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Diabetes Update

Vol. 5 | Issue 46| 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.

- **Analysis of the association between pancreatitis and new onset diabetes using real-world data**
- **Investigation of the factors that impact type 2 diabetes mellitus complicated with diabetic nephropathy followed by the development of a predictive model**
- **Correlation between triglyceride glucose index and all-cause mortality among individuals with cerebrovascular disease**
- **Panniculitis and vasculitis that resembling an unresolved diabetic foot ulcer**

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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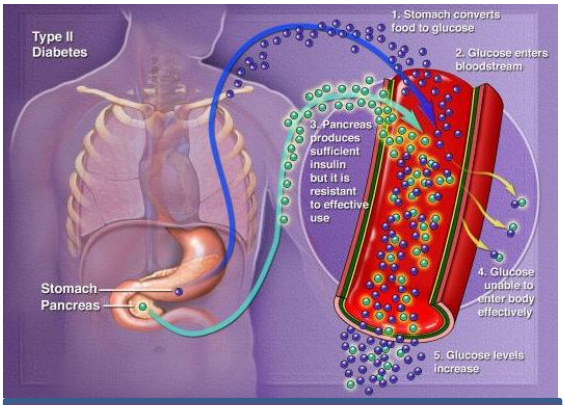
Analysis of the association between pancreatitis and new onset diabetes using real-world data

INTRODUCTION



TYPE 2 DIABETES

Diabetes has been associated with pancreatitis, irrespective of lifestyle, demography, or other medical disorders.

Pancreatic conditions like acute and chronic pancreatitis present significant medical challenges, and their association with diabetes risk remains unclear.[1] Globally, Diabetes mellitus (DM) led to around 1.6 million fatalities and the loss of 57 million years of healthy life in 2016. There is growing acknowledgment of the diverse origins of DM, notably with up to 83% of cases arising as a secondary outcome of pancreatitis.[2] It is probable that the most frequent complication following acute or chronic pancreatitis (AP or CP) occurs in around 23% to 40% of cases. Although elevated blood sugar levels are common in AP or CP patients, the progression and prognosis of diabetes development post-diagnosis are not well-documented. Furthermore, the impact of traditional diabetes risk factors such as obesity, prediabetes, family history, age, gestational diabetes history, non-alcoholic fatty liver disease (NAFLD), and smoking status on diabetes development in the context of CP or AP remains largely unclear.[1] Hence, the study aimed to investigate the association between pancreatitis (both AP and CP) and the emergence of diabetes, while evaluating possible contributing factors that could influence the development of diabetes.

METHODS

A retrospective investigation involved 310,962 individuals aged 18 to 64 years. Using the IBM® MarketScan® commercial claims database from 2016 to 2019, cases of pancreatitis and diabetes, regardless of diagnostic classification, were identified using International Classification of Diseases, Tenth Revision [ICD-10] codes. Descriptive analyses were conducted across three clinical categories (non-pancreatitis (NP), acute pancreatitis (AP), and chronic pancreatitis (CP)) to outline the characteristics of the study group. The incidence of diabetes, as indicated by ICD-10 codes during the follow-up period, was the main outcome of interest. Furthermore, a stratified Cox proportional hazards regression analysis was executed

to determine hazard ratios (HRs) and their corresponding 95% confidence intervals (CIs) regarding the risk of diabetes development across the three clinical categories, with NP serving as the reference group. This analysis controlled for various factors including age, sex, geographical region, overweight or obesity status, prediabetes, family history of diabetes, personal history of gestational diabetes, non-alcoholic fatty liver disease (NAFLD), alcohol and tobacco use, as well as hypertension.

RESULTS

Compared to control subjects without pancreatitis (NP), individuals with acute pancreatitis (AP) had higher rates of alcohol use and overweight/obesity, while those with chronic pancreatitis (CP) exhibited higher rates of tobacco use, prediabetes, non-alcoholic fatty liver disease (NAFLD), and hypertension. Notably, NP individuals had the highest prevalence of a personal history of gestational diabetes. Among men, the unadjusted incidence rate of diabetes was highest in CP individuals, followed by AP and NP, while among women, rates were also higher in CP and AP groups but lower than men. In the age group 55-64 years, CP individuals had the highest unadjusted incidence rate of diabetes, followed by AP and NP. Individuals with alcohol use and AP had a higher unadjusted diabetes incidence compared to non-alcohol users, but lower than corresponding CP groups. Surprisingly, individuals with tobacco use and CP or AP had a lower unadjusted diabetes incidence compared to non-tobacco users. Similarly, overweight or obese individuals with CP had a lower unadjusted diabetes incidence compared to those not overweight or obese, suggesting a possible disconnection between weight status and diabetes in the CP group. Among those with a coexisting diagnosis of NAFLD, AP individuals had the highest unadjusted diabetes incidence. Conversely, CP individuals without NAFLD had a higher unadjusted diabetes incidence compared to those with NAFLD. The unadjusted diabetes incidence rate was higher in individuals with hypertension across all groups. Prediabetes was associated with the highest unadjusted diabetes incidence, particularly among AP individuals. Overall, the unadjusted diabetes incidence rate was highest in CP individuals, followed by AP and NP. In age and sex-stratified analyses, CP individuals had the highest risk of diabetes, followed by the AP group, compared to NP individuals (Table 1). This positive association between pancreatitis status and diabetes risk persisted for both CP and AP groups

Variable	No Pancreatitis	Acute Pancreatitis	Chronic Pancreatitis
Person-years	408,493	75,359	19,422
Diabetes cases, n	9,911	4,589	1,451
Incidence rate, 95% CI per 1000 person-years	24.3 (23.8, 24.7)	60.9 (59.2, 62.7)	74.7 (71.0, 78.7)
Model 1	(reference)	2.46 (2.38, 2.55)	2.60 (2.46, 2.75)
Model 2	(reference)	2.39 (2.30, 2.48)	2.59 (2.45, 2.74)

Table 1. Stratified Cox Hazard ratios for the onset of diabetes in the future among 310,962 individuals

compared to NP individuals.

DISCUSSION

The current study indicated that individuals with pancreatitis face more than twice the risk of developing diabetes. The results from Cho J et al. indicated that individuals with exocrine pancreatic dysfunction (EPD), even those without significant structural damage to the pancreas, were at a higher risk of developing new-onset diabetes.[2] According to the study by Zhi M et al., approximately 23% of patients discharged from the hospital after acute pancreatitis (AP) developed diabetes mellitus (DM). The incidence of DM was higher in cases of severe acute pancreatitis, alcoholic AP, and acute necrotizing pancreatitis.[3]

CONCLUSION

In summary, pancreatitis increases the likelihood of developing diabetes but necessitates enhanced monitoring. This study, utilized age- and sex-specific Cox models and accounted for various potential confounding factors, indicated that individuals with pancreatitis faced more than a two-fold risk of developing diabetes. Existing clinical guidelines established parameters for screening asymptomatic adults for diabetes or prediabetes. Given the elevated risk associated with pancreatitis, it was recommended that screening criteria for diabetes include consideration of pancreatitis. Timely and thorough screening could facilitate preventive interventions and proactive diabetes management.

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Investigation of the factors that impact type 2 diabetes mellitus complicated with diabetic nephropathy followed by the development of a predictive model

INTRODUCTION

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The most effective method for identifying T2DM patients at high risk of DN is random forest.

Diabetic nephropathy (DN) arises as a prevalent microvascular complication of diabetes, contributing significantly to morbidity and mortality among diabetic individuals. It stems from vascular irregularities associated with diabetes, elevating the risk of mortality. DN stands as a primary driver of end-stage renal disease (ESRD) globally and contributes significantly to diabetes-related morbidity and mortality.[1] Early detection, prevention, and slowing the progression of diabetic nephropathy (DN) are crucial for reducing patient mortality. However, conventional methods like random urine measurement of urinary albumin/creatinine ratio and a 24-hour urinary albumin quantification have limitations in diagnosing DN. Renal biopsy was considered the gold standard but faces challenges such as low patient acceptance and high costs. Hence, developing a diagnostic and predictive model for DN was vital in assisting diagnosis. Machine learning techniques, including logistic regression (nomogram), decision trees, and random forest models, were widely utilized in medical prediction. Each model can efficiently extract valuable information from data, but their effectiveness varies depending on the data type. Limited research has compared the predictive performance of these models for DN in patients with type 2 diabetes mellitus (T2DM).[2] Hence, this study developed a predictive model for diabetic nephropathy (DN) in T2DM patients using a nomogram, decision tree, and random forest. The study compared the predictive performance of these three models to offer insights into identifying high-risk populations in clinical settings.

METHODS

The retrospective analysis included clinical data from 210 patients diagnosed with T2DM between August 2019 and August 2022. Patients were categorized into either the DN group (with diabetic nephropathy) or the non-DN group (without diabetic nephropathy). Inclusion criteria comprised individuals aged 18 to 75 years, diagnosed with T2DM according to established criteria, and possessing complete demographic and laboratory data. Multivariate logistic regression analysis identified factors influencing DN in T2DM patients. The dataset was randomly divided into a training set (n = 147) and a test set (n = 63) using a 7:3 ratio. The training set was utilized to construct nomogram, decision tree, and random forest models, while the test set evaluated model performance through sensitivity, specificity, accuracy, recall, precision, and area under the receiver operating characteristic curve comparisons.

RESULTS

Out of 210 patients with type 2 diabetes mellitus (T2DM), 74 had diabetic nephropathy (DN), while 136 did not. Patients in the DN group exhibited higher levels of diabetes duration, fasting

blood glucose (FBG), serum creatinine (Scr), glycated hemoglobin (HbA1c), and blood urea nitrogen (BUN) compared to those in the non-DN group, along with a higher proportion having diabetic retinopathy (DR) ($P < 0.05$). Multivariate analysis indicated that diabetes duration, FBG, Scr, HbA1c, and DR were significant factors influencing DN in T2DM patients ($P < 0.05$). The results from the decision-tree prediction model of DN in T2DM patients highlighted diabetes duration as the primary influencing factor. For patients with T2DM duration ≥ 7 years, the incidence of DN was 6%. Among those with T2DM duration < 7 years, incidences of DN were 5% for those with HbA1c ≥ 7.6% and Scr ≥ 89 μmol/L, and 5% for those with HbA1c < 7.6%, FBG ≥ 7.5 mmol/L, and Scr ≥ 98 μmol/L. The constructed random forest model identified HbA1c, Scr, FBG, diabetes duration, and DR as variables affecting DN in T2DM patients (Figure 1). In the validation set, the nomogram's efficacy in predicting concurrent DN in T2DM patients was comparable to that of the random forest model, while the decision tree model's efficacy was significantly lower (all $P > 0.05$).

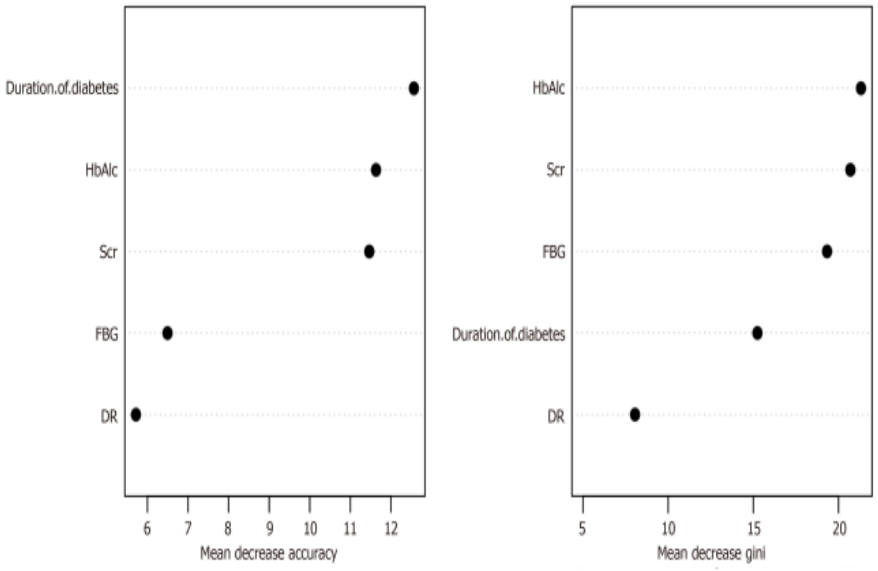

Figure 1. Diabetic nephropathy in patients with type 2 diabetes using the random forest model. FBG- fasting blood glucose; DR- diabetic retinopathy; HbAlc- glycosylated haemoglobin.

DISCUSSION

The current study's findings suggested that among the three prediction models, random forest demonstrated the most effective performance and aided in identifying high-risk patients with type 2 diabetes mellitus (T2DM) for diabetic nephropathy (DN). According to Uddin et al., the Random Forest (RF) algorithm exhibited notably higher accuracy for disease prediction compared to other methods. Out of 17 studies where RF was utilized, it achieved the highest accuracy in 9 studies, accounting for 53%. Subsequently, Support Vector Machine (SVM) ranked first in 41% of the studies where it was employed.[3]

CONCLUSION

This study developed prediction models for type 2 diabetes mellitus (T2DM) complicated by diabetic nephropathy (DN) using machine learning algorithms, including nomogram, random forest, and decision tree models. The findings indicated that the random forest model exhibited strong predictive performance and stability, offering valuable insights for identifying T2DM complicated by DN in clinical settings. Subsequent studies should validate the model using prospective multi-center data, incorporate additional variables, and expand the sample size to enhance the predictive capacity and better inform clinical practice.

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Correlation between triglyceride glucose index and all-cause mortality among individuals with cerebrovascular disease

INTRODUCTION

The results highlight the significant association between TyG and mortality rates in individuals with CVD at 28 and 90 days.

Cerebrovascular disease (CVD) refers to various conditions where brain areas are impacted by hemorrhage or ischemia due to pathological changes in cerebral blood vessels. The interruption of oxygen and nutrient supply results in rapid damage and death of brain cells. Ischemic stroke, hemorrhagic stroke, and transient ischemic attacks are typical types of cerebrovascular disease. It is more prevalent in men than women and ranks as the second leading cause of mortality and the third leading cause of disability, trailing behind heart disease.[1] Insulin resistance (IR) refers to reduced responsiveness to insulin regulation, indicating disturbances in insulin and glucose metabolism. Extensive research has highlighted a strong association between IR and the onset of cardiovascular and cerebrovascular diseases, impacting disease prognosis significantly. The triglyceride glucose (TyG) index, a marker of IR, has been associated with cardiovascular events and shows a close relationship with atherosclerosis, coronary artery disease, and ischemic stroke. However, conflicting findings exist regarding its connection with intracranial hemorrhage, cardiovascular disease, and CVD.[2] In this retrospective analysis, patient demographics, comorbidities, and experimental measures

related to cerebrovascular disease (CVD) were examined using the Medical Information Mart for Intensive Care IV (MIMIC-IV) database. The goal was to comprehensively investigate the relationship between the triglyceride glucose (TyG) index and 28- and 90-day mortality rates in individuals with CVD. The study aimed to devise novel clinical treatment approaches to enhance the prognosis of CVD patients.

METHODS

A retrospective study involving 1,965 patients was conducted, meticulously identifying individuals with cerebrovascular disease (CVD) using specific ICD-9 and ICD-10 codes. Patients aged over 18 years were included, with thorough extraction of their clinical information and a comprehensive range of laboratory parameters, including INR, glucose, triglycerides, PT, PTT, WBC count, chloride, RBC count, platelet count, heart rate, respiratory rate, SBP, and DBP. Comorbidities such as myocardial infarction, congestive heart failure, peripheral vascular disease, dementia, paraplegia, renal disease, atrial fibrillation, and diabetes were meticulously recorded. Disease severity was assessed using the SOFA score, and details of drug therapy, specifically antihyperglycemic and antihyperlipidemic drugs, were documented. A meticulous approach was employed to handle missing data in the MIMIC dataset. The primary outcome was 28-day mortality, with secondary outcomes including 90-day mortality and hospital stay duration. Patient data from the MIMIC-IV database were stratified into TyG quartiles, and survival disparities among TyG subgroups were estimated using Kaplan-Meier survival analysis. Cox proportional risk modeling was used to explore the association between the TyG index and mortality, with generalized summation models applied to fit smoothed curves. The non-linear relationship was analyzed using log-likelihood ratio tests**.**

RESULTS

The study involved 1,965 participants with an average age of 71.97 years, comprising 986 males (50.18%) and 979 females (49.82%). The TyG index, a key variable, had a median value of 8.80 (interquartile range: 8.40–9.24). Notably, there were 395 (20.10%) ICU deaths within 28 days and 481 (24.48%) ICU deaths within 90 days. Individuals with higher TyG indices tended to be younger with higher body weight, WBC, glucose, and triglyceride levels compared to those with lower TyG indices. They also had higher RBC and platelet counts, heart and respiratory rates, and SBP and DBP, but lower chloride levels. Patients with higher TyG indices experienced longer hospital and ICU stays and had a higher incidence of adverse events at both 28- and 90-day follow-ups. Additionally, they were more likely to develop diabetes and renal disease but less likely to develop dementia. They were also more likely to receive antihyperlipidemic drugs. The TyG index showed better predictive ability for 28-day mortality than triglycerides or glucose alone but performed poorly for 90-day mortality. The analysis revealed a linear association between the TyG index and mortality risk, with every 1 mg/dL increase in TyG index corresponding to a 16% increased risk of death within 28 days and an

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18% increased risk within 90 days. This association remained consistent even after adjusting for various factors. Moreover, age, sex, myocardial infarction, peripheral vascular disease, renal disease, and atrial fibrillation influenced the TyG index's association with mortality (Figure 1). Sensitivity analyses confirmed these findings even after excluding patients on antihyperglycemic and antihyperlipidemic drugs.

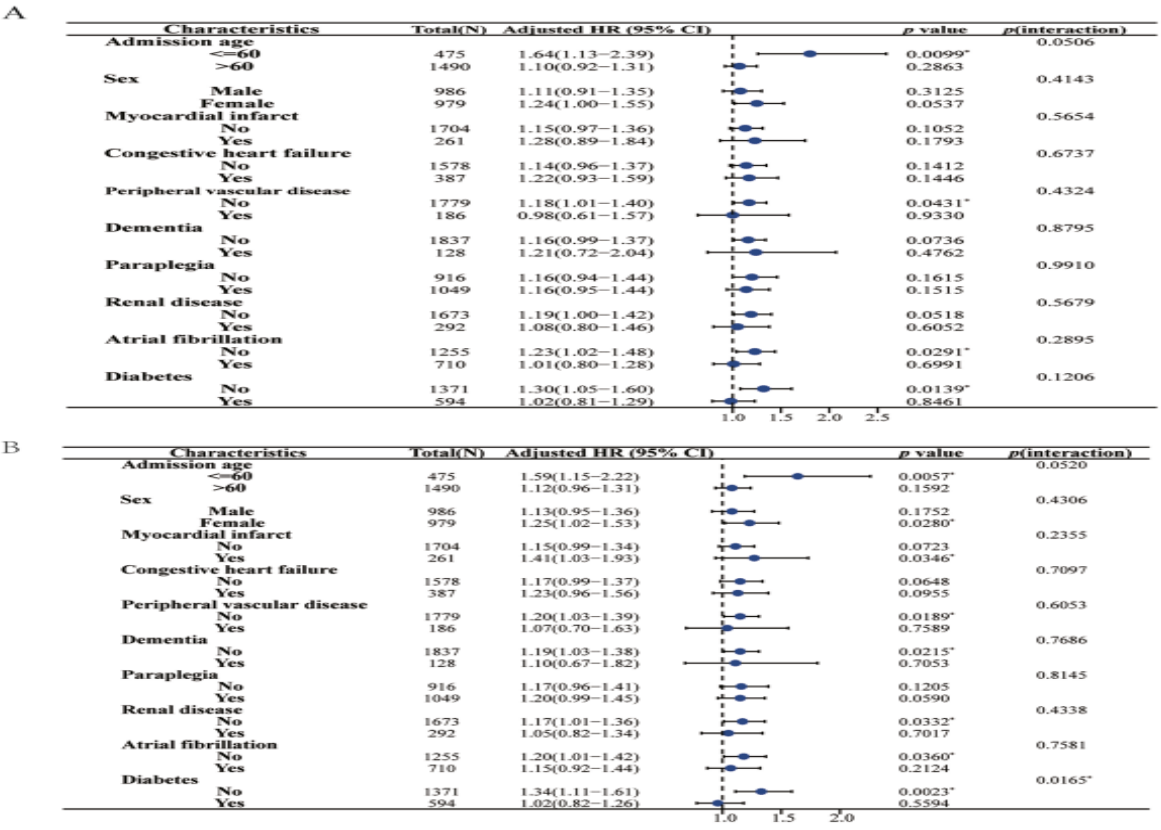

Figure 1. Subgroup examination of 28- and 90-day mortality and TyG index. Deaths after 28 days (A) and 90 days (B). HR, hazard ratio; Confidence interval (CI): 95%

DISCUSSION

This study emphasized a favorable relationship between the TyG index and mortality from cerebrovascular disease (CVD). Li S et al. found that higher TyG index values were notably linked to elevated risk of developing CVD among older individuals.[3] Yan F et al. revealed an association between the TyG index and cerebrovascular disease. However, given the constraints of the meta-analysis, further data and fundamental research were required to confirm the link between the TyG index and cerebrovascular disease.[4]

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CONCLUSION

This study underscored a positive link between the TyG index and mortality from cerebrovascular disease (CVD), particularly pronounced in patients across different age groups and those without diabetes mellitus. The TyG index has emerged as a valuable predictive tool and a reliable stratification factor for individuals with CVD. To confirm and broaden the study's findings, it was essential to conduct future prospective trials. These trials will help validate the significance of the study's findings and their practical implications.

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Panniculitis and vasculitis that resembling an unresolved diabetic foot ulcer

INTRODUCTION

For a diabetic patient with DFU who is unresponsive to traditional wound treatment, doctors must take into account factors other than macrovascular problems. Vasculitis may have a role in the development of diabetic foot ulcers in this patient in addition to macrovascular problems.

Diabetes mellitus (DM) is a long-term metabolic disorder linked to vascular issues, often resulting in peripheral arterial disease (PAD).[1] Diabetic foot ulcer (DFU) is a lasting complication of diabetes mellitus (DM). Recent research indicates that diabetic individuals have about a 25% chance of developing a foot ulcer at some point in their lives.[2] Since DFUs are considered chronic wounds, it's clear that chronic wounds include those with a slow healing process.[1] Chronic wounds remain stuck in the inflammatory phase and struggle to progress to the proliferation phase, which involves increased blood vessel formation and tissue rebuilding. The interplay among various pathways contributing to chronic wound

inflammation is not well understood, but clinically, considerations should include vasculitic and autoimmune causes as well as blood clotting disorders in patients with stubborn chronic wounds. While large-scale studies indicate that nearly 80% of leg ulcers stem from vascular issues (such as venous or peripheral arterial disease), about 20-23% of patients have wounds caused by more complex conditions like vasculitis, pyoderma gangrenosum, and other autoimmune disorders.[3] In this case report, the author presented evidence of another factor contributing to the development of DFUs in a patient with Type 2 diabetes mellitus, which was resistant to standard wound care and vascular treatments. A change in treatment approach was necessary when an autoimmune vasculitis and panniculitis process was confirmed, requiring the use of corticosteroids or immunosuppressants, despite deviating from typical diabetic wound care practices.

CASE PRESENTATION

A 54-year-old male patient was referred to the hospital due to persistent left leg pain following multiple amputation procedures performed at another healthcare facility over the past 2 months. Initially, he developed a blister-like lesion on the sole of his left foot, which worsened despite two rounds of debridement. Further evaluation revealed gangrenous lesions on other parts of the left foot. Oxygen saturation tests showed significant discrepancies between the right and left toes, indicating possible arterial blockages in the left anterior tibialis region. While infection was controlled with antibiotics, the appearance of dark spots on the foot suggested vascular rather than infective issues, possibly vasculitis. Histopathological examination confirmed vasculitis and panniculitis. Treatment initially involved steroids, but due to unpredictable blood glucose levels, the patient was switched to azathioprine. Wound care and monitoring were performed regularly, and long-term aspirin was prescribed for peripheral arterial disease (PAD). With corticosteroids and azathioprine, the patient became pain-free, and his leg wounds gradually improved with significant granulation tissue formation (Figure 1), enhancing his quality of life and allowing him to resume daily activities.

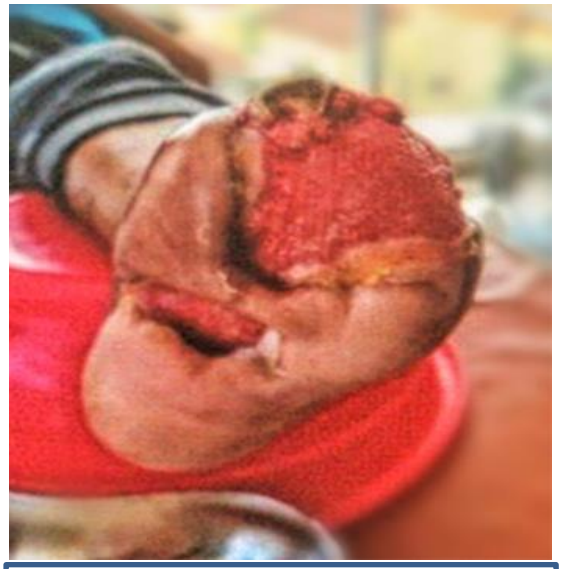

Figure 1. Wound development in the patient after corticosteroid medication and two months after amputation and debridement

DISCUSSION

The histopathological analysis in this study revealed widespread necrosis and granulation tissue in the presence of suppurative inflammation, along with vasculitis and panniculitis. These findings led to the clear diagnosis of vasculitis and panniculitis based on

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histopathological examination.[1] Vasculitis can manifest solely on the skin or indicate signs of systemic vasculitis with internal organ involvement. Damage to small skin blood vessels can lead to reduced blood flow, resulting in localized ischemia and the development of skin ulcers. These ulcers commonly appear in multiple areas and are concentrated on the lower leg and foot, where the microcirculatory structure and blood flow characteristics make them more susceptible. Around 3% to 5% of skin ulcers may be attributed to vasculitic conditions.[4]

CONCLUSION

Considering the evidence, clinicians should explore factors beyond just macrovascular issues when treating a diabetic patient with a DFU that doesn't respond to standard wound care. In such cases, it's important to also consider the possibility of vasculitis contributing to the development of diabetic foot ulcers, alongside macrovascular complications.

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