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Diabetes Update

Vol. 5 | Issue 51| 2024

Dear Doctor,

Greetings from Micro Labs Limited. We are happy to bring you "DIABETES UPDATE" which contains latest and interesting news in the field of Diabetes and Endocrinology.

- **Effects of close and intensive monitoring of different glycemic trajectories on Diabetes Management in Poorly Controlled Type 2 Diabetes**
- **Relationship Between Morning Serum Cortisol Levels and Diurnal Time in Range in Type 2 Diabetes**
- **Association between maternal blood glucose patterns throughout pregnancy and neonatal amino acids and acylcarnitines**
- **Hamman Syndrome in Diabetic Ketoacidosis: Exploring a Rare and Potentially Fatal Complication**

Should you require any specific article or medical information, please feel free to contact us at medicalservices@microlabs.in

Looking forward to your valuable feedback

Best Regards,

Medical Team, Micro Labs Limited

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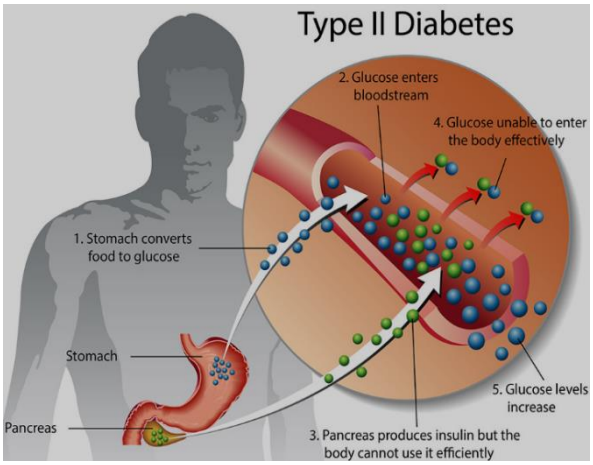
Effects of close and intensive monitoring of different glycemic trajectories on Diabetes Management in Poorly Controlled Type 2 Diabetes

INTRODUCTION



TYPE 2 DIABETES MELLITUS

By evaluating the patient's glycemic background, it may be possible to enhance the management of poorly controlled diabetes by comprehending the difficulties in reaching glycemic objectives.

The prevalence of diabetes mellitus is rising worldwide, with projections estimating that over 643 million individuals will be affected by 2030.[1] Maintaining glycemic control is a crucial therapeutic objective to prevent organ damage and other complications associated with diabetes.[2] Despite significant advancements in diabetes management over recent decades—including the introduction of new medications, dietary and exercise recommendations for blood glucose regulation, and innovative technologies—less than 50% of individuals with type 2 diabetes achieve the target glycated hemoglobin (HbA1c) level of <7%. Several factors contribute to this challenge, such as difficulties with medication adherence and persistence, reluctance or resistance from both patients and physicians to initiate or sustain changes, negative perceptions of lifestyle modifications (e.g., feeling restricted by dietary changes), a tendency to revert to unhealthy habits, sleep disturbances, financial barriers impacting access to healthy food and medications, and the psychological burden of managing the disease.[1] This study was to assess the impact of intensive and supportive glycemic management approaches over a 12-month period in individuals with type 2 diabetes mellitus (T2DM) whose HbA1c level ≥10% and diverse glycemic control histories.

METHODS

This prospective observational study examined glycemic control over 12 months in patients with poorly managed T2DM. Eligible participants were adults aged 18 years or older with a confirmed diagnosis of T2DM and an HbA1c level of ≥10%. They were divided into four groups based on their prior glycemic history: newly diagnosed, previously well-controlled but

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recently deteriorating, consistently off-target with worsening control, and those with persistently high HbA1c levels above 10%. HbA1c levels were assessed quarterly, and participants received tailored medical, educational, and dietary support. The study analyzed the success rates of achieving good glycemic control and the contributing factors within each group.

RESULTS

There were significant reductions in HbA1c levels across all participants. The greatest improvement was observed in individuals newly diagnosed with diabetes, with 65% achieving an HbA1c target of ≤7%. Outcomes differed among groups with varying glycemic histories, showing progressively lower success rates: 39% in those previously well-controlled, 21% in participants with worsening control compared to their earlier state, and only 10% in those with persistently poor glycemic management. The average HbA1c levels for these groups were 6.3%, 7.7%, 8.2%, and 9.7%, respectively. After one year, HbA1c levels of ≤7% were achieved by 65.2% of newly diagnosed patients, 39.3% of the previously controlled group, 21.9% of the deteriorated control group, and 10% of those consistently poorly controlled (Figure 1).

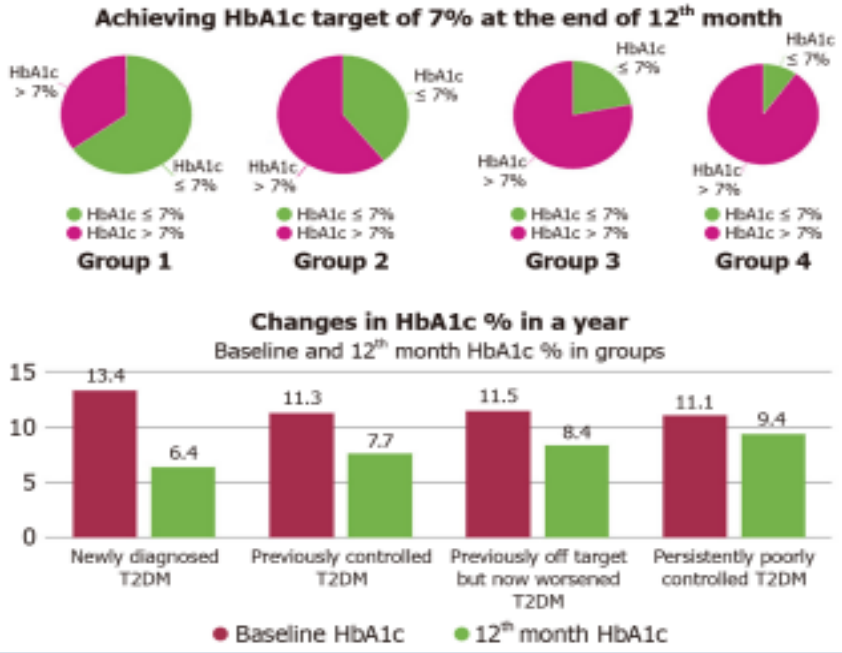

Fig 1. Association of the glycaemic background patterns and diabetes management efficacy in poorly controlled type 2 diabetes

Group 1- Newly diagnosed T2DM

Group 2- Previously controlled T2DM

Group 3- Previously off target bot now worsened

Group 4- Persistently poorly controlled

DISCUSSION

This study stands out from others by including patients with varying glycemic histories and poorly controlled diabetes. Newly diagnosed individuals with type 2 diabetes generally have a

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better chance of achieving good blood glucose control compared to those with long-established diabetes. For instance, an earlier study found that 68.5% of 5,770 newly diagnosed type 2 diabetes patients reached an HbA1c level of 7 or lower after one year.[3] In the present study, the most significant factor affecting glycemic control was the participants' baseline glycemic history. Previous studies have explored HbA1c trajectories in various ways. An LW et al. identified four distinct HbA1c patterns over two years in individuals with established type 2 diabetes, highlighting the evolving nature of glycemic control.[4]

CONCLUSION

In poorly controlled diabetes, the speed at which treatment goals are met was associated with the individual's glycemic history, underscoring the importance of personalized treatment plans. As a result, patients with chronic uncontrolled diabetes require varied and holistic treatment strategies.

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Relationship Between Morning Serum Cortisol Levels and Diurnal Time in Range in Type 2 Diabetes

INTRODUCTION

Cortisol is a steroid hormone produced by the zona fasciculata cells of the adrenal cortex. Its secretion is primarily regulated by the hypothalamic-pituitary-adrenal (HPA) axis, which follows a circadian rhythm, typically high in the morning. During stressful situations, activation of the HPA axis triggers an increase in cortisol levels. Cortisol plays a key role in glucose metabolism and maintaining glucose homeostasis through various mechanisms.

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Morning serum cortisol had a positive correlation with GV indicators and a negative correlation with TIR, particularly diurnal TIR.

Continuous glucose monitoring (CGM) is increasingly used in clinical settings. While HbA1c remains the gold standard for assessing long-term glycemic control over the past 2 to 3 months, it has limitations, such as measurement inaccuracies and insufficient reflection of glycemic variability. Time in range (TIR) refers to the percentage of time blood glucose levels remain within the target range of 3.9–10 mmol/L throughout the day, while the recently introduced time in tight range (TITR) further narrows the target range to 3.9–7.8 mmol/L.[1] Based on various clinical studies, the American Diabetes Association (ADA) has recommended TIR as one of the key indicators for assessing blood glucose control.[2] This study aimed to explore the relationship between morning serum cortisol levels and CGM parameters, particularly TIR and diurnal TIR, in individuals with T2DM.

METHODS

A total of 310 patients with T2DM were included in this retrospective observational study. Eligible participants were adults over 18 years old who had maintained a stable glucose-lowering regimen for the past three months. Serum cortisol levels were measured at 8 a.m. for all participants. Each participant underwent CGM for three consecutive days, after which TIR and glycemic variability (GV) parameters were assessed. Additionally, a 100g standard steamed bread meal test was conducted to collect blood glucose, C-peptide, and insulin levels at various time points, which were used to evaluate insulin sensitivity and pancreatic function.

RESULTS

Patients with higher cortisol levels showed lower TIR, TITR, and daytime TIR, while parameters such as Time Above Range (TAR), HbA1c, and GV markers, including Mean Blood Glucose (MBG), Largest amplitude of glucose excursions (LAGE), Average Daily Risk Range (ADDR), and High Blood Glucose Index (HBGI), tended to be higher. A negative correlation was found between cortisol and TIR, TITR ($r=-0.241$, -0.218, $P<0.001$), as well as with Low Blood Glucose Index (LBGI) ($r=-0.129$, $P=0.033$). The negative correlation between cortisol and daytime TIR ($r=-0.231$, $P<0.001$) was stronger than that with overnight TIR ($r=-0.134$, $P=0.028$). Additionally, cortisol was negatively correlated with indicators of pancreatic β-cell function, such as homeostasis model assessment of β-cell function (HOMA-β), Insulinogenic Index (IGI), area under the curve of C-peptide at 30 minutes (AUCCp0.5 h), and area under the curve of C-peptide at 3 hours (AUCCp3h) ($r=-0.248$, -0.176, -0.140, -0.185, respectively, $P<0.05$). In contrast, cortisol was positively correlated with TAR ($r=0.217$, $P<0.001$), Time Below

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Range (TBR) (r=0.01, P=0.865), HbA1c (r=0.210, P<0.001), and GV parameters such as MBG, mean amplitude of glucose excursion (MAGE), largest amplitude of glucose excursion (LAGE), HBGI, mean of daily differences (MODD), and ADDR (P values for MAGE and MODD >0.05). Furthermore, cortisol levels at 8 a.m. were identified as an independent factor influencing TIR (ß = -0.042, P=0.019), TITR (ß = -0.036, P=0.033), and daytime TIR (ß = -0.047, P=0.015), with daytime TIR showing the strongest correlation (Table 1).

Table 1. Multiple stepwise regression analysis of influencing factors of TIR, TITR and diurnal TIR

	β	P	95%Cl
Dependent Variable: TIR (R2=0.244)			
(Constant)	130.658	<0.001	94.745 to 166.571
Cortisol	-0.042	0.019	-0.076 to -0.007
Duration	-0.577	0.027	-1.089 to –0.066
HbA1c	-3.633	<0.001	-5.139 to -2.127
Creatinine	-0.127	0.022	-0.864 to -0.085
Dependent Variable: TITR (R2=0.137)			
(Constant)	76.748	<0.001	62.463 to 91.034
HbA1c	-3.710	<0.001	-5.129 to -2.290
Creatinine	-0.074	0.016	-0.134 to -0.014
Cortisol	-0.036	0.033	-0.069 to -0.003
Dependent Variable: Diurnal TIR (R2=0.218)			
(Constant)	119.070	<0.001	103.217 to 134.934
HbA1c	-4.240	<0.001	-5.801 to -2.679
Creatinine	-0.109	0.002	-0.176 to -0.041
Cortisol	-0.047	0.015	-0.085 to -0.009
TG	-1.057	0.021	-1.965 to -0.159
Duration	-0.495	0.035	-0.956 to -0.035

Abbreviation: Cp: C-peptide, Glu: postprandial glucose, TIR: time in range, TITR: time in tight range, SBP: systolic blood pressure

DISCUSSION

In this study, CGM was used to investigate the association between cortisol levels and GV parameters. As a newly recognized indicator, TIR offers a comprehensive, continuous, and reliable assessment of short-term blood glucose fluctuations. Additionally, TIR can be used to predict diabetic complications and assess clinical outcomes in the long term.[3] Additionally, TIR is strongly associated with HbA1c, and both are currently recommended as key indicators for evaluating individual glycemic control.[4] A stronger negative correlation was observed between cortisol and TIR compared to the current gold standard, HbA1c. Unlike previous studies that relied on fasting plasma glucose (FPG) and blood glucose at various time points as indicators, GV parameters derived from CGM provided a more comprehensive and detailed analysis. The findings indicated that higher cortisol levels were associated with lower LBGI, and higher TAR, TBR, HbA1c, and other GV parameters such as TAR, MBG, HBGI and LAGE. These results suggest that cortisol is a negative factor affecting glucose stability, contributing new compelling evidence to this ongoing issue.[5]

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CONCLUSION

Morning serum cortisol levels are negatively correlated with TIR, particularly diurnal TIR, and positively linked to GV parameters. Abnormal cortisol secretion may negatively impact glucose homeostasis in T2DM.

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Association between maternal blood glucose patterns throughout pregnancy and neonatal amino acids and acylcarnitines

INTRODUCTION

Maternal glucose trajectories during pregnancy were significantly correlated with the urea cycle pathway, fatty acid oxidation pathway, and neonatal arginine and proline metabolism.

Gestational hyperglycemia, including gestational diabetes mellitus (GDM), type 1 diabetes mellitus (T1DM), and type 2 diabetes mellitus (T2DM), is estimated to impact 21.1 million (16.7%) pregnancies globally.[1] Maternal hyperglycemia is a well-recognized and modifiable risk factor for both immediate and long-term health outcomes in offspring, including preterm birth, macrosomia, and adverse long-term effects such as neurodevelopmental, cardiovascular, and metabolic disorders. Recent studies have shown that maternal hyperglycemia during Pregnancy can lead to prenatal alterations in the offspring's metabolic processes, significantly impacting their long-term metabolic health and neurodevelopment. These findings emphasize the important role of maternal hyperglycemia in shaping fetal metabolism.[2] There are limited studies on the specific metabolic changes in newborns caused by hyperglycemia after the 24th to 28th week of pregnancy. To address this gap, the present study utilized a large sample size to explore the

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potential relationship between hyperglycemia patterns throughout pregnancy and neonatal amino acids (AAs) and acylcarnitines (ACs).

METHODS

This prospective cohort study, part of the Beijing Birth Cohort Study, included 11,457 pregnant women without pre-existing diabetes and their newborns, born between July 2021 and October 2022. Participants were aged 18 to 50 and between 6 and 13 weeks pregnant at recruitment. Maternal glucose patterns throughout the three trimesters were classified using a latent class model, and the study explored how these patterns related to neonatal blood metabolites, including 11 amino acids and 33 acylcarnitines, while adjusting for potential confounders.

RESULTS

The study identified three distinct maternal glucose trajectory groups: consistent normoglycemia (n = 8,648), mid-to-late gestational hyperglycemia (n = 2,540), and early-onset hyperglycemia (n = 269). Figure 1 illustrates the 11 neonatal metabolites linked to these maternal glucose patterns. Mid-to-late gestational hyperglycemia was associated with lower levels of amino acids (alanine, arginine, ornithine, and proline) involved in the arginine and proline metabolism and urea cycle, along with higher levels of C4DC+C5-OH and lower levels of C6DC and C10:1. Early-onset hyperglycemia was linked to higher levels of free acylcarnitine and

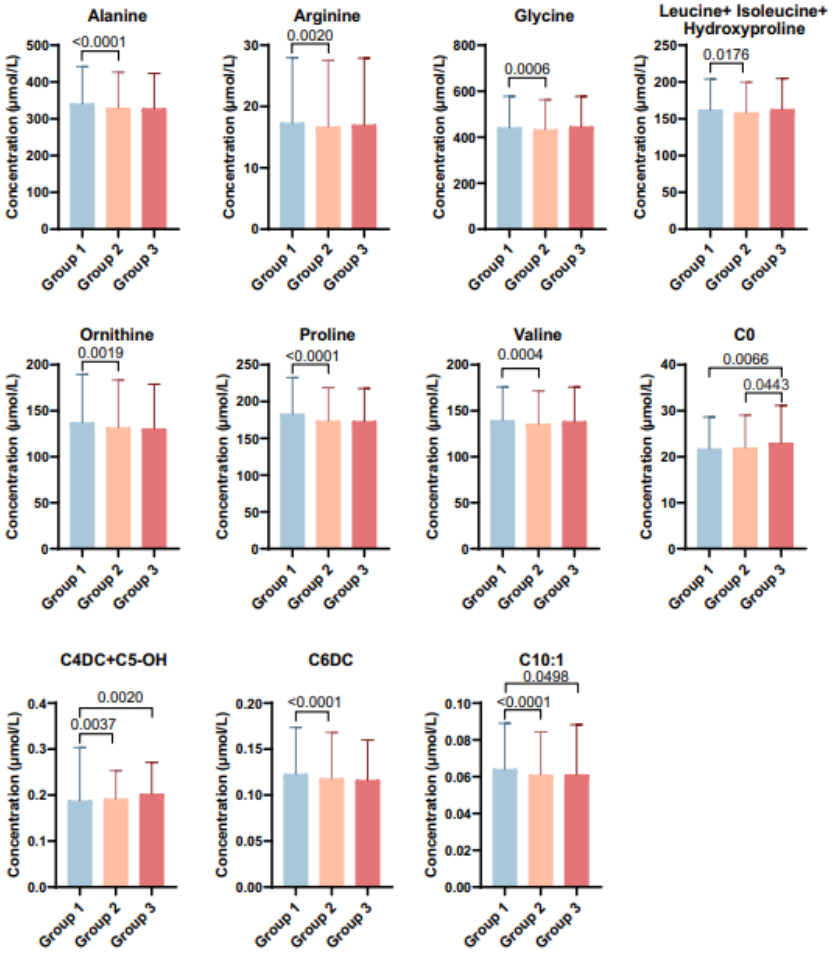

Figure 1. Differential neonatal metabolites between maternal glucose trajectory groups

C4DC+C5-OH and lower levels of C10:1. These associations were primarily observed in male neonates rather than females.

DISCUSSION

The present study found a notable relationship between maternal blood glucose levels during pregnancy and neonatal circulating metabolites, covering a broad range of AAs and ACs. Previous studies have also demonstrated a link between maternal hyperglycemia and neonatal metabolomics, particularly concerning metabolites such as AAs, lipids, and associated ACs.[3,4,5,6]

CONCLUSION

A strong association was found between maternal glucose patterns during pregnancy and neonatal metabolism of arginine, proline, the urea cycle, and fatty acid oxidation. These findings emphasize the importance of maintaining optimal blood glucose levels throughout pregnancy to support healthy metabolic outcomes in neonates.

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Hamman Syndrome in Diabetic Ketoacidosis: Exploring a Rare and Potentially Fatal Complication

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INTRODUCTION

> When a patient exhibits respiratory difficulty, chest discomfort, or evidence of air leakage into the mediastinum, Hamman syndrome should be considered in the differential diagnosis.

Spontaneous pneumomediastinum (SPM) or Hamman syndrome, is an uncommon condition marked by the presence of free air in the mediastinum, frequently associated with subcutaneous emphysema.[1] This condition usually occurs when alveolar walls rupture, causing air to leak into the mediastinal and subcutaneous tissues.[2] Although SPM is usually triggered by factors such as intense physical activity, coughing, vomiting, or other forms of respiratory strain, it remains relatively rare in clinical practice. A particularly uncommon and poorly understood situation is the occurrence of Hamman syndrome alongside diabetic ketoacidosis (DKA), a serious metabolic complication primarily seen in type 1 diabetes patients. The development of SPM in DKA is infrequent, but it is thought to arise from increased intrathoracic pressure, primarily caused by Kussmaul breathing and severe vomiting, both of which are key characteristics of DKA.[3] This study presents a case of an 18-year-old male with poorly managed type 1 diabetes who developed DKA complicated by pneumomediastinum, subcutaneous emphysema, and a small pneumothorax.

CASE PRESENTATION

An 18-year-old male with a history of type 1 diabetes, diagnosed at age eight, presented with a 48-hour history of severe vomiting, widespread abdominal pain, respiratory distress, and worsening shortness of breath. His diabetes had been poorly controlled, as reflected in a recent HbA1c of 7.4% obtained two months earlier. The patient also reported additional symptoms, such as muscle aches, headaches, and vague chest tightness that began a week before his admission. However, he had delayed seeking medical help. His history included occasional hyperglycemia and hypoglycemia, typically due to missed meals or irregular insulin dosing. His family had a history of autoimmune disorders, with his mother having hypothyroidism and his father having rheumatoid arthritis. The patient led a largely sedentary lifestyle with minimal physical activity. Upon presentation, he displayed tachypnea and signs of dehydration, such as dry mucous membranes and reduced skin turgor but was alert and oriented throughout the exam. Vital signs included a heart rate of 110 beats per minute, respiratory rate of 30 breaths per minute, blood pressure of 115/76 mmHg, and oxygen saturation of 92% on room air. His blood glucose was over 4 g/l, and his urine dipstick showed three acetone crosses. Laboratory tests confirmed DKA. Due to ongoing respiratory distress, he was admitted to the ICU, where a contrast-enhanced thoracic computed tomography (CT) scan revealed significant pneumomediastinum, subcutaneous emphysema, and a small pneumothorax, consistent with Hamman syndrome in the context of DKA (Figure 1). Treatment included intravenous insulin to control blood glucose and fluids for hydration and electrolyte balance. Given his respiratory

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difficulties and CT scan findings, oxygen supplementation at 2 L/min was provided to support oxygen levels. Close monitoring of vital signs, blood gases, and oxygen saturation was performed to guide further treatment. Over the next 24 hours, the patient's condition improved significantly, such as vomiting stopped, blood glucose levels stabilized, and respiratory symptoms resolved. He was discharged after three days in the ICU with advice on improving blood glucose monitoring. A follow-up CT scan one month later showed complete resolution of the pneumomediastinum, pneumothorax, and subcutaneous emphysema (Figure 2). To prevent recurrence of pneumomediastinum in DKA, it is crucial to treat ketoacidosis promptly with insulin, rehydration, and electrolyte correction. Reducing hyperventilation, which is often caused by acidosis, is also important, as is managing acidosis quickly and avoiding aggravating factors like stress or pain. Identifying and treating underlying causes, such as infections or missed insulin doses, are essential. Monitoring for pulmonary complications and avoiding actions that increase chest pressure, like intense coughing, is also key. Finally, educating patients on diabetes management and the importance of regular follow-ups can help prevent future episodes.

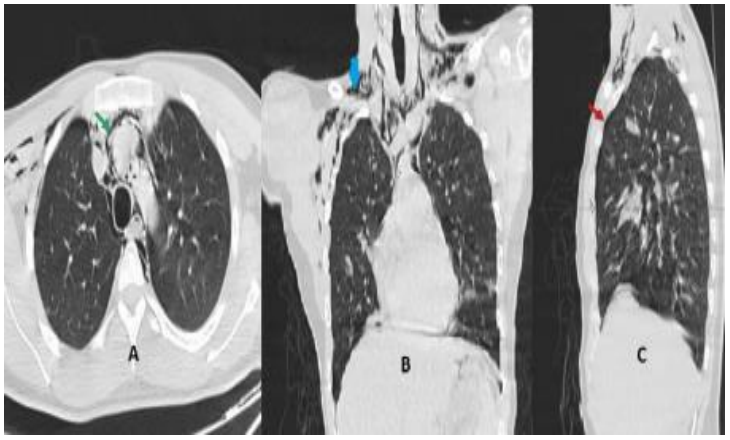

Figure 1. Thoracic CT imaging in axial (A), coronal (B), and sagittal (C) views showing pneumomediastinum (green arrow), subcutaneous emphysema (blue arrow), and minimal pneumothorax (red arrow).

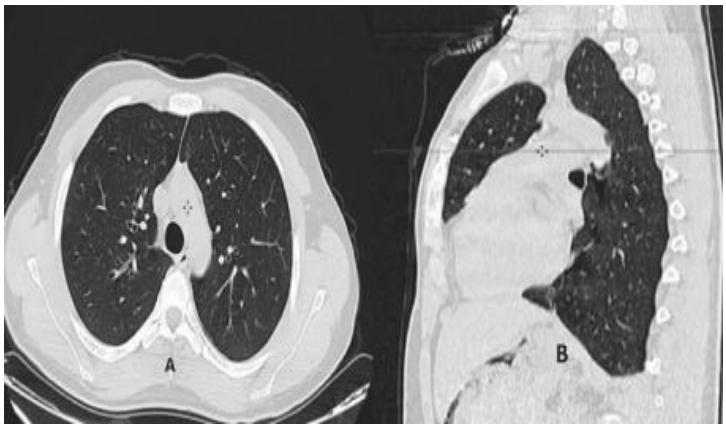

Figure 2. Follow-up Thoracic CT imaging in axial (A) and sagittal (B) views demonstrating complete resolution of pneumothorax and pneumomediastinum.

DISCUSSION

The characteristic clinical feature of pneumomediastinum is Hamman's crunch, which involves crackling or popping sounds heard at the cardiac apex. These sounds occur synchronously with cardiac contraction and are caused by the movement of air within the mediastinum.[4] Another

frequent finding is subcutaneous emphysema, especially in the neck and supraclavicular areas. In this case, the patient exhibited mild subcutaneous emphysema, which aligns with prior reports of pneumomediastinum in DKA. CT imaging remains the gold standard for diagnosing pneumomediastinum.[5] CT imaging showed pneumomediastinum, subcutaneous emphysema, and a small pneumothorax, all of which resolved on their own with conservative treatment. The self-limiting nature of pneumomediastinum in DKA underscores the significance of supportive care in managing these patients.

CONCLUSION

While Hamman syndrome is an uncommon complication of DKA, it should be included in the differential diagnosis when patients present with respiratory distress, chest pain, or symptoms suggesting air leakage into the mediastinum. Prompt identification of this rare yet serious complication can enable timely intervention and lead to positive outcomes, as most cases resolve on their own with conservative treatment.

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