron or erythropoietin stimulating agents (ESA) 13. The Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guideline for
diabetes in CKD recommended periodic monitoring with CGM derived glycaemic indices may be useful in CKD stages G4-5, where HbA1c is not concordant with measured blood glucose levels or clinical symptoms14. Uremia, acidosis, hypoxia, fluid status or dialysates might impact the accuracy of CGM sensors in patients with end stage kidney disease (ESKD). In a study of 30 diabetes patients on continuous ambulatory peritoneal dialysis (CAPD) with dextrose solutions, sensor glucose readings (Medtronic Guardian Sensor 3) showed good accuracy with a mean absolute relative difference (MARD) of 10.4 % against laboratory gold standard glucose, similar to non-CKD counterparts15,16. There are limited accuracy studies in ESKD comparing different brands of CGM sensors and reports in hemodialysis are less consistent17. Patients are thus advised to follow manufacturers’ recommendations for CGM usage.

Older Adults

Despite concerns regarding acceptability or ease of use of technologies in older adults, most studies reveal a similar benefit of CGM in older as compared with younger age groups. The Wireless Innovation for Seniors with Diabetes Mellitus (WISDM) RCT examined the use of CGM in reducing hypoglycaemia in older adults who were 60 years or older with T1D. They were randomised to rtCGM vs regular BGM for six months. In the study, rtCGM reduced median time with glucose levels below 3.9 mmol/L per day 1.9 % (~27 minutes per day); 95 % CI, -2.8 % to -1.1 % [-40 to -16 minutes per day]; p < 0.001) without an improvement in HbA1c18. In a subanalysis of the MOBILE study, participants ≥ 65 years old using CGM had a greater increase in TIR and reduction in HbA1c than those using BGM, with similar benefits as seen in younger adults. However, participants in these trials were a selective group, generalisability to frail older adults with complex comorbidities remains unknown.

TIME IN RANGES AND CLINICAL TARGETS FOR DIFFERENT PATIENT GROUPS

For adults with T1D and T2D, the international consensus recommends a time-in-range of 3.9 -10 mmol/L of 70 % which approximately equivalent to HbA1c 7.0 %. An improvement in TIR of 5 % is regarded as clinically significant19. The recommended Time below range (TBR) < 3.9 mmol/L is less than 4 %. (Fig 1). For older adults or vulnerable patients with T1D or T2D, minimisation of hypoglycaemia is of higher priority and targets of TBR < 1 % and TIR 50 % are recommended. There is a different pregnancy target range of 3.5 - 7.8 mmol/L due to changes in glucose physiology during pregnancy, with a recommended goal of achieving 70 % pregnancy TIR. Recently, a time-in-tight-range (TITR) of 3.9 - 7.8 mmol/L has been proposed, which might apply to well-controlled patients on automated insulin delivery systems or those with prediabetes or early diabetes. A TITR of 50 % was suggested to be equivalent to 70 % TIR 3.9-10 mmol/L20.

EDUCATION AND ACCESS

The provision of CGM technology alone without alignment of diabetes education may not improve population outcomes. In a large T1D registry in the US, the number of CGM users quadrupled from 7 to 30 %, but overall HbA1c was higher in 2018 compared with 201221. This suggests that either technology users may be a self-selecting group or that the provision of technology itself, without self-management education may not improve population outcomes.

Several structured CGM education programmes have been developed. For example, SPECTRUM (Structured Patient Education and Treatment Programme for Self-Reliant Continuous Glucose Monitoring) is a CGM programme adapted for different ages and applicable to all CGM systems and insulin types in Germany21,22.

Fig. 1: Time in ranges for adults with type 1 or type 2 diabetes, older high risk adults and pregnancy in type 1 diabetes. (Adapted from references 19)
Another programme termed FLASH was developed to assist CGM users in optimising diabetes management. In a RCT of 216 patients on intensive insulin therapy, FLASH education compared to the control group had greater HbA1c improvements at six months (between-group difference of -0.17 %, 95% CI -0.01 % to -0.33 %; p = 0.033)\(^2\).

In Hong Kong, CGM devices are mostly out-of-pocket, with some support from public hospital programmes and non-governmental organisations. The expenses associated with diabetes technologies may accentuate inequalities in health. Studies have revealed health care disparities in access to CGM with ethnic minorities and those in low socio-economic groups less likely to be using CGM\(^4\). In Australia, for example, provision of universal subsidised access to CGM for all T1D patients aged below 21 years was more cost-effective than a universal subsidised access to CGM for all T1D patients (CONCEPTT): a multicentre international randomised controlled trial. The Lancet. 2017;390(10110):2347-2359.

CONCLUSIONS

In summary, there is substantial evidence that CGM can support day-to-day treatment decisions, behavioural change and improve glycaemic outcomes in insulin-treated and T1D and T2D, as well as in pregnant with TID. For non-insulin treated diabetes, pregestational T2D and GDM evidence is still emerging. CGM may be used to motivate behavioural change with positive results seen with continuous use and potentially with periodic use. The choice of CGM should be guided by patient preference and clinical targets should be customised by patient needs. We highlight the importance of aligning structured education to empower patients to make the best use of technologies. Finally, we have a duty as a community of healthcare professionals to promote equitable access to diabetes technologies for the benefit all people with diabetes.

References


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Effective in short term and over 30 days¹

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更多資訊:
The theme of the June 2024 issue of the Medical Diary is Diabetes. In the spirit of disease prevention and awareness, I refer to the words of the Hong Kong’s Department of Health1, "Regular physical activity... reduces the risk of developing many chronic diseases. It helps to maintain an optimum body weight... Lack of physical activity is one of the major risk factors for ... diabetes mellitus...". We all know this, but when the call comes for a physical activity, will you join?

This very occasion came on 5th February, when the Federation of Medical Societies of Hong Kong (FMSHK) sent out an email to member organisations asking if they would be interested in joining the charity races for Médecins Sans Frontières (MSF) the following month. MSF, which translates in English to Doctors without Borders, has organised its signature event since 2002. Since the popular race filled its quotas promptly after the launch of the general registration period, the event had been closed to new entries months before the FMSHK’s email. What an opportunity!

Several doctors joined the MSF event as invited race VIPs including, FMSHK President Prof Bernard Man-yung Cheung, Honorary FMSHK President Dr Raymond See-kit Lo, Immediate Past FMSHK President Dr Mario Wai-kwong CHAK, Dr Au Yiu-kai (Fig. 1), who volunteers in South Sudan for MSF, Dr Johnson Tam, a Member of the Medical Licentiate Society of Hong Kong, and myself as President of the Medical Licentiate Society of Hong Kong.

The race took place on Sunday morning of 18th March 2024. Upon arrival, the MSF staff welcomed us to the start area at the main dam of the Plover Cove Reservoir in Tai Mei Tuk, Tai Po. We checked-in our bags, applied an extra layer of sunscreen, and participated in the pre-race warmup and stretch session with over 1,000 other runners. The MSF staff guided us to the space in front of the starting line (Fig. 2) for group photos and opening remarks by various invited dignitaries, including FMSHK President Prof Bernard Cheung.

Staff handed the race VIP’s opening horns. We could see the jittery energy in the eyes of the elite runners as they wiggled and stretched at the start line behind us. An inspiring crowd of some of Hong Kong’s fittest...
filled the area. With a countdown of 10, followed by a loud collective honk (Fig. 3), we sent them off to start the race. After the 1,000+ runners started, the race VIPs crossed the start mat and we also ran the course. After the initial excitement of sending off the mass of runners, we settled into our own individual running paces along the flat path at the top of the dam. The day was sunny and hot, but the loop course ensured we stayed in contact with all of the other runners. To keep seeing everyone else, proved a durable source of support for the entire 10 km.

The spirited MSF staff also encouraged runners to add oil; several staff wore costumes to brighten the festive mood even more. The finish line came quickly. Later, we reunited with colleagues and friends (Fig. 4) and posed for more photos (Fig. 5). Participating in MSF’s well-organised event with such friendly staff was a great experience. I would definitely recommend joining in the future. Hope to see you next time.

References
1. Physical Activity. Center for Health Protection, Hong Kong Department of Health. Website: https://www.chp.gov.hk/en/healthtopics/content/25/8804.html. Last Revision Date: 2023/01/12; Accessed 7 April 2024.
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- **Sunday 1:**
  - Zoom: The HKMA CME Lecture for District Health Network CME Programme - 2024
  - Updates on Vaccination

- **Monday 2:**
  - Zoom: Intensive Lipid-Lowering Therapy for Reducing Cardiovascular Risks
  - Certificate Course on Medical Ultrasound 2024 (Video Lectures)

- **Tuesday 3:**
  - Zoom: The Voice Unveiled: Navigating Common Vocal Cord Diseases
  - Certificate Course on Cytogenomics 2024 (Video Lectures)

- **Wednesday 4:**
  - Personal / Zoom: Management of HPV Infection & External Genital Warts
  - Certificate Course on Mental Health 2024 (Video Lectures)

- **Thursday 5:**
  - Zoom: Update on Topical Retinoid Therapy in Acne
  - Certificate Course on Medical Ultrasound 2024 (Video Lectures)

- **Friday 6:**
  - Zoom: Two Disordered Breathing: Obstructive Sleep Apnea
  - Certificate Course on Mental Health 2024 (Video Lectures)

- **Saturday 7:**
  - Zoom: The HKMA CME Live Lecture for District Health Network CME Programme - 2024
  - Updates on Vaccination

- **Sunday 8:**
  - Zoom: The HKMA Men’s Health Campaign 2024 CME Symposium
  - Certificate Course on Mental Health 2024 (Video Lectures)

- **Monday 9:**
  - The Hong Kong Neurosurgical Society Monthly Academic Meeting – To be confirmed
  - Certificate Course on Medical Ultrasound 2024 (Video Lectures)

- **Tuesday 10:**
  - Zoom: The HKMA CME Lecture for District Health Network CME Programme - 2024
  - Updates on Vaccination

- **Wednesday 11:**
  - In-person: The Voice Unveiled: Navigating Common Vocal Cord Diseases
  - Certificate Course on Cytogenomics 2024 (Video Lectures)

- **Thursday 12:**
  - Zoom: Management of HPV Infection & External Genital Warts
  - Certificate Course on Medical Ultrasound 2024 (Video Lectures)

- **Friday 13:**
  - Zoom: Update on Topical Retinoid Therapy in Acne
  - Certificate Course on Medical Ultrasound 2024 (Video Lectures)

- **Saturday 14:**
  - Zoom: The HKMA CME Live Lecture for District Health Network CME Programme - 2024
  - Updates on Vaccination

- **Sunday 15:**
  - Zoom: In-person: The Voice Unveiled: Navigating Common Vocal Cord Diseases
  - Certificate Course on Cytogenomics 2024 (Video Lectures)

- **Monday 16:**
  - The HKMA CME Lecture for District Health Network CME Programme - 2024
  - In-person: The Voice Unveiled: Navigating Common Vocal Cord Diseases

- **Tuesday 17:**
  - Zoom: Management of HPV Infection & External Genital Warts
  - Certificate Course on Medical Ultrasound 2024 (Video Lectures)

- **Wednesday 18:**
  - In-person: The Voice Unveiled: Navigating Common Vocal Cord Diseases
  - Certificate Course on Cytogenomics 2024 (Video Lectures)

- **Thursday 19:**
  - Zoom: Management of HPV Infection & External Genital Warts
  - Certificate Course on Medical Ultrasound 2024 (Video Lectures)

- **Friday 20:**
  - Zoom: Update on Topical Retinoid Therapy in Acne
  - Certificate Course on Medical Ultrasound 2024 (Video Lectures)

- **Saturday 21:**
  - Zoom: The HKMA CME Live Lecture for District Health Network CME Programme - 2024
  - Updates on Vaccination

- **Sunday 22:**
  - Zoom: In-person: The Voice Unveiled: Navigating Common Vocal Cord Diseases
  - Certificate Course on Cytogenomics 2024 (Video Lectures)

- **Monday 23:**
  - The HKMA CME Lecture for District Health Network CME Programme - 2024
  - In-person: The Voice Unveiled: Navigating Common Vocal Cord Diseases

- **Tuesday 24:**
  - Zoom: Management of HPV Infection & External Genital Warts
  - Certificate Course on Medical Ultrasound 2024 (Video Lectures)

- **Wednesday 25:**
  - In-person: The Voice Unveiled: Navigating Common Vocal Cord Diseases
  - Certificate Course on Cytogenomics 2024 (Video Lectures)

- **Thursday 26:**
  - Zoom: Management of HPV Infection & External Genital Warts
  - Certificate Course on Medical Ultrasound 2024 (Video Lectures)

- **Friday 27:**
  - Zoom: Update on Topical Retinoid Therapy in Acne
  - Certificate Course on Medical Ultrasound 2024 (Video Lectures)

- **Saturday 28:**
  - Zoom: The HKMA CME Live Lecture for District Health Network CME Programme - 2024
  - Updates on Vaccination

- **Sunday 29:**
  - Zoom: In-person: The Voice Unveiled: Navigating Common Vocal Cord Diseases
  - Certificate Course on Cytogenomics 2024 (Video Lectures)
<table>
<thead>
<tr>
<th>Date / Time</th>
<th>Function</th>
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<tbody>
<tr>
<td><strong>3 MON</strong></td>
<td>2:00 PM</td>
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<tr>
<td></td>
<td>Zoom</td>
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<tr>
<td></td>
<td>The HKMA CME Live Lecture for District Health Network CME Programme - 2024 Updater on Vaccination</td>
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<tr>
<td></td>
<td>Organiser: The HKMA District Health Network &amp; HA-KLN East Cluster</td>
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<tr>
<td></td>
<td>Speaker: Dr Rocky SHUM</td>
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<td>Enquiry / Remarks: Mr Peter HO</td>
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<td></td>
<td>Tel: 3108 2514</td>
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<tr>
<td></td>
<td>HKMA-HKSHE CME Programme 2023-2024</td>
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<tr>
<td></td>
<td>Topic: The Voice Unveiled: Navigating Common Vocal Cord Diseases</td>
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<tr>
<td></td>
<td>Organiser: The Hong Kong Medical Association &amp; Hong Kong Sanatorium &amp; Hospital</td>
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<td>Speaker: Dr NG Yiu-wing</td>
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<tr>
<td></td>
<td>Venue: The HKMA Wanchai Premises, 5/F, Duke of Windsor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong</td>
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<td>Certificate Course on Cytogenomics 2024 (Video Lectures)</td>
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<td>Organiser: The Federation of Medical Societies of Hong Kong</td>
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<td>Speaker: Dr Stephanie HO</td>
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<td>Invasive Lipid-Lowering Therapy for Reducing Cardiovascular Risks</td>
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<td>Organiser: The Hong Kong Medical Association</td>
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<td>Speaker: Dr Chan Kit</td>
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<td></td>
<td>Certificate Course on Medical Ultrasound 2024 (Video Lectures)</td>
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<td>Organiser: The Federation of Medical Societies of Hong Kong</td>
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<tr>
<td></td>
<td>Speaker: Dr Wisely Hok-him TANG</td>
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<td>Certificate Course on Mental Health 2024 (Video Lectures)</td>
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<td>Organiser: The Federation of Medical Societies of Hong Kong</td>
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<td>Speaker: Dr TAM Fung-ling</td>
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<td><strong>11 TUE</strong></td>
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<td></td>
<td>(Live) Management of HPV Infection &amp; External Genital Warts</td>
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<td>Organiser: The Hong Kong Medical Association</td>
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<td>Speaker: Dr Ho King-man</td>
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<td>Certificate Course on Cytogenomics 2024 (Video Lectures)</td>
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<td>Organiser: The Federation of Medical Societies of Hong Kong</td>
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<td></td>
<td>Speaker: Dr Shirley CHENG</td>
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<td><strong>12 WED</strong></td>
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<td>The Hong Kong Neurosurgical Society Monthly Academic Meeting – To be confirmed</td>
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<td>Chairman: Dr FANG Kai-yuen</td>
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<td>Venue: Seminar Room, G/F, Block A, Queen Elizabeth Hospital; or via Zoom meeting</td>
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<td></td>
<td>HKMA-CUHK Medical Centre CME Programme 2024</td>
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<td></td>
<td>Men’s Health - Topic: Novel Treatment for BPH and Prostate Cancer</td>
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<td>Organiser: The Hong Kong Medical Association</td>
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<td>CUHK-Medical Centre</td>
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<td>Speaker: Dr Peter Ka-fung CHIU</td>
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<td></td>
<td>Venue: The HKMA Wanchai Premises, 5/F, Duke of Windsor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong</td>
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<td>Certificate Course on Medical Ultrasound 2024 (Video Lectures)</td>
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<td>Organiser: The Federation of Medical Societies of Hong Kong</td>
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<td></td>
<td>Speaker: Dr Christie Ho-ting WONG, Dr Natalie Kar-yin MOK</td>
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<td><strong>13 THU</strong></td>
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<td>Certificate Course on Mental Health 2024 (Video Lectures)</td>
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<td>Speaker: Dr PEI Fei-chou</td>
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<td></td>
<td>Update on Topical Retinoid Therapy in Acne</td>
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<td>Organiser: The Hong Kong Medical Association</td>
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<td>Speaker: Dr LEE Tze-yuen</td>
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<td><strong>18 TUE</strong></td>
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<td></td>
<td>HKMA-GHK CME Programme 2024 - Strategies of Tumor Clearance by Management of Colorectal Diseases</td>
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<td>Organiser: The Hong Kong Medical Association &amp; Gleneagles Hong Kong Hospital</td>
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<td>Speaker: Dr Alex Li-chang LEUNG</td>
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<td></td>
<td>Venue: The HKMA Wanchai Premises, 5/F, Duke of Windsor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong</td>
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<td>Certificate Course on Medical Ultrasound 2024 (Video Lectures)</td>
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<td>Organiser: The Federation of Medical Societies of Hong Kong</td>
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<td>Speaker: Dr Grace HO</td>
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<td>Enquiry / Remarks: HKMA CME Dept.</td>
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<td><strong>20 THU</strong></td>
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<td>Certificate Course on Mental Health 2024 (Video Lectures)</td>
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<td>Speaker: Dr LUK Jing-si</td>
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<td>Enquiry / Remarks: HKMA CME Dept.</td>
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<td>FMSHK Executive Committee Meeting</td>
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<td>Organiser: The Federation of Medical Societies of Hong Kong</td>
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<td></td>
<td>Venue: Council Chamber, 4/F, Duke of Windsor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong</td>
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<td>Enquiry / Remarks: Ms Nancy CHAN</td>
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<td><strong>22 SAT</strong></td>
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<td>In-person</td>
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<td>Organiser: The Hong Kong Medical Association</td>
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<td>Speaker: Dr Thomas Yu-chung LAM, Dr Raymond TSO</td>
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<tr>
<td></td>
<td>Venue: Star Room, 42/F, Cordis Hotel, 555 Shanghai Street, Mongkok, Kowloon</td>
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<td>Enquiry / Remarks: HKMA CME Dept.</td>
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<td>Tel: 3108 2507</td>
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<td>2 CME point</td>
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Calendar of Events

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<th>Date / Time</th>
<th>Function</th>
<th>Enquiry / Remarks</th>
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<tbody>
<tr>
<td>25 TUE 2:00 PM</td>
<td>Zoom Integrity and Professional Ethics for Doctors</td>
<td>HKMA CME Dept. Tel: 3108 2507 1 CME Point</td>
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<tr>
<td>26 WED 2:00 PM</td>
<td>In-person The HKMA CME Lecture for District Health Network CME Programme in Physical Attendance Mode</td>
<td>Mr Peter HO Tel: 3108 2514 1 CME Point</td>
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<tr>
<td>26 WED 7:00 PM</td>
<td>Certificate Course on Medical Ultrasound 2024 (Video Lectures)</td>
<td>Ms ToTo CHAN Tel: 2527 8898</td>
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<tr>
<td>27 THU 7:00 PM</td>
<td>Certificate Course on Mental Health 2024 (Video Lectures)</td>
<td>Ms ToTo CHAN Tel: 2527 8898</td>
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Upcoming Event

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<tr>
<th>Date</th>
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<th>Enquiry</th>
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<tbody>
<tr>
<td>5 to 7 July 2024</td>
<td>Hong Kong Primary Care Conference 2024 - “Family Medicine in the Community: Strengthening Connections”</td>
<td>Ms Ally CHAN/Ms Nana CHOY Tel: 2871 8899 Fax: 2866 0616</td>
</tr>
<tr>
<td>14 July 2024</td>
<td>HKCMA ASM 2024‘Frontiers in Clinical Practice: Bridging Primary and Specialist Care’ (Hybrid)</td>
<td>Mr Kelvin WONG Ms Lucy LAU Tel: 2527 8898</td>
</tr>
</tbody>
</table>

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Answers to Radiology Quiz

Answers:

1. A retrocardiac lesion with air fluid level is noted.
2. Findings are suggestive of a hiatal hernia.
3. Further investigation includes fluoroscopy and OGD.

Dr NG Yuk-yiu
MBBS, FRCR

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