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Diabetes Update

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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.

- **Correlation Between Cardiovascular Disease Prevalence, Bone Mineral Density, and Fracture Incidence in Men with Type 2 Diabetes Mellitus**
- **Examination of within-Day Glycemic Variability Throughout Hospitalization in Type 2 Diabetes Patients Using Continuous Glucose Monitoring: A Retrospective Observational Study**
- **Characterization of Clinical and Molecular Genetic Factors Contributing to Insulin Secretion Defects in Obese Children and Adolescents**
- **Case Report on Hemichorea-Hemiballismus, an Uncommon Neurological Symptom of Diabetes Mellitus in a Patient with Diabetic Striatopathy**

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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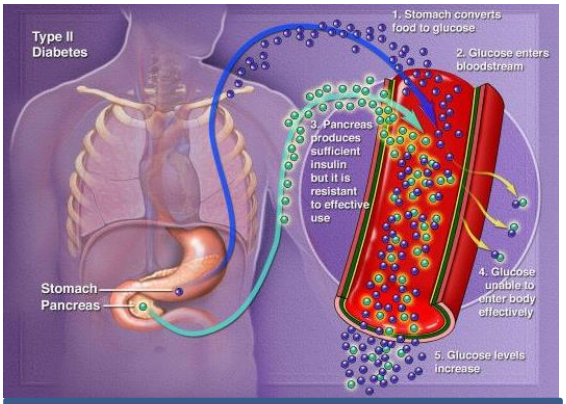
Correlation Between Cardiovascular Disease Prevalence, Bone Mineral Density, and Fracture Incidence in Men with Type 2 Diabetes Mellitus

INTRODUCTION

Osteoporosis, a metabolic disorder affecting the whole body, is marked by diminished bone mineral densities (BMDs) and the deterioration of bone microstructure, leading to heightened bone fragility and susceptibility to fractures.[1] Cardiovascular diseases (CVDs) primarily result from circulatory issues induced by atherosclerosis, encompassing conditions such as coronary heart disease, congestive heart failure, and cerebrovascular diseases. It's noteworthy that osteoporosis and CVD represent significant health challenges, significantly impacting the well-being and longevity of older individuals with type 2 diabetes mellitus (T2DM). Recent studies have highlighted an association between low BMD and fractures with CVD, indicating that individuals with decreased BMD face elevated risks of developing cardiovascular conditions.[2] Looking back at past studies, there's strong evidence suggesting a higher occurrence of osteoporosis and hip fractures among elderly men with diabetes, indicating a negative impact of diabetes on bone health in this demography.[3] Numerous comprehensive case-control studies in individuals with hip fractures have revealed a notable elevation in the risk of postoperative cardiac events among diabetic patients compared to those without diabetes, alongside an extended hospital stay of 1-4 days. This underscores the importance of further investigating the association between CVD and fractures in men with T2DM.[2] The objective of this study analysis was to investigate the correlation between BMD, fracture incidence, and the prevalence of CVD in men with T2DM.



TYPE 2 DIABETES

Men with T2DM who have a lower risk of CVD, particularly if they also have hypertension, should benefit from early management and FN-BMD monitoring.

METHODS

In this retrospective cross-sectional study, 856 men diagnosed with T2DM were included. Dual-energy X-ray absorptiometry (DEXA) was utilized to measure BMD at the lumbar spine

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(L2-4), femoral neck (FN), and total hip (TH). Basic information regarding prior fractures was recorded through questionnaires in electronic health records (EHRs). The CVD outcome was determined by the presence of various conditions, including congestive heart failure, coronary heart disease, angina pectoris, myocardial infarction, the need for coronary artery revascularization, and stroke, identified through self-reports and diagnostic records in the EHRs. The relationship between BMDs and CVD was explored using restricted cubic spline curves and logistic regression models.

RESULTS

The prevalence of diabetic peripheral neuropathy (DPN), diabetic retinopathy, previous fractures, hypertension, and the usage of antihypertensive medications were notably higher in the group with CVD compared to the non-CVD group. Conversely, BMD at the FN or TH, as well as estimated glomerular filtration rate (eGFR), were significantly lower in the CVD group than in the non-CVD group. Figure 1 illustrated the restricted cubic spline curves depicting the association between BMD (g/cm2) and CVD events. Specifically, BMDs at the FN ($p < 0.01$) and TH ($p < 0.05$) exhibited a negative correlation with CVD events. Additionally, a nonlinear relationship was observed between L2-4 BMD and CVD events (p for nonlinearity = 0.047). The unadjusted odds ratios (ORs) for CVD events per 1-standard deviation decrease in BMDs at L2-4, FN, and TH were 1.22, 1.22 and 1.13 respectively (model 1). After comprehensive adjustments for confounding variables, the ORs for each 1-standard deviation decrease in BMD at L2-4, FN, and TH were 1.34, 1.30 and 1.26 respectively (model 3). Notably, T-scores of < 1 for L2-4 ($p < 0.05$) and FN ($p < 0.05$), but not for TH ($p = 0.384$), were independently associated with CVD events, even after adjusting for age and other clinical risk factors. A clinical diagnosis of osteopenia/osteoporosis based on the combined T-score was also independently linked to CVD events. Individuals with previous fractures had a higher likelihood of developing CVD events compared to those without. Furthermore, a 1-standard deviation decrease in BMDs at L2-4, FN, and TH was associated with a

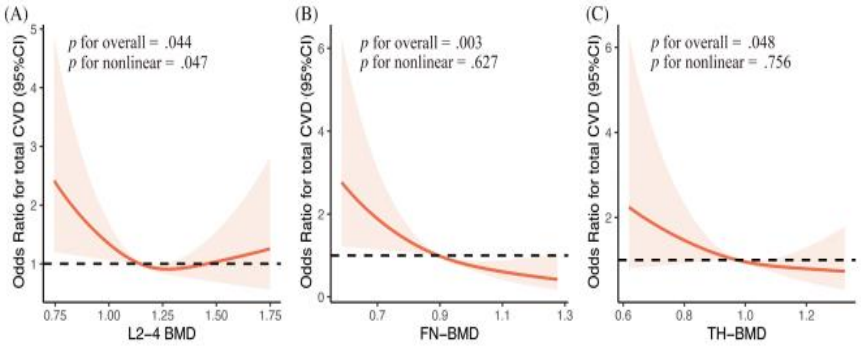

Figure 1. Restricted cubic spline of the relationship between BMD and events related to CVD in males with type 2 diabetes. OR = 1 was shown by the grey line. The OR value was given by the red line. (A) The prevalence of CVD in males and the L2-4 BMD RCS curve (g/cm2). (B) Men's CVD prevalence and the FN-BMD RCS curve (g/cm2). (C) Men's CVD prevalence and the TH-BMD RCS curve (g/cm2). BMD-bone mineral density; CVD- cardiovascular disease; FN-femoral neck; OR-odds ratio; RCS-restricted cubic spline; TH-total hip.

higher risk for CVD events across almost all subgroups. Specifically, the decrease in BMD at L2-4 emerged as an independent risk factor for CVD events in nearly all subgroups. Conversely, FN-BMD decrease served as an independent risk factor for CVD events. Notably, there was a significant interaction observed in the associations between FN-BMD and CVD in the subgroup analyses of hypertension. Specifically, for every 1-standard deviation reduction in FN-BMD, the risk of CVD events in the hypertension subgroup increased by 55%.

DISCUSSION

The findings of this study highlight a significant association between decreased BMD and CVD events. Recent research suggested that BMD could serve as a valuable tool in assessing the risk of CVD. For example, a prospective cohort study conducted in Korea revealed that low BMD was linked to a heightened risk of major adverse cardiovascular events in individuals with predialysis chronic kidney disease.[4] Similarly, an investigation involving a biracial cohort revealed a notable correlation between volumetric BMD at the spine and the risk of CVD in white men.[5] This study stood out for investigating the relationship between BMD and the risk of CVD events in men, particularly those with T2DM. In contrast to previous research focusing on older women, recent studies have indicated that the impact of diabetes on the incidence of both clinical fractures and hip fractures in older men was comparable to that observed in older women. Additionally, a significant portion of this risk was attributed to diabetes-related comorbidities.[6]

CONCLUSION

In men with T2DM, there was an inverse relationship observed between BMD levels, particularly at femoral neck (FN), and the prevalence of CVD. Furthermore, prior fracture history was independently linked to a heightened risk of CVD. The study postulated that monitoring FN-BMD and implementing early intervention strategies could aid in mitigating the risk of CVD in men with T2DM, particularly those with hypertension.

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Examination of within-Day Glycemic Variability Throughout Hospitalization in Type 2 Diabetes Patients Using Continuous Glucose Monitoring: A Retrospective Observational Study

INTRODUCTION

The likelihood of recurrent within-day GV may be reduced by using drugs designed for decreasing postprandial blood glucose.

Glycated hemoglobin (HbA1c) has long been considered a conventional indicator of glycemic control in individuals with type 2 diabetes (T2D). However, as it reflects average blood glucose levels over the preceding 2–3 months, it does not capture daily acute fluctuations. These fluctuations, known as glycemic variability (GV), can persist even when patients with T2D achieve their target HbA1c levels.[1] In a hospital setting, implementing rigorous glycemic control measures helps to mitigate the risks of hyperglycemia-related complications in patients with uncontrolled T2D.[2] Nevertheless, rapid decreases in overall blood glucose levels may elevate within-day GV, potentially increasing the risk of hypoglycemia. Therefore, it was essential to monitor within-day GV, encompassing both amplitude and frequency, in hospitalized patients with T2D. Multiple studies have demonstrated that heightened GV was independently linked to prolonged hospital stays and increased short-term and long-term mortality rates among diabetic patients, whether critically ill or non-critically ill. Hence, adopting a dual assessment approach focusing on both the amplitude and temporal stability of within-day GV was vital for managing hospitalized T2D patients.[1] The objective of the study was to evaluate the magnitude and occurrence of within-day GV in hospitalized individuals with type 2 diabetes, as well as to investigate the factors that influence within-day GV.

METHODS

A retrospective observational study was conducted at a single center, focusing on patients with T2D admitted due to poor glycemic control. Hospital records and 10-day real-time continuous glucose monitoring (rtCGM) data were analyzed to investigate within-day GV. Eligible

participants were adult patients (aged ≥18 years) with T2D who underwent rtCGM for more than 10 days. The study cohort comprised 1050 individuals, divided into two cohorts: 358 patients in Cohort 1 and 692 in Cohort 2. The primary outcome measured the amplitude and frequency of within-day GV in hospitalized patients with T2D. Secondary objectives included identifying factors associated with within-day GV. Within-day GV was assessed using the coefficient of variation (%CV). Antidiabetic medications administered during hospitalization were categorized into different classes. The frequency of within-day GV was evaluated based on consecutive days (CD) within the target %CV range after first reaching it (CD after first reaching the target) and the maximum consecutive days of maintaining within the target %CV range (Max-CD). The target %CV range aimed to be less than 24.4%. Factors influencing within-day GV were analyzed using COX regression and Poisson regression models.

RESULTS

Cohort 1 exhibited higher median HbA1c values at 8.5% (69.4 mmol/mol), with the most prevalent comorbidities being diabetic polyneuropathy (48.3%), hypertension (42.7%), and chronic kidney disease (32.6%). Among the antidiabetic medications used, insulin (58.1%), α-glucosidase inhibitors (31.4%), and TZDs (21.1%) were the most frequently prescribed. Over the span of 10 days, there was a significant decrease observed in the median fasting plasma glucose (FPG) from 8.7 mmol/L to 7.4 mmol/L ($p<0.01$), as well as in the median postprandial glucose excursion (PPGE) from 4.7 mmol/L (3.6 mmol/L, 6.6 mmol/L) to 3.15 mmol/L (1.9 mmol/L, 4.5 mmol/L) ($p<0.01$) among all participants (Fig. 1). Nearly all patients (94.8%) reached the target %CV range for the first time within 10 days, with 86.5% achieving it by day 6. The cumulative incidence of first reaching the target %CV range was notably higher in Cohort 1 compared to Cohort 2 ($P<0.01$). On average, patients remained hospitalized for 7 days after first reaching the target %CV range, with 63.9% experiencing a maximum consecutive day within this range equal to or less than half of their remaining hospitalization days. Regarding within-day GV, 67.3% of patients in Cohort 1 had a standard deviation (SD) of %CV ranging between 0.05 and 0.1, while 82.1% of patients in Cohort 2 exhibited an SD of %CV within the range of 0.05 to 0.15. Male patients were found to be less likely to achieve the target %CV range for the first time compared to female patients (HR: 0.86, 95% CI: 0.75–0.98, $P<0.05$). Furthermore, the likelihood of reaching the target %CV range for the first time decreased with advancing age, while individuals with higher HbA1c levels had a higher probability of achieving this target. Conversely, the usage of certain antidiabetic medications such as glinide, insulin, sulfonylurea, and TZDs reduced the likelihood of reaching the target %CV range for the first time. Additionally, an increasing mean postprandial glucose excursion (PPGE) value was associated with a decreased likelihood of reaching the target %CV range for the first time. From the Poisson regression analysis, it was observed that higher HbA1c values, use of glinide, insulin, α-glucosidase inhibitors, and GLP-1 agonists, along with mean FPG and PPGE values, were principal factors affecting the maximum consecutive days within the target

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%CV range (Max-CD). Patients with higher HbA1c values were more likely to have an increased Max-CD, while the use of α-glucosidase inhibitors and GLP-1 agonists contributed to an increase in Max-CD. Conversely, the administration of glinide and insulin, along with an increase in average FPG and PPGE values, may contribute to a decrease in Max-CD.

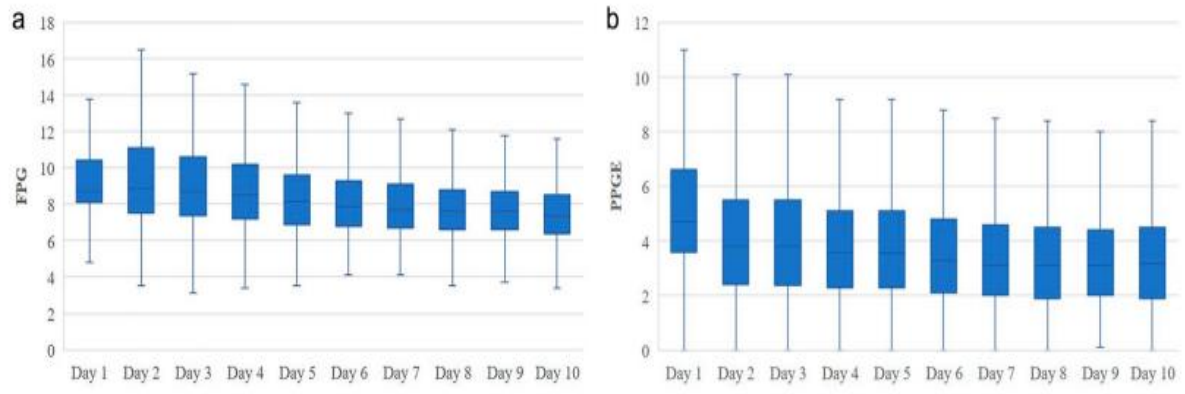

Figure 1. The FPG and PPGE within-day values vary during the course of time following hospital admission. The hospitalisation day was shown by the x-axis, while the FPG or PPGE values were indicated by the y-axis. Using the FPG or PPGE readings of every patient, boxplots were created on each day of hospitalisation.

DISCUSSION

This study identified a significant correlation between the stability of within-day GV and factors such as the use of antidiabetic medications, PPGE, and HbA1c values. The data from this study indicate that elevated postprandial glucose spikes were associated with increased within-day GV. Consistent with the findings of Monnier et al.[3] and Candido et al.[4], half of the total within-day GV was attributed to postprandial glucose spikes. These findings suggest that PPGE plays a crucial role in the complex interplay between within-day GV and factors such as HbA1c. Furthermore, the data from this study suggested that patients with higher HbA1c values may contribute to the stabilization of within-day GV. This was supported by findings from an observational study, which suggests that the proportion of PPGE to total glucose diminishes as HbA1c levels rise.[5]

CONCLUSION

The findings emphasize the volatility of glycemic fluctuations among hospitalized patients with T2D and reveal a discrepancy between glycemic stability and control in clinical settings. While our results underscore the importance for healthcare providers to prioritize within-day glycemic variability in future practices, they also call for further investigations conducted

within a structured data collection framework to mitigate measurement biases. This study observation also supports a cautious approach to understanding the relationship between anti-glycemic medications, postprandial glucose surges, and within-day glycemic variability instability. This underscores the necessity of developing improved glycemic management strategies.

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Characterization of Clinical and Molecular Genetic Factors Contributing to Insulin Secretion Defects in Obese Children and Adolescents

INTRODUCTION

Enabling customised diabetes treatment and identifying family members who are at risk can be made feasible by a successful molecular genetic diagnosis, which is critical for affected individuals and their families.

Obesity often leads to secondary conditions within the realm of metabolic syndrome, including high blood pressure, abnormal lipid levels, and compromised glucose control.[1] Diabetes mellitus manifests through deficiencies in insulin secretion and/or insulin action, encompassing diverse types with unique pathogenic mechanisms and clinical manifestations. Alongside type 1 diabetes, the significance of type 2 diabetes (T2D) was escalating within high-risk populations due to the rising prevalence of obesity. Monogenic diabetes forms contribute to approximately 1-4% of diabetes cases in youth. "Maturity Onset Diabetes of the Young" (MODY) denotes a cluster of monogenic diabetes types inherited

dominantly, typically emerging in childhood, adolescence, or young adulthood (often before 25 years). Fourteen MODY variants exist, stemming from mutations in genes pivotal to pancreatic beta-cell development or function. Genetic influences, especially related to beta-cell function, were substantial. Individuals with MODY or T2D in their youth frequently exhibit a familial history of diabetes.[2] The objective of this study was to evaluate the occurrence of impaired glucose regulation and type 2 diabetes among a substantial group of overweight children and adolescents. Additionally, the research aimed to analyze insulin sensitivity and secretion patterns using data from oral glucose tolerance tests (OGTT). Furthermore, the study examined a pilot subset displaying indications of insulin secretion irregularities and screened for uncommon, harmful mutations associated with insulin secretion, such as monogenic diabetes forms (MODY).

METHODS

This study enrolled 903 children and adolescents who regularly visited the obesity outpatient clinic from January 2010 to March 2015. Participants, aged 2 to 19 years, had a body mass index (BMI) exceeding the 90th percentile. The research involved individuals with obesity who underwent an OGTT at the clinic, assessing both glucose and insulin levels. Various metrics, including the Matsuda index, area under the curve (AUC) for insulin and glucose (AUC (Ins/Glu)), and oral disposition index (ISSI-2), were computed to gauge insulin resistance and beta-cell function. The investigation identified subjects with impaired glucose regulation (IGR) and diminished insulin secretion (maximum insulin during OGTT <200 mU/l), subsequently examining a subset through next-generation sequencing to identify potential mutations in 103 candidate genes.

RESULTS

Impaired glucose regulation, encompassing impaired glucose tolerance (IGT), impaired fasting glycemia (IFG), and T2D, affected 12.7% of all patients. Specifically, 9.4% presented with IGT, 1.2% with T2D, and 4.5% with IFG. Additionally, 1.7% displayed a combination of IFG and IGT, while 0.8% had both IFG and T2D. Insulin resistance was evident in 72.3% of the cohort, with a direct correlation observed between insulin resistance and higher weight categories. Among 12 patients, heterozygous mutations of known diabetes genes or genes associated with pancreas development were detected in 5 cases. Figure 1 depicted insulin sensitivity (Matsuda index) plotted against insulin secretion (Total AUC (Ins/Glu)), with their product known as the disposition index (ISSI-2I), demonstrating a hyperbolic correlation. In individuals with normal glucose tolerance, heightened insulin resistance corresponds to increased insulin secretion, with a median disposition index of 2.07 (1.74-2.50). However, in patients with IGT and T2D, increased insulin resistance was not adequately compensated by heightened insulin secretion, indicating relative insulin deficiency. ISSI-2 significantly

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decreased (p <0.001) in these groups, with a median ISSI-2 of 1.30 (1.00-1.66) in the IGT group and 0.60 (0.44-0.86) in patients with T2D. Among 39 patients with low insulin secretion, genetic testing identified five monogenetic defects, including ABCC8 (n = 3), GCK (n = 1), and GLI2/PTF1A (n = 1).

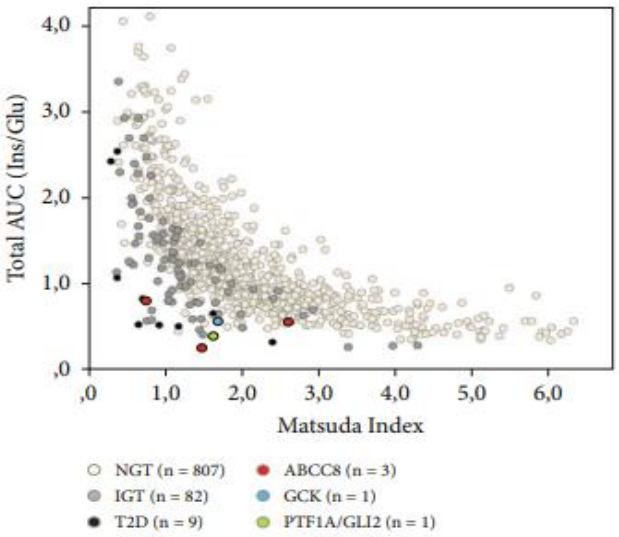

Figure 1. Insulin sensitivity (measured by Total AUC (Ins/Glu)) and insulin secretion (measured by Matsuda index) have a hyperbolic relationship.

DISCUSSION

In this initial investigation, 12 out of 39 patients underwent screening for rare, harmful mutations associated with insulin secretion through targeted enrichment of multiple genomic regions. Among these, monogenic defects were identified in 5 patients, accounting for 41.7% of the screened subset. Extrapolating this finding to a broader cohort of children and adolescents suspected of having insulin secretion disorders suggested that approximately 16 individuals within this group could be affected. When considering the entire cohort, this implies a proportion of at least 16 out of 903 patients (1.7%) with monogenic forms of diabetes. Notably, to date, no study with a similar cohort size and focus on testing for monogenic diabetes forms has been published. In contrast, in the ethnically diverse TODAY cohort comprising 488 children and adolescents with obesity and T2D, screening for monogenic diabetes forms revealed positive results in 4.5% of the total cohort. Pathogenic mutations predominantly affected classic MODY genes such as GCK, HNF4A, and HNF1A.[3] In another study, individuals diagnosed with early-onset type 2 diabetes underwent examination for mutations in the HNF1A, HNF4A, and GCK genes, resulting in a diagnosis of monogenic diabetes in 4% of cases.[4]

CONCLUSION

In this study involving obese children and adolescents, a notable segment showed impaired glucose regulation as part of the metabolic syndrome. Conducting an OGTT allows for the assessment of an oral disposition index. A diminished disposition index might suggest beta-cell dysfunction in response to insulin resistance or the existence of a genetic condition influencing insulin secretion, potentially linked to variations in genes associated with monogenic diabetes. Achieving an accurate molecular genetic diagnosis holds critical

significance for both affected individuals and their families, as it facilitates personalized diabetes treatment and the identification of family members at risk.

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Case Report on Hemichorea-Hemiballismus, an Uncommon Neurological Symptom of Diabetes Mellitus in a Patient with Diabetic Striatopathy

INTRODUCTION

The quality of life can be significantly improved by treating and diagnosing DS as soon as possible.

Diabetic striatopathy (DS) stands as an uncommon neurological complication arising from diabetes mellitus (DM), posing an engaging clinical conundrum. Manifesting as involuntary limb movements, this condition has received limited attention within medical literature. With a prevalence estimated at 1 in 100,000, its actual occurrence might be higher owing to potential underdiagnosis.[1] A systematic review revealed that the majority of reported cases were documented in Asia. Conversely, another study indicated that DS was frequently overlooked in Western populations. Typically manifesting in older individuals, DS exhibits a higher prevalence among females and may either resolve within days following treatment of underlying hyperglycemia or persist for years. Recognizing DS was crucial as it signifies a distinctive expression of diabetes-related neurological impairment.[2] In this case study, they outlined the clinical information of a patient with DS, a condition that was frequently missed or incorrectly diagnosed.

CASE PRESENTATION

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A 55-year-old woman presented with involuntary movements affecting her left upper and lower limbs over a two-week period. She reported no weakness or tingling sensations between episodes. Her medical history included 15 years of diabetes managed with Gliclazide and metformin, as well as previous mechanical mitral and tricuspid valve repairs in 2010, requiring daily warfarin. Recent echocardiography revealed a reduced ejection fraction and left ventricle dilation. On examination, she had a Glasgow Coma Scale score of 15/15, normal vital signs, clear lungs, and a soft abdomen. Non-contrast CT brain imaging showed hyperdensities in the right caudate nucleus, lentiform nucleus, and globus pallidus (Fig 1). Her random blood sugar was elevated, and her INR was within therapeutic range. Full blood count, liver, and renal function tests were normal.

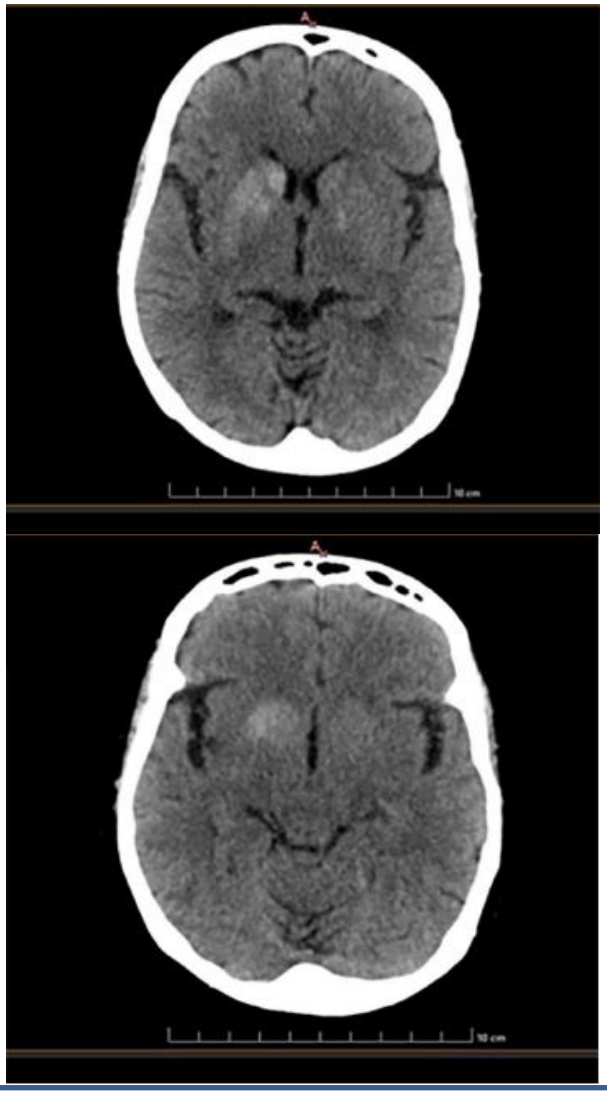

Figure 1. A non-contrast computed tomography scan of the brain showed hyperdensity in the lentiform, globus pallidus, and caudate nuclei on the right side.

DISCUSSION

Chorea and ballism primarily result from dysfunction within the basal ganglia and subthalamus.[3] Chorea involves involuntary, rhythmic, purposeless, jerky movements affecting the distal limbs, whereas ballism was characterized by larger amplitude movements involving proximal muscles.[4] DS was defined by the abrupt onset of hemichorea or hemiballismus linked to hyperglycemia and abnormalities in the striatum.[5] DS typically affects elderly individuals and was more prevalent among women. While it can manifest as the initial sign of diabetes mellitus, it was commonly associated with longstanding, inadequately managed type 2 diabetes, often characterized by an average hemoglobin A1c level of 13.1%.[4]

CONCLUSION

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This case underscores the uncommon occurrence of DS, emphasizing the importance of considering it in diabetic patients exhibiting movement disorders. It also highlighted the risk of misdiagnosing DS as an intracerebral hemorrhage (ICH) in individuals receiving long-term anticoagulation, potentially resulting in delays in proper treatment and premature discontinuation of anticoagulant therapy. Timely identification and management of DS can greatly enhance the patient's quality of life.

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