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Review Article

Hemolysis and Vaso-Occlusive Crisis in Sickle Cell Disease: A Review

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ABSTRACT

Sickle Cell Disease (SCD) is an inherited condition characterised by haemolysis and Vaso-occlusive crisis (VOC), resulting in considerable morbidity and organ impairment. These crises lead to consequences like stroke, splenic sequestration, and acute chest syndrome, significantly affecting patients quality of life. This review combines information on hemolysis and Vaso-occlusive crises in sickle cell disease, highlighting their aetiology, clinical implications, and prospective treatment approaches to alleviate disease severity.

A systematic review was performed using PRISMA principles. Relevant publications from PubMed, Google Scholar, Web of Science, Scopus, and ScienceDirect were examined, focusing on research published between 2000 and 2024. A total of 68 research articles were included. Haemolysis in sickle cell disease leads to oxidative stress, endothelial dysfunction, and an increased risk of thrombosis. Volatile organic compounds (VOCs) exacerbate these effects, resulting in persistent discomfort, multi-organ impairment, and an increased healthcare burden. Although hydroxyurea remains a fundamental treatment, novel therapies, including voxelotor, crizanlizumab, and gene therapy, exhibit potential. Moreover, antioxidant supplementation, encompassing vitamins D, A, E, and C, has shown promise in mitigating oxidative damage, but clinical results are variable.

Hemolysis and Vaso-occlusive crises are pivotal to the pathophysiology of sickle cell disease, substantially exacerbating consequences and patient distress. Progress in pharmacological and supportive therapy provides optimism for enhanced management. Further study is necessary to determine long-term effectiveness and accessibility.

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INTRODUCTION

Sickle Cell Disease (SCD) is a hereditary disorder characterised by an autosomal recessive inheritance pattern, which leads to alterations in the structure and function of the Haemoglobin (Hb) molecule. This modification converts red blood cells into a sickle or crescent morphology. Sickle cell disease is a highly prevalent genetic disorder with an autosomal recessive inheritance pattern observed globally (Figure 1).[1, 2] Vaso-occlusive crises are pivotal in the pathophysiological process characterising sickle cell disease.

Sickle cell disease (SCD) is a heterogeneous condition characterised by diverse clinical severity, predominantly shaped by genetic differences. Sickle Cell Anaemia (HbSS), the most severe kind, arises from homozygosity for the sickle haemoglobin (HbS) gene and is characterised by recurrent Vaso-occlusive crises (VOC), chronic haemolysis, and an elevated risk of stroke and organ damage.[3] Haemoglobin Sickle C Disease (HbSC), resulting from the co-inheritance of the HbS and Haemoglobin C (HbC) genes, often manifests with less severe anaemia but a heightened risk of consequences, including retinopathy, avascular necrosis, and thrombosis.[4]

HbS-β-thalassemia results from the conjunction of HbS with a β-thalassemia mutation, exhibiting a severity spectrum from moderate (β^+-thalassemia, which maintains partial normal haemoglobin synthesis) to severe (β^0-thalassemia, which resembles HbSS owing to the complete absence of normal haemoglobin)[5] Genotype-based variations affect clinical symptoms and therapeutic responses to hydroxyurea, transfusions, and novel treatments. Comprehending the genetic and phenotypic variation in sickle cell disease is essential for formulating personalised therapy strategies (Table 1).[6]

The relationship between anaemia and crises exerts a significant impact on the manifestation of bone pain.[7-9] The rising incidence of sickle cell disease is generating growing apprehension within the realm of global healthcare. Based on projections, it is anticipated that around 400,000 infants will be diagnosed with sickle cell anaemia by the year 2050.[10-12] The present pathological state is distinguished by the presence of homozygosity in

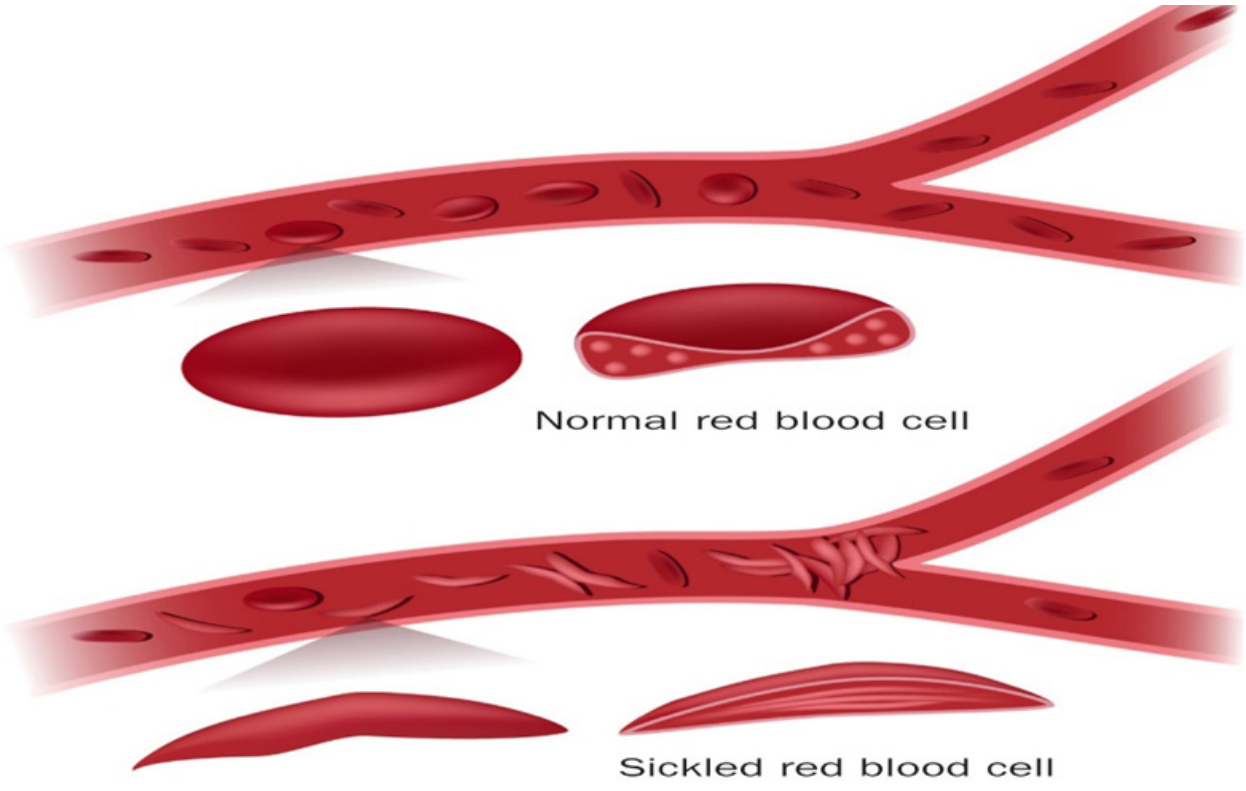

Figure-1. The inherent circular and flexible characteristics of typical red blood cells enable them to navigate the vasculature seamlessly. Sickle cell disease is characterized by abnormal haemoglobin, which results in the deformation of erythrocytes into a sickle or crescent shape, causing them to lose their flexibility. Cells exhibiting anomalous characteristics tend to impede the flow of blood through narrower blood vessels, leading to reduced oxygen supply to tissues, a condition known as tissue hypoxia, which subsequently triggers episodes of distressing pain. Alila Medical Media has produced the visual representation presented in the preceding content.[18]

Table 1. Major Sickle Cell Disease (SCD) Genotypes and Associated Clinical Features.

Genotype	Genetic Basis	Severity	Complications	References
HbSS (SCA)	Homozygous for HbS	Most severe	VOC, chronic hemolysis, stroke, organ damage	[19, 20]
HbSC	HbS + Hemoglobin C	Moderate	Less severe anemia, higher risk of retinopathy, and thrombosis	[21-23]
HbS-β^0-thalassemia	HbS + β^0-thalassemia mutation	Severe	Similar to HbSS	[24, 25]
HbS-β^+-thalassemia	HbS + β^+-thalassemia (partial HbA)	Milder	Moderate symptoms	[26, 27]

the Sickle Haemoglobin S (HbS) gene, resulting from a missense mutation (Glu6Val, rs334) in the -globin gene (HBB). Sickle cell disease is a highly prevalent medical condition that impacts a substantial population globally, exhibiting a higher prevalence among persons of African, South or Central American, Caribbean, Mediterranean, Indian, or Saudi Arabian ancestry. With hemolytic and Vaso-occlusive effects, SCD exhibits a range of thrombotic manifestations, including the occurrence of ischemic stroke.[13, 14] Furthermore, several recent research studies suggest that individuals diagnosed with SCD may exhibit increased susceptibility to Venous Thromboembolism (VTE).[15-17]

Sickle cell disease encompasses a diverse range of potential adverse outcomes, including, but not limited to, hemolytic stress, renal and hepatic insufficiency, and hemolytic and Vaso-occlusive effects. This study examines hemolysis and Vaso-occlusive crises, their significant impact on patients, and the mitigation of these occurrences in affected individuals.

METHODS

Database Selection

This review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standards. PRISMA stands for Preferred Reporting Items for Systematic Reviews and Meta-Analyses. A thorough search was performed utilising PubMed, Google Scholar, Web of Science, Scopus, and ScienceDirect.

Search Strategy

The further search phrases employed were sickle cell disease, haemolysis, Vaso-occlusive crisis, stroke, antioxidants, hydroxyurea, voxelotor, and gene therapy.

Inclusion criteria

The inclusion criteria were papers published between 2000 and 2024, publications addressing hemolysis, Vaso-occlusive crises, oxidative stress, novel treatment strategies in sickle cell disease, and clinical trials or meta-analyses.

Exclusion criteria

The exclusion criteria included studies not conducted in English, animal research, case reports, and conference papers.

Hemolysis

Although the evidence is not as definitive and relies on indirect measures, there is confirmation of a correlation between hemolysis and stroke. Numerous scholarly inquirie.[13] Prior research has established a link between reduced levels of haemoglobin and the incidence of cerebrovascular accidents in individuals with sickle cell disease. Prior research.[13,28,29] has indicated that individuals who have been diagnosed with sickle cell anaemia and thalassemia exhibit a reduced likelihood of experiencing a stroke. Based on the existing empirical evidence, it can be inferred that the implementation of chronic transfusion therapy in young patients diagnosed with sickle cell disease and presenting elevated Transcranial Doppler (TCD) velocities is linked to a simultaneous reduction in hemolysis, plasma haemoglobin concentration, and the likelihood of suffering a stroke. The abovementioned discovery supports the proposition presented in.[30] Concerning the association between hemolysis and the likelihood of experiencing a stroke. Sources.[31, 32] The generation of Reactive Oxygen Species (ROS) in erythrocytes can be attributed to the inherent instability of HbS and an augmented autooxidation mechanism. Furthermore, hemolysis leads to the release of heme, haemoglobin, and iron into the plasma, increasing extracellular ROS concentrations. The acceleration of the Fenton reaction, which leads to the degradation of proteins and polyunsaturated lipids, facilitates a specific process by the presence of iron and heme within the plasma. The one-mentioned event destabilises

erythrocyte membranes, which subsequently causes hemolysis.[33, 34]

Hemolysis is widely recognized as the primary pathophysiological manifestation of SCD, referring to the ongoing breakdown of red blood cells. Prior studies have demonstrated that the repetitive manifestation of this phenomenon results in a decline in antioxidant defences, thereby initiating the onset of oxidative stress.[35-37]

Substantial evidence for the documented roles of vitamins A and E in preventing lipid peroxidation and the disruption of the oxidative process in membranes and lipoproteins.[38, 39] It has been observed that Vitamin D can augment the activation of specific genes, specifically Nrf2 and Klotho, thereby increasing the synthesis of antioxidant enzymes and maintaining redox homeostasis. As a result, this can lead to the manifestation of an antioxidant effect.[40] Multiple studies have provided evidence to support the notion that Vitamin E exhibits the capacity to replenish Vitamin C levels, consequently augmenting the antioxidant characteristics of Vitamin C. Moreover, it has been observed that Vitamin D plays a role in facilitating the synthesis of the tripeptide Glu-Cys-Gly. This tripeptide serves as the primary redox agent and is crucial for maintaining cellular homeostasis and antioxidant mechanisms.[41-43]

Combined with vitamins, minerals such as zinc and selenium demonstrate antioxidative properties. The inhibitory effect of zinc on the NADPH oxidase enzyme has been documented, alongside its ability to confer stability to sulfhydryl proteins. Moreover, zinc competes with other metals capable of undergoing redox reactions, such as copper and iron, to facilitate the Fenton reaction, generating free radicals.[44,45] Zinc serves as a cofactor for the enzymatic activity of Superoxide Dismutase (SOD). Vitamin D Deficiency (VDD) among individuals of Kurdish origin in Iraq who experienced SCD. In particular, a notable proportion of the observed cases, amounting to 78%, displayed a significant insufficiency in vitamin D.[46, 47]

A potential correlation exists between the observed outcome and an increased susceptibility to erythrocyte hemolysis. Individuals who have been diagnosed with Sickle Cell Anaemia (SCA) and sickle cell trait-thalassemia exhibit notably decreased concentrations of total cholesterol, Low-density Lipoprotein (LDL) cholesterol, and High-density Lipoprotein (HDL) cholesterol when exposed to hemolytic stress (Figure 2).[46, 48]

Vaso-Occlusive Crisis

Sickle cell disease is primarily characterised by Vaso-occlusive crisis, also known as acute painful crisis, which represents the primary morbidity associated with this condition. The presence of fever is commonly documented, even in cases of seemingly straightforward painful episodes. This demonstrates that

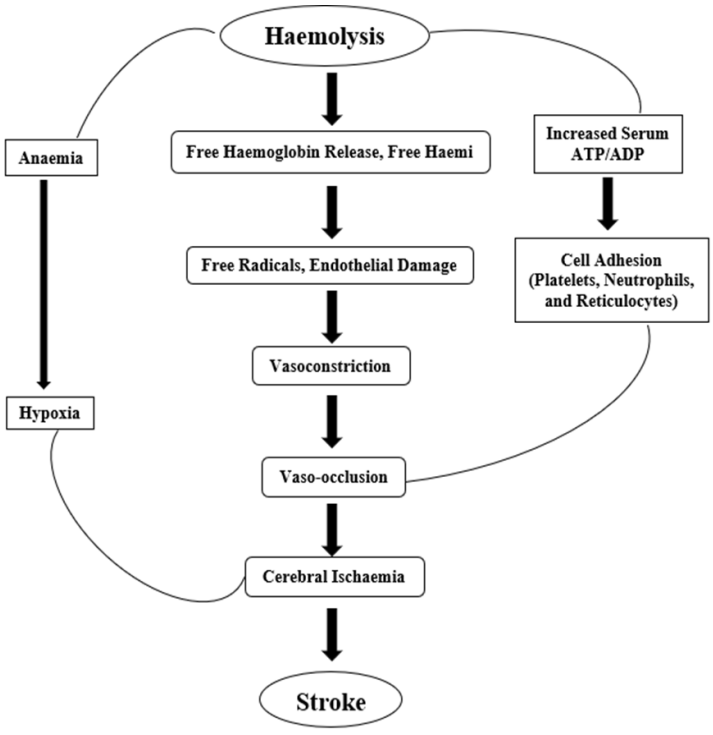

Figure 2. Pathophysiology of Stroke in Sickle Cell Disease (SCD) Hemolysis in sickle cell disease results in anemia, the liberation of free hemoglobin, and elevated ATP/ADP levels. These result in Vaso-occlusion, cerebral ischemia, and ultimately, a stroke.

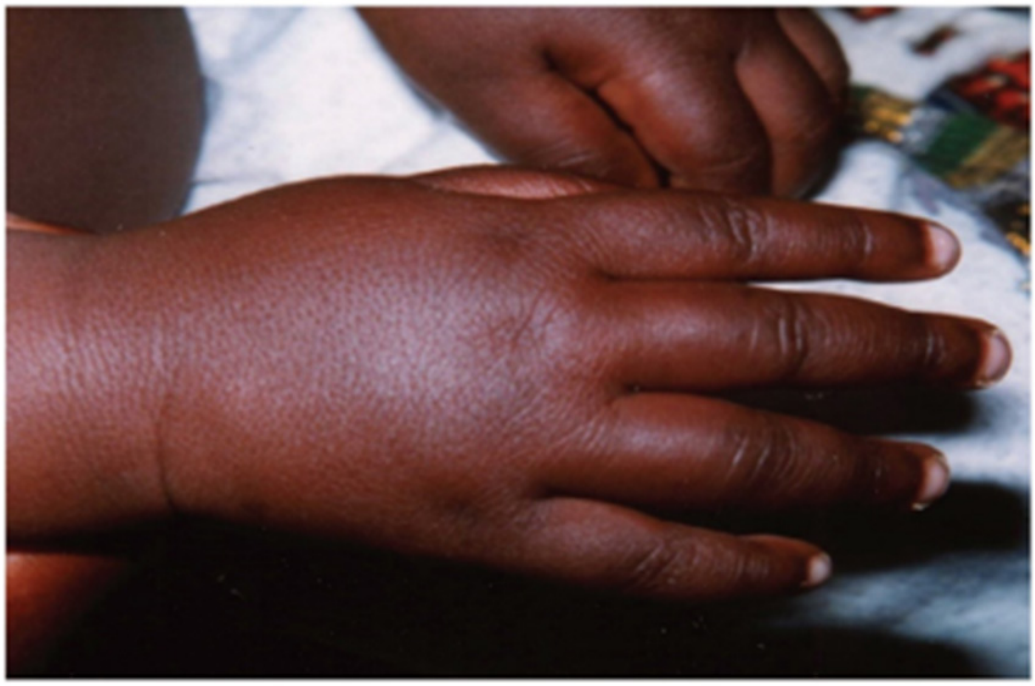

Figure 3. The provided image showcases the hand of a young child exhibiting dactylitis, a distressing medical condition characterised by inflammation and swelling of the digits, specifically the fingers or toes. Tom D. Thacher, MD, generously provided the photograph .[53]

fever can manifest as an isolated occurrence and does not necessarily indicate the presence of a pathological condition.[49, 50] The primary focus of clinical management of Vaso-occlusive Episodes (VOEs) is to assess pain intensity and administer appropriate analgesic medications expeditiously. Dactylitis, a condition characterised by discomfort and swelling in the hands and feet of the individual experiencing it, is commonly observed in infants and toddlers and is believed to result from infarctions. This particular condition has the potential to act as the primary indication of complications linked to SCD (Figure 3).[51, 52]

Sickle Cell Disease is a pathological condition that exhibits four distinct pain syndromes: hemolytic anaemia and its associated consequences, potential organ dysfunction involving infectious processes, and related ailments. The presence of four different components characterises the tetrad and can occur spontaneously or as a result of the other three elements, with pain being the primary clinical manifestation.[54-56]

Pharmacology remains the primary approach for addressing the current situation. Contemporary pain management approaches have advanced to incorporate the physiological dimensions of pain, as well as the psychological, social, and behavioural factors intricately linked to each instance.[57] Implementing a comprehensive pain management strategy is crucial in enhancing the overall well-being of individuals.[58] The findings from studies on pain-related issues suggest that incorporating cognitive behavioural therapy as an adjunctive strategy to complement other pain management interventions may offer benefits for individuals who have been diagnosed with sickle cell disease. The phenomenon above can be attributed to its capacity to alleviate psychological distress and enhance an individual's sense of competence and adaptability.[59]

The Vaso-occlusive crisis encountered by patients has the potential to affect six key domains, namely physical, psychological, social, role-related, overall life satisfaction, and perceived health status.[60] The available empirical evidence indicates that various psychological, societal, and spiritual factors can influence pain perception. In adherence to current guidelines, it is crucial to promptly provide personalised analgesic treatment based on the self-reported pain levels of individuals experiencing Vaso-occlusive crises.[61, 62] Quantitative Sensory Testing (QST) has been employed to determine that individuals aged seven years and older who are affected by SCD exhibit neuropathic pain. This is notable considering that Vaso-occlusive episodes typically result in nociceptive pain.[63, 64]

The available empirical evidence indicates the

presence of a positive correlation between age and the incidence of chronic pain in individuals diagnosed with sickle cell disease.[65] This phenomenon has been linked to the dysfunction of bodily organs, chronic inflammation, and the manifestation of opioid-induced hyperalgesia.[66] Consequently, there have been suggestions to include various supplemental pharmacological substances, for instance, the administration of ketamine at a low dosage level into the course of treatment. In clinical environments, it functions as a regulator of opioid tolerance and opioid-induced excessive pain despite the continued reliance on opioids as the primary method of pain relief. Despite the growing interest in employing this therapeutic approach, there appears to be a lack of available data on its effectiveness in managing pain related to Sickle Cell Disease, as indicated by various sources.[67-69]

Sickle cell disease is distinguished by the presence of Vaso-occlusive crisis (VOC), which can serve as an initial indication of several potentially life-threatening complications, including Acute Chest Syndrome (ACS), stroke, splenic sequestration, and multisystem organ failure.[70] Research findings have suggested that certain instances of Vaso-occlusive Crisis (VOC), a distressing medical condition, may be effectively addressed in a home setting, obviating the necessity for immediate medical intervention or hospital admittance.[71, 72] The mitigation of Volatile Organic Compounds (VOCs) holds significant significance for medical professionals, as these compounds adversely influence the Quality of Life (QOL) experienced by individuals afflicted with SCD. Sickle cell disease imposes a substantial economic burden on affected individuals, negatively impacting their overall health and well-being.[73]

Based on estimations, it was found that minors below the age of 18 who received a diagnosis of SCD accumulated an average yearly expenditure of US$14,772 for employer-provided insurance and US$11,702 for Medicaid healthcare in the year 2005.[74] The insufficient accessibility of preventive and comprehensive healthcare services is a contributing factor to the increasing financial burden associated with medical care for adult patients afflicted with SCD.[75] The circumstances above can be attributed to insufficient insurance coverage and a shortage of healthcare professionals. Consequently, a significant portion of the populace is compelled to seek medical care promptly, leading to an escalation in healthcare expenditures.[76]

Based on a research analysis examining healthcare expenditures from 2001 to 2005, it was determined that the mean monthly healthcare expenditure for individuals within the 50- to 64-year age range was $262. The quantity above exceeded the comparable expenses incurred by individuals aged 0 to 9 by a factor of three.[77] The intricate management of SCD substantially contributes to the disease's intricacy and economic burden. The prioritisation of preventive measures aimed at reducing sudden cardiac death (SCD) during the early stages of life holds great importance.[78]

Preventive measures encompass neonatal screening, the administration of anti-infective injections, and prophylactic antibiotic therapy that is initiated shortly after birth and maintained until the completion of the initial round of vaccinations that specifically target encapsulated microorganisms.[79] Furthermore, a yearly assessment employing transcranial Doppler ultrasound is conducted to ascertain the need for prophylactic transfusion therapy in the prevention of initial strokes and to monitor the probability of stroke incidence for the prediction of neurological complications.[80] The treatment of SCD has witnessed notable progress with the incorporation of various therapeutic modalities, including bone marrow transplant, L-glutamine, voxelotor, and crizanlizumab-tmca, alongside established maintenance medications such as blood transfusions and hydroxyurea. Previous research has shown the effectiveness of Hydroxyurea (HU) in reducing the occurrence of VOC and ACS while also reducing the necessity for blood transfusions and overall utilisation of Healthcare Resources (HCRU).[81] However, the full potential of HU has yet to be fully realised. The efficient management of SCD is hindered by the significant obstacle posed by the increased utilisation of healthcare resources (HCRU) associated with this condition. The utilisation of HCRU is significantly impacted by expensive hospitalisations and emergency room visits, necessitated by heightened service levels and resource requirements.[81, 82]

An abrupt and severe onset characterises the VOC, necessitating prompt interventions such as urgent medical attention and hospital admission to mitigate the potential for serious consequences.[52, 80]. The effective management of VOCs has emerged as a pivotal consideration in the formulation of treatment approaches for Acute Kidney Injury (AKI) associated with sepsis, owing to its significant influence on the utilisation of healthcare resources and related expenses, as well as its correlation with adverse health consequences such as morbidity and mortality.[83]

Stroke

Stroke is a significant and serious consequence of sickle cell disease (SCD), impacting individuals throughout their lives. Retrospective cohort research at the French Adult Sickle-Cell Disease Referral Centre examined 69 stroke cases from a total of 2,875 persons with SCD between 1970 and 2008. The research recorded 104 strokes, including 80 ischemic incidents, 22 hemorrhagic incidents, and 2 cerebral sinus thromboses. Hemorrhagic strokes primarily affected adults and were linked to an increased mortality risk relative to ischemic strokes.[84] The Stroke Prevention Trial in Sickle Cell Anaemia (STOP) was a pivotal, multicenter trial that assessed the efficacy of frequent blood transfusions in reducing the occurrence of first strokes in children with Sickle Cell Disease (SCD). The experiment indicated that sustaining sickle haemoglobin levels at or below 30% with periodic transfusions markedly reduced the incidence of first stroke by a minimum of 70% in comparison to usual treatment.[85]

Notwithstanding progress in preventative measures, current data reveal that the burden of cerebrovascular illness in SCD persists significantly. Research employing statewide data from California indicated that among 7,636 individuals with SCD, the cumulative incidence of the first ischemic stroke was 2.1% by age 20 and 13.5% by age 60.[86] Moreover, studies have indicated that the prevalence of hemorrhagic stroke among SCD patients escalates with advancing age. Structural vascular anomalies, including moyamoya arteriopathy and aneurysms, frequently contribute to hemorrhagic incidents, indicating that screening for these disorders may be advisable.[87]

Antioxidants

Oxidative stress significantly contributes to the pathogenesis of SCD, resulting in hemolysis and Vaso-occlusive crises. Numerous research studies have investigated the potential benefits of antioxidant supplementation in mitigating these symptoms. A Cochrane analysis evaluated the effectiveness of various antioxidants, including vitamin C, in combination with vitamin E, zinc, N-acetylcysteine (NAC), L-arginine, and omega-3 fatty acids. The review indicated that L-arginine could alleviate pain intensity and that zinc could elevate haemoglobin levels; however, the data were inconsistent, and the overall advantages of antioxidants in SCD remain ambiguous.[88] Further research found that omega-3 fatty acids, vitamin A, and zinc enhanced haemolysis parameters, including haemoglobin and hematocrit levels. However, high doses of vitamin C and E supplementation exacerbated haemolysis, as indicated by elevated reticulocyte and lactate dehydrogenase levels.[89]. Furthermore, studies indicate that nutraceuticals abundant in antioxidants, such as alkaloids, polyphenols, vitamins, and minerals, may be prospective therapeutic agents for SCD by mitigating oxidative stress and Vaso-occlusive crises (Table 2).[90, 91]

Therapeutic Interventions

Hydroxyurea

Hydroxyurea has been thoroughly investigated as a treatment for sickle cell disease (SCD), showing considerable advantages across diverse patient groups. A pivotal randomised controlled experiment in 1995 shown that hydroxyurea treatment significantly decreases the incidence of painful crises in people with sickle cell disease, resulting in fewer hospitalisations and transfusion needs.[102] Subsequent studies have validated these findings, emphasising hydroxyurea's effectiveness in reducing Vaso-occlusive events and acute chest syndrome in adults and children.[103, 104]. Hydroxyurea increases foetal haemoglobin (HbF) levels, preventing sickle haemoglobin's polymerisation, thereby diminishing haemolysis and Vaso-occlusion.[105]

Table 2. Antioxidant Agents Studied in Sickle Cell Disease: Clinical Effects and Limitations.

Antioxidant	Benefit	Clinical Evidence/Limitations	References
Vitamin A	Prevent lipid peroxidation	Some positive, inconsistent outcomes	[92]
Vitamin C	Antioxidant effect	High doses increase hemolysis markers	[93, 94]
Vitamin D	Supports enzyme activation/redox	High prevalence of deficiency among SCD patients	[95, 96]
Vitamin E	Membrane/lipoprotein protection	Can enhance vitamin C activity, but high doses may be harmful	[97]
Zinc	Enhances Hb; SOD cofactor	Generally beneficial, some support for pain reduction1	[98]
Omega-3 Fatty Acids	Improved hemolysis parameters	Positive findings in some studies	[99-101]

Moreover, hydroxyurea has demonstrated efficacy in reducing leukocyte and platelet counts, diminishing the expression of endothelial adhesion molecules, and elevating nitric oxide levels, all of which enhance vascular function and mitigate disease consequences.[106] Long-term trials have shown the safety and sustained effectiveness of hydroxyurea, indicating a decrease in mortality among treated individuals (Table 2).[107]

Voxelotor

Voxelotor, branded as Oxbryta, is a crucial therapeutic drug for managing sickle cell disease (SCD) by inhibiting haemoglobin S polymerisation, which reduces haemolysis and elevates haemoglobin levels. The phase 3 HOPE study revealed that voxelotor dramatically increased haemoglobin levels and reduced haemolysis indicators in individuals with sickle cell disease, suggesting its potential as a disease-modifying treatment.[108] Subsequent longitudinal follow-up investigations corroborated these findings, demonstrating persistent enhancements in haemoglobin levels and hemolytic indicators over prolonged durations.[109] Pediatric trials have demonstrated voxelotor's effectiveness, revealing substantial haemoglobin increases in children aged 4 to 11 years (Table 2).[110]

Gene Therapy

Gene therapy has emerged as a viable therapeutic strategy for sickle cell disease (SCD), addressing the genetic basis of the condition. Conventional therapies have predominantly focused on symptom management, although recent innovations offer potential solutions. A significant technique involves procuring autologous hematopoietic stem cells (HSCs) from patients who have undergone ex vivo genetic modification to reduce the propensity for sickling and then reinfusing them. This method has demonstrated considerable therapeutic advancements in many trials, employing lentiviral vector-mediated gene addition to impede haemoglobin aggregation.[111]

In December 2023, the U.S. Food and Drug Administration authorised lovotibeglogene autotemcel (Lyfgenia) for individuals aged twelve and older with sickle cell disease and a history of Vaso-occlusive episodes. This therapy involves the extraction of the patient's hematopoietic stem cells, genetically modifying them to produce a non-sickling variant of haemoglobin, and subsequently reinfusing them after myeloablative conditioning. Clinical trials indicated that 88% of individuals attained full remission of Vaso-occlusive events within six to eighteen months following therapy.[112] Another novel method utilizes CRISPR/Cas9 gene-editing technology to restart fetal hemoglobin synthesis, thereby offsetting the impaired production of adult hemoglobin. This approach has shown encouraging outcomes in the first clinical studies, with patients exhibiting substantial decreases in illness symptoms (Table 3).[113]

Table 3. Comparison of Main Therapeutic Options for Sickle Cell Disease.

Therapy	Mechanism of Action	Efficacy	Limitations	References
Hydroxyurea	Increases HbF, reduces sickling/hemolysis	Reduces VOC, ACS, and improves survival	Adherence, genotype dependence	[114, 115]
Voxelotor	Inhibits HbS polymerization	Increases Hb, lowers hemolysis	New, long-term safety data are limited	[116]
Gene Therapy	Genetic correction of HbS	High remission rates in trials	Cost, accessibility, and unknown long-term effects	[117, 118]

DISCUSSION

This review emphasises the pivotal role of haemolysis and Vaso-occlusive crises in sickle cell disease (SCD), connecting them to stroke, oxidative stress, and inflammation. Current research indicates that hemolysis-induced liberation of free haemoglobin elevates reactive oxygen species (ROS), exacerbating endothelial dysfunction and vascular occlusion.[119] The evidence linking low haemoglobin levels to stroke risk in sickle cell disease is substantial; however, several studies indicate that genetic variables, such as co-inheritance of α-thalassemia, may reduce this risk.[120] Although substantial data support hydroxyurea's efficacy in decreasing VOCs and enhancing foetal haemoglobin levels, its success is contingent upon patient genotype, and adherence continues to pose a barrier.[103] Recently sanctioned therapies, like voxelotor (which mitigates haemolysis) and crizanlizumab (which addresses inflammation), have potential; nonetheless, long-term safety data remain insufficient.[120] Emerging gene treatments provide promising therapeutic solutions, yet their exorbitant cost and accessibility challenges persist as obstacles.[121]

The efficacy of antioxidant treatment in sickle cell disease remains a topic of contention. Although vitamins A, C, D, and E are posited to mitigate oxidative stress, clinical investigations have yielded inconsistent outcomes. Elevated dosages of certain antioxidants may induce oxidative damage, raising concerns about their regular use.[122] This analysis highlights the emotional and economic impact of SCD, a phenomenon that is often overlooked in clinical studies. Numerous patients contend with chronic pain, depression, and opioid dependence, highlighting the necessity for multidisciplinary pain treatment strategies, including cognitive-behavioural therapy (CBT) and alternative analgesics such as low-dose ketamine.[123] Future research should focus on (1) individualised treatment approaches informed by genotype, (2) longitudinal safety data about novel SCD medicines, (3) enhancing antioxidant therapy, and (4) mitigating gaps in healthcare access. Integrating genetic, pharmacological, and psychological strategies will enhance outcomes for SCD patients globally.

CONCLUSIONS

Sickle Cell Disease is a considerable global health concern, with haemolysis and Vaso-occlusive crises substantially exacerbating its course. The pathophysiological pathways encompass inflammation, oxidative stress, and endothelial dysfunction, leading to severe outcomes such as stroke, acute chest syndrome, and organ failure. While hydroxyurea has substantially reduced disease severity, novel medicines like voxelotor, crizanlizumab, and gene editing methods provide compelling alternatives. Nevertheless, barriers to accessibility and the lack of long-term safety data persist as ongoing issues. Antioxidant therapy, primarily utilizing vitamins A, C, D, and E, has shown promise in mitigating oxidative stress; however, variable clinical results necessitate further investigation. A customised therapy approach improves therapeutic outcomes by considering genetic factors, including HbS genotypic variations and co-inherited modifiers such as α-thalassemia. Alongside medicinal interventions, the emotional and financial difficulties of SCD must be addressed. Comprehensive treatment modalities, including cognitive-behavioral therapy and multidisciplinary pain management, are essential for improving patients' quality of life. Future research must focus on improving treatment approaches, expanding access to innovative drugs, and addressing the healthcare disparities that consistently affect individuals with SCD worldwide.

Conflict of Interest

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Authors' Contribution

Study Conception: A.M.Q., A.H.H; Study Design: A.M.Q.; A.H.H; Literature Review: A.H.H; Critical Review: A.M.Q; Writer: A.H.H.; A.M.Q..

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Original Article

The Role of Inflammatory Markers in Predicting Autoimmune Comorbidities among Patients with Type 1 Diabetes Mellitus

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ABSTRACT

Background Type 1 diabetes mellitus (T1DM) frequently coexists with other autoimmune diseases, which may enhance systemic inflammation and affect clinical outcomes. Novel inflammatory indices, including the pan-immune-inflammation value (PIV) and systemic immune-inflammation index (SII), have emerged as potential markers of immune activation. This study aimed to evaluate whether these markers could distinguish T1DM patients with comorbid autoimmune diseases from those without.

Methods In this retrospective analysis, patients with T1DM were stratified according to the presence or absence of comorbid autoimmune diseases. Demographic, metabolic, laboratory, and inflammatory parameters, including PIV, SII, and leukocyte subsets, were compared between groups using appropriate non-parametric tests.

Results Patients with autoimmune comorbidities exhibited significantly higher PIV (559.5 ± 390.5 vs. 225.5 ± 187.5, $p<0.001$) and SII (810.6 ± 407.7 vs. 503.1 ± 257.9, $p<0.001$) values compared with those without autoimmune conditions. Neutrophil and monocyte counts were also elevated (neutrophils: 5.7 ± 1.9 vs. 4.0 ± 1.3, $p<0.001$; monocytes: 0.68 ± 0.25 vs. 0.50 ± 0.14, $p<0.001$), whereas lymphocyte counts did not differ significantly ($p=0.127$). No statistically significant differences were observed in age, BMI, glycemic control (HbA1c: 8.7 ± 1.7% vs. 8.6 ± 1.6%, $p=0.494$), lipid profiles, or other standard laboratory parameters.

Conclusion T1DM patients with comorbid autoimmune diseases display a markedly elevated inflammatory profile, as indicated by PIV and SII despite similar metabolic and demographic characteristics. These findings suggest that inflammatory indices may serve as adjunctive biomarkers for the detection or monitoring of autoimmune comorbidities in T1DM, warranting further prospective studies to evaluate their diagnostic and prognostic utility.

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INTRODUCTION

Type 1 diabetes mellitus (T1DM) is a chronic autoimmune disorder characterized by the destruction of insulin-producing β-cells in the pancreas.[1] This autoimmune etiology predisposes individuals with T1DM to the development of other autoimmune diseases.[2] The most common comorbidities include autoimmune thyroid disorders, affecting over 90% of individuals with T1DM, and other autoimmune conditions such as rheumatoid arthritis and celiac disease.[3]

The presence of these comorbid autoimmune diseases in T1DM patients may exacerbate systemic inflammation, potentially influencing disease progression and complications. Chronic low-grade inflammation is a hallmark of both T1DM and autoimmune comorbidities, contributing to endothelial dysfunction, insulin resistance, and increased cardiovascular risk.[4]

Recent studies have introduced novel inflammatory indices, such as the Pan-Immune-Inflammation Value (PIV) and the Systemic Immune-Inflammation Index (SII), which integrate various hematological parameters to provide a comprehensive assessment of systemic inflammation. The PIV, calculated as (neutrophil × platelet)/lymphocyte count, and the SII, calculated as (neutrophil × platelet)/lymphocyte count, have shown promise in predicting outcomes in various diseases, including cancer, cardiovascular diseases, and diabetic complications.[5,6]

However, the relationship between these inflammatory indices and autoimmune comorbidities in T1DM patients remains underexplored. Understanding this relationship is crucial, as it may offer insights into the pathophysiology of T1DM and its associated comorbidities, and potentially serve as a tool for early detection and monitoring of autoimmune-related complications.

This study aims to evaluate the association between PIV, SII, and the presence of comorbid autoimmune diseases in patients with T1DM. By examining these relationships, we seek to enhance our understanding of the inflammatory landscape in T1DM and its comorbidities, potentially informing clinical practices and therapeutic strategies.

METHODS

Study Design and Participants

This retrospective observational study included 136 patients diagnosed with type 1 diabetes mellitus (T1DM) who were followed at tertiary education and research hospital between 2023 and 2024. Patients were stratified according to the presence or absence of comorbid autoimmune diseases. Inclusion criteria comprised a confirmed diagnosis of T1DM based on standard clinical and laboratory criteria, age ≥18 years, and availability of complete clinical, laboratory, and inflammatory data. Patients with acute infections, recent surgery, malignancy, or incomplete records were excluded from the analysis. Additionally, patients with a history of infection within the last month were excluded from the study to avoid biasing the results. In our study, patients with a history of anti-inflammatory treatment, steroid treatment, antibiotic therapy, and immunosuppressive treatment in the last month were not included in the study. The presence of an autoimmune disease in the study was considered as having one or more autoimmune diseases.

The diseases queried in the autoimmune disease category included autoimmune thyroiditis, Addison's disease, celiac disease, rheumatoid arthritis, and antibody-positive rheumatological diseases such as SLE.

To confirm the presence of a disease, the hospital data system was used to check for antibody positivity. Patients without sufficient data for diagnosis were excluded from the study.

Data Collection

Demographic characteristics, including age, sex, height, weight, and body mass index (BMI), were obtained from electronic medical records. Disease duration and academic/professional characteristics were also recorded. Patients' laboratory parameters were reviewed and recorded from the hospital data system. Patients' comorbidities were recorded.

Laboratory and Inflammatory Parameters

Routine laboratory assessments included fasting blood glucose (FBG), glycated hemoglobin (HbA1c), lipid profile (HDL, LDL, triglycerides), liver function tests (ALT), renal function tests (creatinine), hemoglobin, and thyroid-stimulating hormone (TSH). In addition, inflammatory markers were calculated, including the pan-immune-inflammation value (PIV) and the systemic immune-inflammation index (SII). Complete blood count parameters, including neutrophil, lymphocyte, and monocyte counts, were also recorded.

PIV was calculated: (neutrophil × platelet)/lymphocyte

SII was calculated: (neutrophil × platelet)/lymphocyte

Statistical Analysis

Continuous variables were expressed as mean ± standard deviation (SD) or median with interquartile

range (IQR), depending on the distribution. Categorical variables were presented as frequencies and percentages. Comparisons between patients with and without autoimmune comorbidities were performed using the Mann-Whitney U test for continuous variables and chi-square or Fisher's exact test for categorical variables.

All analyses were two-sided, with $p<0.05$ considered statistically significant. Statistical analyses were conducted using SPSS version 26.0 (IBM Corp., Armonk, NY, USA) and R version 4.3.

RESULTS

Data Acquisition and Preprocessing

Data Collection

A total of patients with T1DM were analyzed and stratified according to the presence of comorbid autoimmune diseases.

In the demographic comparison, no significant differences were observed between groups. The mean age was similar in patients with and without autoimmune diseases (35.1 ± 9.8 years vs. 34.8 ± 10.2 years, p = 0.725). Likewise, height, weight, and BMI values did not differ significantly (all p>0.05) (Table 1).

With regard to metabolic and laboratory parameters, glycemic control was comparable between groups (HbA1c: 8.7 ± 1.7% vs. 8.6 ± 1.6%, p=0.494; FBG: 187.6 ± 72.2 vs. 156.8 ± 70.5 mg/dl, p=0.944). Lipid levels, renal function, and hepatic enzymes also showed no significant differences. However, there was a trend toward lower HDL cholesterol levels (42.1 ± 3.4 vs. 43.7 ± 4.3 mg/dL, p = 0.065) and higher TSH concentrations (2.5 ± 0.98 vs. 2.2 ± 0.95, p = 0.060) in the autoimmune group (Table 2).

In contrast, inflammatory parameters showed marked differences between groups. Patients with autoimmune

Table 1. The relationship between comorbid autoimmune diseases and demographic characteristics in patients with type 1 DM

	Autoimmune Diseases NO		Autoimmune Diseases YES		p
	Mean ± SD	Median (Min-Max)	Mean ± SD	Median (Min-Max)	
Age	34.8±10.2	34(18-66)	35.1±9.8	36(18-54)	0.725
Height, cm	165.1 ± 9.5	165(150-191)	163.8 ± 8.6	162(152-182)	0.494
Weight, kg	64.5 ± 10.2	65(42-95)	61.8 ± 9.4	59.5(50-88)	0.125
BMI, kg/m^2	23.5 ± 2.6	23.1(17.3-35.2)	22.9 ± 2.1	22.9(19.8-32.3)	0.161

*Mann-Whitney U test

Table 2. The relationship between comorbid autoimmune diseases and laboratory parameters in patients with type 1 DM

	Autoimmune Diseases NO		Autoimmune Diseases YES		p
	Mean ± SD	Median (Min-Max)	Mean ± SD	Median (Min-Max)	
FBG, mg/dl	156.8±70.5	176(85-341)	187.6±72.2	178(87-355)	0.944
Hba1c, %	8.6 ± 1.6	8.2(5.7-12.6)	8.7 ± 1.7	8.4(5.9-12.7)	0.494
HDL, mg/dl	43.7 ± 4.3	43.5(35-71)	42.1 ± 3.4	42.5(30-48)	0.065
TG, mg/dl	115.2± 28.7	111(53-228)	119 ± 23.2	115.5(80-165)	0.337
LDL, mg/dl	116.4± 26.7	116.5(55-247)	113.2 ± 25.9	115(51-198)	0.694
ALT (U/L)	20.9±9.0	20(9-76)	22.3±7.4	21(9-40)	0.199
Creatinine, mg/dl	0.89±0.12	0.90(0.66-1.14)	0.92±0.12	0.92(0.70-1.16)	0.329
Hgb, g/dL	13.5 ± 1.4	13.1(10.9-16.8)	13.1 ± 1.3	12.7(10.6-16.5)	0.117
TSH	2.2 ± 0.95	2.1(0.79-7.8)	2.5 ± 0.98	2.5(1.0-4.3)	0.060

*Mann-Whitney U test
FBG: Fasting blood glucose; Hgb: hemoglobin; TG: Triglycerides; ALT: Alanine aminotransferase

Table 3. The relationship between comorbid autoimmune diseases and inflammatory parameters in patients with type 1 DM

	Autoimmune Diseases NO		Autoimmune Diseases YES		p
	Mean ± SD	Median (Min-Max)	Mean ± SD	Median (Min-Max)	
PIV	225.5±187.5	233.5(36.7-1408)	559.5±390.5	453(107-1842)	**<0.001**
SII	503.1 ± 257.9	459.7(122.4-1760.1)	810.6 ± 407.7	693.7(214-2133.5)	**<0.001**
Neutrophil	4.0 ± 1.3	3.8(1.08-8.8)	5.7 ± 1.9	5.4(2.8-11.1)	**<0.001**
Lymphocyte	2.3 ± 0.67	2.2(0.92-5.03)	2.1 ± 0.87	2.1(0.70-5.41)	0.127
Monocyte	0.50± 0.14	0.48(0.24-0.95)	0.68 ± 0.25	0.61(0.30-1.31)	**<0.001**

*Mann-Whitney U test
PIV: pan-immune inflammation value; SII: Systemic immune-inflammation index

comorbidities had significantly higher PIV (559.5 ± 390.5 vs. 225.5 ± 187.5, p<0.001) and SII (810.6 ± 407.7 vs. 503.1 ± 257.9, p<0.001) values compared to those without autoimmune conditions. Neutrophil counts (5.7 ± 1.9 vs. 4.0 ± 1.3, p<0.001) and monocyte counts (0.68 ± 0.25 vs. 0.50 ± 0.14, p<0.001) were also significantly elevated, while lymphocyte counts were slightly lower in the autoimmune group, although not statistically significant (p=0.127) (Table 3).

Overall, while demographic and metabolic parameters were largely similar between groups, patients with autoimmune comorbidities demonstrated a significantly heightened inflammatory profile, characterized by elevated PIV, SII, neutrophil, and monocyte levels.

DISCUSSION

This study aimed to evaluate the role of inflammatory markers, specifically the PIV and the SII, in identifying autoimmune comorbidities among patients with T1DM. Our findings demonstrate that T1DM patients with comorbid autoimmune diseases exhibit significantly higher levels of PIV and SII, suggesting that these markers may serve as adjunctive tools for detecting autoimmune comorbidities in this population.

The elevated PIV and SII values observed in T1DM patients with autoimmune comorbidities align with previous studies that have highlighted the association between systemic inflammation and the presence of autoimmune diseases.[7] For instance, a study by Zhang et al.[8] reported that higher PIV levels were significantly associated with increased risks of all-cause, cardiovascular, cancer, and diabetes mortality, underscoring the importance of systemic inflammation in disease prognosis. Similarly, Huang noted that the SII, initially developed in oncology and cardiovascular research, has demonstrated potential utility in autoimmune diseases, suggesting its broader applicability in inflammatory conditions.[9]

Interestingly, our study found that neutrophil and monocyte counts were significantly elevated in T1DM patients with autoimmune comorbidities, while lymphocyte counts did not differ significantly between groups. This finding is consistent with the concept of a pro-inflammatory state characterized by an imbalance in the immune cell profile, which has been implicated in the pathogenesis of autoimmune diseases.[10] The predominance of neutrophils and monocytes may reflect an innate immune response that contributes to the systemic inflammation observed in these patients.

The lack of significant differences in metabolic and laboratory parameters, such as glycemic control (HbA1c), lipid profiles, and renal function, between T1DM patients with and without autoimmune comorbidities suggests that the observed inflammatory differences are independent of these factors. This finding highlights the potential utility of PIV and SII as markers that specifically reflect inflammatory processes associated with autoimmune comorbidities, rather than general metabolic disturbances. When the literature was examined, these inflammatory markers were found to be associated with the presence of autoimmune disease and the activation of existing disease.[11]

In a comprehensive study by Liu et al.[12], a total of 37,604 patients were examined between 1999 and 2018. The study found a positive correlation between SII and rheumatoid arthritis, and it was thought that SII could be used to determine the risk of rheumatoid arthritis. Additionally, studies have identified relationships between SII and the severity of autoimmune disease in the literature.[13] In another study, it was found that the

Systemic Immune Inflammation Index could be used in the diagnosis of systemic lupus erythematosus.[14]

On the other hand, the relationship between PIV and autoimmune diseases has been demonstrated in numerous studies. One study planned a retrospective cohort study of 281 patients treated for acute pericarditis between 2014 and 2023. The study revealed PIV as a predictive marker of disease severity and prognosis.[15] A study by Tutan D. demonstrated that PIV serves as a valuable marker for distinguishing between remission and active RA compared with healthy individuals. It has also been stated that it can be used to assess disease activity in patients with active rheumatoid arthritis.[16]

Furthermore, the absence of significant differences in demographic characteristics, including age, sex, and BMI, between the two groups strengthens the validity of our findings, as it suggests that the elevated inflammatory markers are not confounded by these variables. This reinforces the notion that PIV and SII may specifically identify inflammatory changes related to autoimmune comorbidities in T1DM patients.[17,18]

The clinical implications of our findings are noteworthy. Given the high prevalence of autoimmune comorbidities in T1DM patients, as reported in a study by Popoviciu et al, the ability to identify these comorbidities early through accessible inflammatory markers could facilitate timely interventions and improve patient outcomes.[3,19] The use of PIV and SII as adjunctive diagnostic tools could enhance the accuracy of screening processes and enable more personalized management strategies for T1DM patients.

In conclusion, our study provides evidence that elevated PIV and SII values are associated with the presence of autoimmune comorbidities in T1DM patients. These findings suggest that these inflammatory markers may serve as valuable adjunctive tools for the detection and monitoring of autoimmune comorbidities in this population. Further prospective studies are warranted to validate these markers and assess their prognostic significance in the context of T1DM and associated autoimmune diseases.

Strengths & Limitations

This study's strengths include its retrospective design, which allowed for the analysis of a substantial cohort of T1DM patients, and the comprehensive assessment of a wide range of inflammatory markers. The inclusion of both PIV and SII provides a multifaceted view of systemic inflammation, enhancing the robustness of our findings.

However, several limitations must be acknowledged. The retrospective nature of the study inherently limits the ability to establish causality. Additionally, the single-center design may affect the generalizability of the results. The reliance on electronic medical records for data collection may also introduce information bias, as the accuracy of the data depends on the completeness and correctness of the records. Furthermore, the study did not account for potential confounding factors such as medication use, disease duration, or the presence of other comorbid conditions, which could influence inflammatory marker levels.

CONCLUSIONS

In summary, our study suggests that elevated PIV and SII values are associated with autoimmune comorbidities in T1DM patients, independent of metabolic and demographic factors. These findings highlight the potential of these inflammatory markers as adjunctive tools for the detection and monitoring of autoimmune comorbidities in this population. Further research is needed to confirm these results and explore the clinical utility of PIV and SII in the management of T1DM patients with autoimmune comorbidities.

Ethical Statement

The study was approved by the Institutional Review Board of the participating center (Approval Date: March 19, 2025; Decision No: 2025-6/1) and conducted in accordance with the ethical principles outlined in the Declaration of Helsinki. Written informed consent was obtained from all participants prior to enrollment.

Conflict of Interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Authors' Contribution

Study Conception: NY, NK; Study Design: NY, NK; Material: NY; Literature Review: NY; Critical Review: NK; Writer: NY, NK.

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Case Report

Unveiling Multiple Endocrine Neoplasia Type 1 (MEN-1) in a Young Pakistani Male with Recurrent Hypoglycemia: A Diagnostic Odyssey in a Resource-Limited Setting

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ABSTRACT

This case report describes a 32-year-old Pakistani male who was initially admitted to a tertiary care hospital with Typhoid fever, but later developed recurrent life-threatening hypoglycemia. Extensive investigations revealed elevated insulin and C-peptide levels, a pituitary microadenoma, and a somatostatin-avid gastric lesion, leading to the diagnosis of Multiple Endocrine Neoplasia type 1 (MEN-1). Management included dextrose infusions, somatostatin - analogue therapy, and supportive care. The case highlights the diagnostic challenges of MEN-1 in atypical presentations and resource-limited settings, and underscores the need for a multidisciplinary approach to treatment and psychosocial support.

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INTRODUCTION

Multiple Endocrine Neoplasia type 1(MEN-1) is a rare autosomal dominant disorder characterized by the development of neoplasms in multiple endocrine organs, most commonly involving the parathyroid glands (95%), pancreatic islet cells (40-70%), and the anterior pituitary (30-60%).[1-2] Clinical manifestations vary greatly depending on the hormonal activity of the involved tumors, often leading to delayed diagnosis, particularly in young patients or when classical symptoms are absent.[3] Recurrent hypoglycemia, primarily when associated with elevated insulin and C-peptide levels in the absence of diabetes or exogenous insulin use, may suggest the presence of insulin-secreting tumors such as insulinoma (Figure 1). Whipple's triad is mainly observed in cases of insulinoma.[4] Also, pituitary tumors, commonly prolactinomas or somatotroph adenomas, can lead to significant complications, including vision loss, acromegaly, or infertility.[5] Our case highlights recurrent and severe hypoglycemia after a recent infection, that was initially considered to be a sequela of infection

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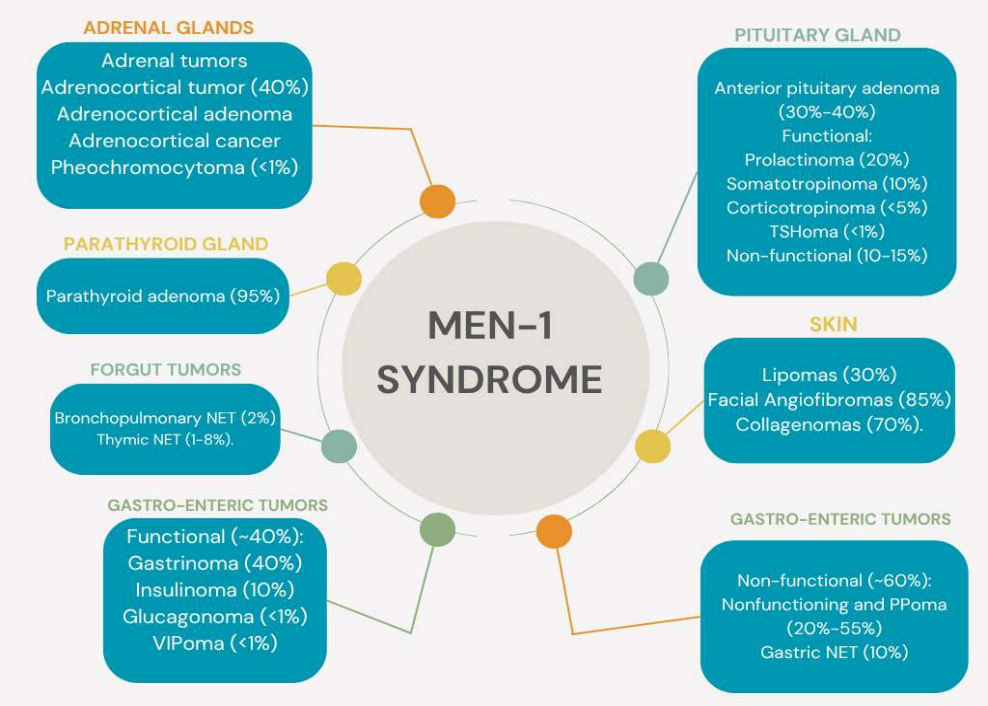

Figure 1. Spectrum of Neoplasia in Men-1 Syndrome

later on proved to be the result of a rare clinical disorder (MEN syndrome). The complexity was further amplified by overlapping symptoms, prolonged hospitalization, infections, and visual impairment, thus, ultimately revealing MEN-1 as the underlying diagnosis.

The primary objective of this report is to detail the clinical progression and diagnostic journey of a young male patient with recurrent hypoglycemia, later confirmed as a case of MEN-1. We aim to emphasize the importance of maintaining a high index of suspicion in atypical presentations and to highlight the diagnostic and management challenges of MEN-1 in resource-limited settings. In doing so, we underscore the necessity of a multidisciplinary approach and timely referral to tertiary centers for rare endocrine disorders.

CASE PRESENTATION

A 32 years old male with no previous co-morbid, presented to the emergency department of POF hospital Wah Cantt, Pakistan in November 2023 with the presenting complaints of dizziness and palpitations for the last two days followed by unconsciousness. On arrival in the emergency department, he was unconscious with a Blood pressure of 100/70mmHg, pulse 80/min regular, and temperature 98.6°F. The systemic examination, including a detailed neurological examination, didn't reveal any abnormal findings.

His blood sugar levels were immediately checked in the emergency department, which was found to be 21mg/dL, and he was managed with intravenous glucose infusions. After that, he regained his consciousness. He was then admitted to the indoor medicine department for further evaluation and management. He had a history of admission in the same hospital two weeks before with typhoid fever that was managed with IV antibiotics, and he was discharged. During his current admission in the hospital, he developed multiple episodes of severe and persistent hypoglycemia despite receiving continuous infusions of IV dextrose.

The hypoglycemia was thought to be attributed to ongoing sepsis secondary to typhoid fever or because of gastric issues. A detailed blood workup, including complete blood counts, metabolic profile, thyroid hormone levels, septic screen, and urine tests, was performed, which didn't reveal any abnormal findings.

Due to persistent hypoglycemic episodes of unknown cause, he was referred to a specialized

tertiary care Hospital, CMH Rawalpindi, where he was admitted for further evaluation. In January 2024, he developed visual impairment and mentioned he can't see on the sides (peripheral vision) and has a history of on-and-off headaches. During that stay, his physical examination showed bitemporal hemianopia. A multidisciplinary team of consultants evaluated him at CMH and planned some investigations for further evaluation. His hypoglycemia was persistent and severe despite repeated glucose infusions, so a central venous line was passed due to difficulty in IV access. He developed line-related sepsis with Methicillin-resistant Staphylococcus Aureus (MRSA) infection that was treated with antibiotics (Table 1).

Glycemic assessment revealed a normal HbA1c of 5.6% and a normal extended oral glucose tolerance test (OGTT); however, fasting insulin levels were markedly elevated at 83 µIU/mL, accompanied by a significantly raised C-peptide level of 8.2 ng/mL, suggestive of endogenous hyperinsulinemia. The insulin-like growth factor 1 (IGF-1) was within normal limits at 18.8 nmol/L. Serial capillary glucose monitoring from January 1 to 7, 2024 (Table 2) demonstrated fasting values consistently between 50 and 55 mg/dL and postprandial levels ranging from 65 to 70 mg/dL. Prolactin was elevated at 405 nIU/l, while testosterone and morning cortisol levels were within normal ranges at 12.2 nmol/L and 535 nmol/L, respectively. Notably, islet cell antibodies were positive, further supporting an autoimmune component in the pathophysiology. These findings and the history of headaches with visual disturbances collectively pointed toward a diagnosis of MEN-1 with functional pancreatic and pituitary involvement; therefore, further tests were planned accordingly. A contrast-enhanced CT (CECT) scan of the abdomen, performed in January 2024, was unremarkable, showing no visible pancreatic or abdominal masses. However, an MRI of the brain conducted earlier on January 2, 2024, revealed a small focal enhancement in the left pituitary gland measuring 7×8×6.7 mm, suggestive of a pituitary microadenoma. The neck ultrasound revealed a TIRADS 1 pattern with hypoechoic lesions, raising suspicion of a possible parathyroid adenoma. However, a subsequent parathyroid scan on January 19, 2024, was negative for adenomatous activity. Further evaluation with an octreotide scan in February 2024 identified a somatostatin-avid lesion in the gastric antrum extending to the greater curvature, indicating a neuroendocrine tumor. A PET-CT scan performed on March 15, 2024, revealed prominent lymph nodes. A 2D echocardiogram showed a normal ejection fraction (>60%) with no structural cardiac abnormalities. These imaging findings collectively supported the diagnosis of MEN-1, involving both pituitary and gastrointestinal neuroendocrine

Table 1. Diagnostic investigations

Parameter	Value	Reference Range	Units	Remarks
HbA1c	5.6%	4.0–5.6%	%	Normal
Extended OGTT	Normal	-	-	Normal
Serum Insulin (Fasting)	8.3	2.6–24.9	µIU/mL	Normal
C-peptide (Fasting)	8.2	0.8–3.1	ng/mL	Elevated
IGF-1	18.8	7.3–18.0	nmol/L	Elevated
Serum LDL	3.01	<2.6	mmol/L	Elevated
Total Serum Cholesterol	4.76	<5.2	mmol/L	Normal
Serum Triglycerides	1.06	<1.7	mmol/L	Normal
Serum HDL	1.27	>1.0	mmol/L	Normal
Serum Testosterone	12.2	8.7–29.0	nmol/L	Normal
Serum Cortisol (Morning)	535	138–690	nmol/L	Normal
Serum Prolactin	405	86–324	mIU/L	Elevated
Serum Free T3	1.86	2.5–5.8	pmol/L	Low
Serum Free T4	16	9.0–19.0	pmol/L	Normal
Serum TSH	1.71	0.4–4.0	mIU/L	Normal
Serum Calcium	2.27	2.1–2.6	mmol/L	Normal
Serum Phosphates	1.34	0.81–1.58	mmol/L	Normal
Serum Magnesium	0.89	0.7–1.0	mmol/L	Normal
Islet Antibodies	Positive	Negative	-	Abnormal

Table 2: Capillary Blood Glucose Monitoring (January 1–7, 2024)

Date	Time	Fasting (mg/dL)	Post-Prandial (mg/dL)
Jan 1	**Morning**	52	67
	Afternoon	54	69
	Evening	53	66
Jan 2	**Morning**	51	68
	Afternoon	55	70
	Evening	52	67
Jan 3	**Morning**	50	66
	Afternoon	53	68
	Evening	54	69
Jan 4	**Morning**	55	70
	Afternoon	52	67
	Evening	51	65
Jan 5	**Morning**	53	69
	Afternoon	50	66
	Evening	55	70
Jan 6	**Morning**	52	68
	Afternoon	54	67
	Evening	53	66
Jan 7	**Morning**	51	65
	Afternoon	50	67
	Evening	55	70

components (Figure 2).

Therapeutic Interventions

The patient was initially managed conservatively with intravenous dextrose infusions and frequent carbohydrate-rich meals to stabilize blood glucose levels. Despite these efforts, he continued to experience recurrent hypoglycemic episodes. In light of persistent symptoms and suggestive radiologic findings, a therapeutic trial of a long-acting somatostatin analog, Octreotide (30 mg intramuscularly, monthly), was initiated in February 2024. This intervention resulted in a significant reduction in hypoglycemic episodes. The patient received additional doses in March and April 2024, and intermittently in December 2024 and April 2025, subject to the availability of the medication. The administration of Octreotide was done under close monitoring. The patient was admitted to the ICU for each dose, where baseline vitals, electrocardiogram (ECG), and blood sugar readings were recorded. Oral carbohydrates were administered prior to the injection, and post-injection monitoring included repeat vital signs and ECG to ensure hemodynamic stability and prevent hypoglycemia.

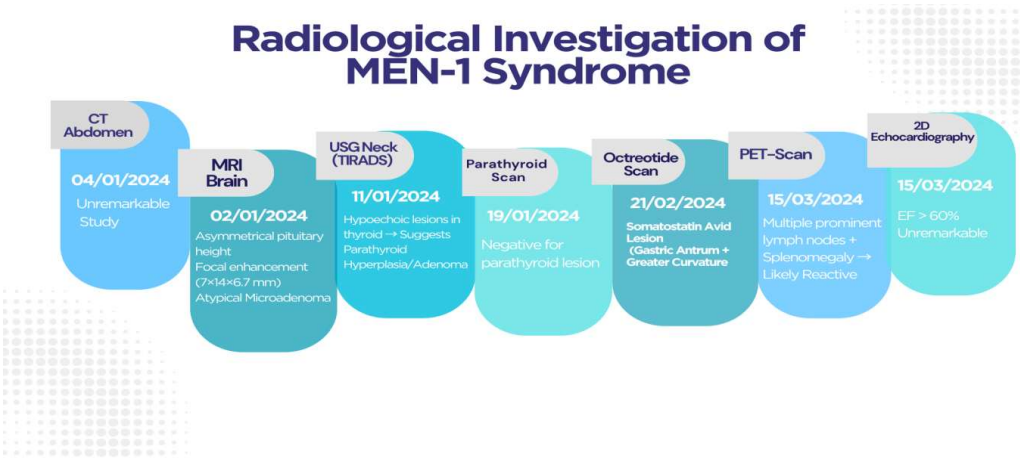

Figure 2. Radiological Investigation of MEN-1 Syndrome

Given the presence of a pituitary microadenoma, a neurosurgical consultation was sought. However, surgical intervention was deferred due to the high risk of perioperative severe hypoglycemia. A follow-up evaluation with neurosurgery is planned once better glycemic stability is achieved. Additional pharmacologic support included the initiation of Acarbose in June 2025 to reduce postprandial glucose excursions and Amitriptyline to manage neuropathic pain, likely secondary to repeated severe hypoglycemic episodes. The patient was also prescribed 25% dextrose ampoules three times daily and advised on strict dietary modifications, including two-hourly meals and the use of apple cider vinegar to support weight management and glycemic control .

DISCUSSION

MEN-1 is a complex endocrine disorder that often presents with subtle or nonspecific symptoms, leading to delayed diagnosis and management. In this patient, the initial symptom—recurrent, severe hypoglycemia-served as the clinical clue that eventually led to a systemic endocrinological workup. The elevated insulin and C-peptide levels, in the absence of exogenous insulin use and normal HbA1c, were highly suggestive of endogenous hyperinsulinism, possibly due to an insulinoma, which is reported in 10–15% of MEN-1 cases.[6]

Interestingly, imaging studies such as CECT abdomen and parathyroid scans were unremarkable, which is not uncommon in insulinoma patients, where tumors are small and often missed on conventional imaging, in line with a previous study conducted in the Netherlands. The positive octreotide scan, highlighting somatostatin-avid gastric lesions, points toward a neuroendocrine origin, which is supportive of a MEN-1 diagnosis, consistent with prior literature that notes gastrinomas and somatostatinomas as additional pancreatic tumors associated with the syndrome.[7]

The patient's pituitary micro-adenoma, discovered on MRI brain, aligns with the known spectrum of MEN-1–associated pituitary tumors. While prolactinomas are most common, growth hormone-secreting tumors leading to acromegalic changes, as seen in this case, are also described in other studies. Notably, the patient gained 28 kg, developed bi-temporal hemianopia, and exhibited distinct facial changes consistent with a somatotroph adenoma and previously described in MEN-1 cases.[1]

One of the major complications in this patient's management was a central line-associated bloodstream infection (CLABSI) due to MRSA, necessitated by repeated intravenous dextrose infusions for hypoglycemia. Central venous catheter infections are well-documented risks in the long-term management of endocrine syndromes that require continuous parenteral support, especially when immune status is compromised.[8] Another key concern was the psychosocial impact of prolonged hospitalization, loss of functional independence, and separation from family. The patient's inability to return to work, drive independently, or maintain normal social roles reflects the heavy burden MEN-1 can place on mental health and quality of life, particularly in young adults. Studies have shown that patients with MEN syndromes frequently report higher rates of anxiety, depression, and impaired daily functioning.[9] From a therapeutic perspective, the introduction of long-acting somatostatin analogs (Octreotide) proved beneficial in reducing hypoglycemic episodes. Literature supports the use of somatostatin analogs for controlling hormone hypersecretion in functional neuroendocrine tumors and managing hypoglycemia in unresectable insulinoma.[10] However, accessibility and affordability issues, as seen in this patient's case, limit consistent use in many regions and necessitate systemic support for healthcare.

Lastly, neurosurgical intervention was deferred due to the risk of perioperative hypoglycemia, highlighting the delicate balance clinicians must maintain between addressing tumor burden and preventing life-threatening metabolic complications. Research confirms that endocrine tumor surgery in MEN-1 must be carefully timed, especially when metabolic derangements are not yet stabilized.

CONCLUSIONS

This case underscores the importance of a high index of suspicion for MEN-1 syndrome in patients presenting with unexplained hypoglycemia, especially when conventional imaging is unrevealing. Early endocrine workup, neuroimaging, and multidisciplinary management are crucial. Furthermore, addressing psychosocial challenges in such chronic, rare conditions is essential for comprehensive patient care.

Conflict of Interest

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