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The Interconnection Between Type 1 Diabetes Mellitus and Idiopathic Inflammatory Myopathies: Genetic, Immunological, and Clinical Insights

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ABSTRACT

Autoimmune disorders arise when the immune system mistakenly targets healthy tissues, leading to chronic inflammation and systemic complications. Type 1 diabetes mellitus (DM1) and idiopathic inflammatory myopathies (IIMs), such as polymyositis and dermatomyositis, demonstrate genetic and immunological similarities that influence their progression. Epidemiological studies indicate that between 4.2% and 29% of individuals with diabetes may develop IIMs, underscoring a significant correlation between these conditions. Genetic research has identified shared susceptibility genes, including phospholipase B1 (PLB1) and cystic fibrosis transmembrane conductance regulator (CFTR). Moreover, transcriptomic analyses highlight unique inflammatory pathways, particularly the activation of type I interferon signalling in dermatomyositis. Advanced diagnostic techniques, such as FDG-PET imaging and muscle biopsies, enhance detection rates, while lifestyle factors, including diet and glycemic control, play a crucial role in disease management. This review aims to explore the molecular connections between DM1 and IIMs, emphasizing early detection, preventive approaches, and personalized treatment strategies to mitigate their combined impact on patient health.

Keywords: Autoimmune diseases, type 1 diabetes mellitus, idiopathic inflammatory myopathies, polymyositis, dermatomyositis, genetic susceptibility, glycemic control.

1. INTRODUCTION

Autoimmune-mediated diseases occur when the immune system mistakenly attacks healthy cells in the body. Type 1 Diabetes Mellitus (DM1) is one such autoimmune disease, where the pancreas is attacked, leading to high blood sugar levels and often substantial insulin resistance. In addition, the inflammation of muscles characterizes myositis, an autoimmune disease. Recent research has revealed that patients with DM1 frequently experience idiopathic inflammatory myopathies (IIMs), with studies indicating that between 4.2% and 29% of diabetes patients are affected by this disease.

This frequency is notably higher compared to age- and sex-matched healthy controls [1], diabetes can also lead to complications like diabetic myonecrosis, a rare condition marked by tissue inflammation and necrosis, commonly observed in individuals with long-term uncontrolled diabetes [2], [3]. Despite the notable prevalence of diabetes among IIM patients, clinicians often overlook the disease's onset and presence, making it essential to examine the risk associated with the coexistence of diabetes mellitus and myositis. Preventive measures are critical to reduce the adverse cardiovascular effects linked to this combined condition. The studies have highlighted a positive association between diabetes mellitus and mortality in patients with polymyositis and dermatomyositis, with a reported hazard ratio of 2.57 (HR=2.57, 95% CI: 1.38-4.80, P<0.0001) [4]. Genetic research has also revealed common genetic associations between juvenile dermatomyositis (JDM) and type 1 diabetes, with genes like phospholipase B1 (PLB1) and cystic fibrosis transmembrane conductance regulator (CFTR) playing a role in both conditions [5]. Additionally, transcriptome analysis shows different gene expression patterns in dermatomyositis and polymyositis, with dermatomyositis significantly involving the type 1 interferon signaling system [6]. Advanced diagnostic methods, such as hybrid imaging models, FDG-PET imaging, and MRI scanning, have improved the detection of myositis linked to diabetes, enhancing diagnostic precision by combining conventional and novel techniques [7], [8], [9]. Muscle biopsy remains a crucial tool for confirming the presence of these conditions, with studies indicating a 29% prevalence of diabetes in IIM.

The pathways related to the both diseases have found in the studies such as, autoantibodies directed against proteins such as TRIM72 interfere with muscle regeneration, which accelerates the development of myositis and may be connected to immunological dysregulation brought on by diabetes [10]. Research indicates a notable

infiltration of macrophages and T lymphocytes in myositis, which could be impacted by diabetic metabolic conditions [11]. These findings underscore the need for greater awareness and early detection of both diseases, to mitigate their combined impact on patient health.

In managing both diabetes and myositis, dietary habits play a significant role. For myositis patients, diets rich in gluten, vitamin D, creatine, and protein, as well as anti-inflammatory foods, have been explored for their potential benefits. Specific ingredients such as red yeast rice, oyster mushrooms, soy products, and various grains, which are potential sources of statins, should be considered in patients with immune-mediated necrotizing myopathy [12]. Similarly, diabetes patients face lifestyle challenges like immobility, unhealthy eating habits, and disrupted biological clocks, which can exacerbate inflammation and oxidative stress, triggering further health complications [13]. Although no particular diet or nutritional supplementation is universally endorsed for managing myositis, individualized therapies focusing on diet, exercise, and self-management are crucial for both conditions.

Addressing these distinct lifestyle issues, with an emphasis on dietary modifications and musculoskeletal health, helps control diabetes while improving the management of associated conditions such as myositis. The interconnected nature of these diseases requires a holistic approach to patient care, ensuring that both metabolic and muscular health are effectively managed.

The aim of this study is to explore how this connection between diabetes mellitus and idiopathic inflammatory myopathies (IIM) can offer insights into disease pathogenesis, enhance diagnostic treatments, and inform preventive measures. By recognizing the risk factors and addressing the early signs of diabetes in IIM patients, it may be possible to reduce the incidence of severe cases. This underscores the importance of predicting the risk of diabetes development in IIM patients and highlights the need for a comprehensive, individualized approach to treatment and prevention.

2. DIABETES AND MYOSITIS

The diabetes and myositis are two complex autoimmune diseases. The, study is focused whether these two diseases shares genetic susceptibility. A number of factors, such as the frequency of musculoskeletal problems, particular pathologies like diabetic myonecrosis, and the underlying pathophysiological processes, are involved in the relationship between diabetes mellitus and myositis. Diabetes has a major effect on the musculoskeletal system, increasing the risk of diseases like myositis, which can progress to diabetic myonecrosis, an uncommon but dangerous consequence of poorly managed diabetes [14], [15]. Vasculopathy, neuropathy, and chronic low-intensity inflammation are important variables that connect diabetes to musculoskeletal conditions [16]. Aberrant insulin levels brought on by hyperglycemia might exacerbate musculoskeletal issues and neuropathic pain [17]. Diabetes and hypertension are more common in people with IIM, indicating a strong correlation between the two diseases [18].

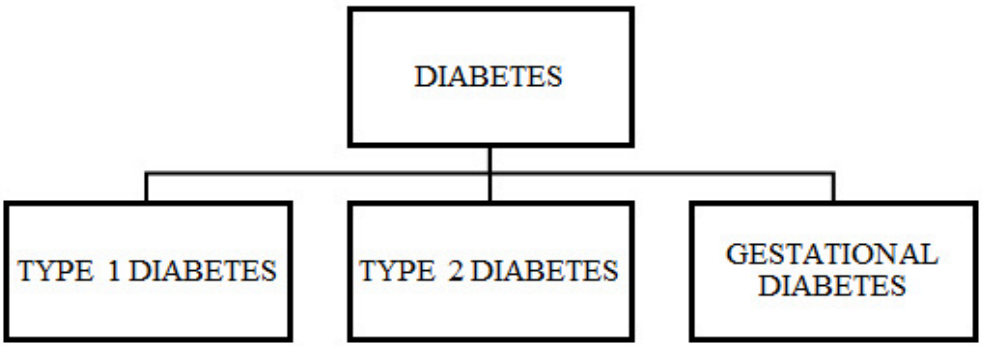

Fig. 1: TYPES OF DIABETES

IIMs are often classified into three subtypes: polymyositis (PM), dermatomyositis (DM), and inclusion body myositis (IBM). However, new subgroups, such as necrotising autoimmune myopathy (NAM) and anti-synthetase syndrome, have recently been found [19]. Each of these subtypes has distinct clinical, immunopathologic, and histologic criteria, although they all have characteristics such as moderate-to-severe muscular weakness, endomysial inflammation, and increased creatine kinase levels. Since each subtype has a unique prognosis and response to treatment, identifying the right one is essential to effective disease management [20].

Diabetes mellitus comes in three primary forms (Fig. 1): The body's inability to create enough insulin leads to type 1 diabetes. This kind was once known as "juvenile diabetes" or "insulin-dependent diabetes mellitus" (IDDM). The reason is not known. Insulin resistance is the first stage of type 2 diabetes, a disorder in which cells do not react appropriately to insulin. A deficiency in insulin may also arise as the illness worsens. "Non-insulin-dependent diabetes mellitus" (NIDDM) or "adult-onset diabetes" were the prior names for this kind of the disease. Being overweight and not exercising enough are the main causes. The third primary kind, gestational diabetes, is brought on by elevated blood glucose levels in pregnant women who have never had diabetes before [21].

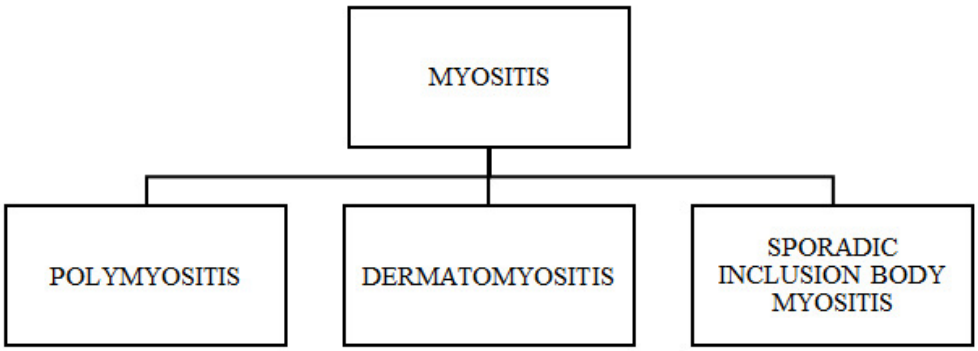

Fig. 2: TYPES OF MYOSITIS

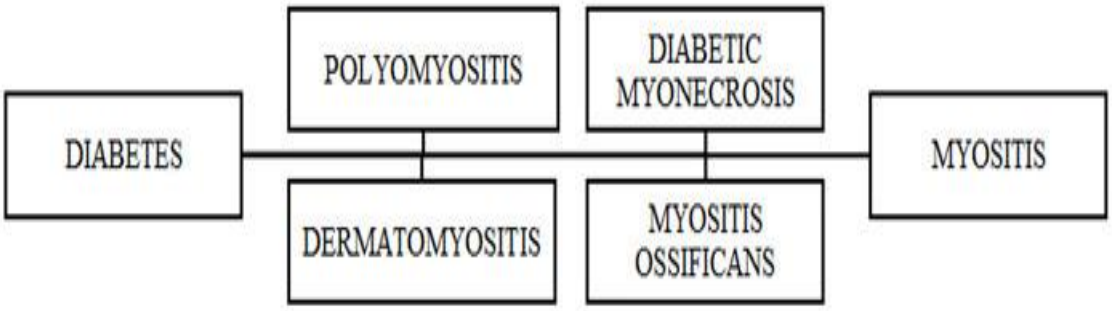

Fig. 3: LINKS BETWEEN DIABETES AND MYOSITIS

As the prevalence of myositis (Fig.2) increases the diabetes mellitus get associated (Fig.3). In type 1 diabetes, the absence of insulin and its effects result in decreased levels of insulin-like growth factor (IGF-1) and insulin-like growth factor binding protein 3 (IGFBP-3). Additionally, osteoblast differentiation, quantity, and function decline, which lowers bone turnover and appears to be osteoporosis. Diabetes-related problems in the upper limbs typically affect periarticular soft tissues. One of the most prevalent illnesses is diabetic cheiroarthropathy, which is the sole diabetes-specific symptom, with a frequency of 3.5-58% among DM patients.

Furthermore, it is more prevalent in patients with type 1 diabetes (Fig.4, [16]). The condition is characterised by skin thickening and finger flexion contracture. It may be identified by the "prayer sign," which is the inability to bring the palms and fingers together. Finger stiffness and skin thickening might be obvious, thus a differential diagnosis between scleroderma and diabetic cheiroarthropathy must be made. Diabetic cheiroarthropathy is a hand function-limited condition that is frequently exacerbated by polyneuropathy, severely restricting everyday tasks [16].

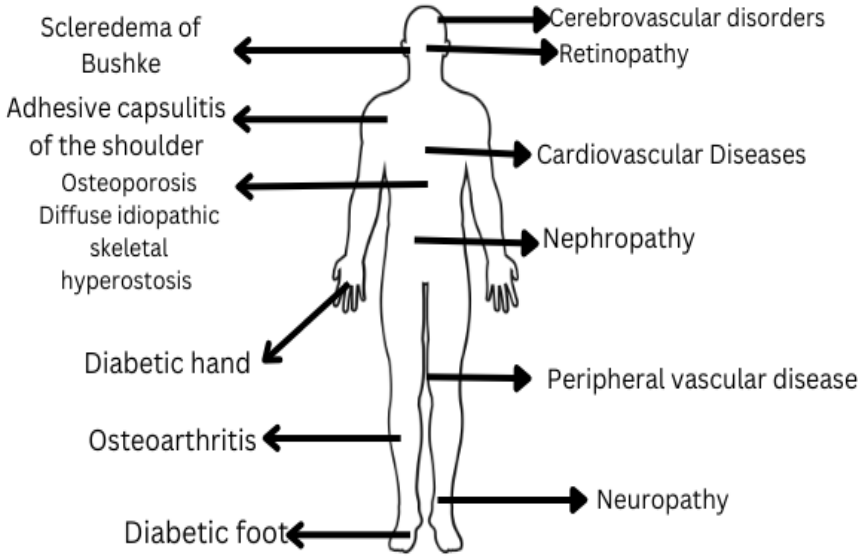

Fig. 4: Common musculoskeletal complications of diabetes mellitus

3. LIFESTYLE

Diabetic myonecrosis is an uncommon but dangerous consequence of poorly managed diabetes that has a major influence on the lifestyle of those who have it. These individuals frequently have severe discomfort and swelling in the afflicted muscles, mainly in the thighs, which limits their range of motion and ability to do everyday tasks. Supportive treatment, such as pain management and stringent glycemic control, is usually part of management, and it may have an impact on their general lifestyle decisions.

Patients often show up with acute, localised thigh pain and oedema, frequently without any history of trauma [22] Fever, malaise, and weight loss are some symptoms that point to systemic involvement [23]. People who have had diabetes for a long time and other microvascular problems are more likely to have the disease [24].

Inadequate glycaemic management, the majority of instances involve those with poorly controlled diabetes, emphasising how crucial blood sugar control is sedentary action, Complications such as myonecrosis might arise as a result of insufficient physical exercise [25], [26]. Even though diabetic myonecrosis is frequently disregarded, medical professionals must take it into account when diabetic patients exhibit abrupt muscular complaints. While early detection and treatment can greatly enhance results, the long-term outlook is still worrisome along with that series of managing tools should be taken into consideration to control this disorder [27] (Fig. 5, [28]).

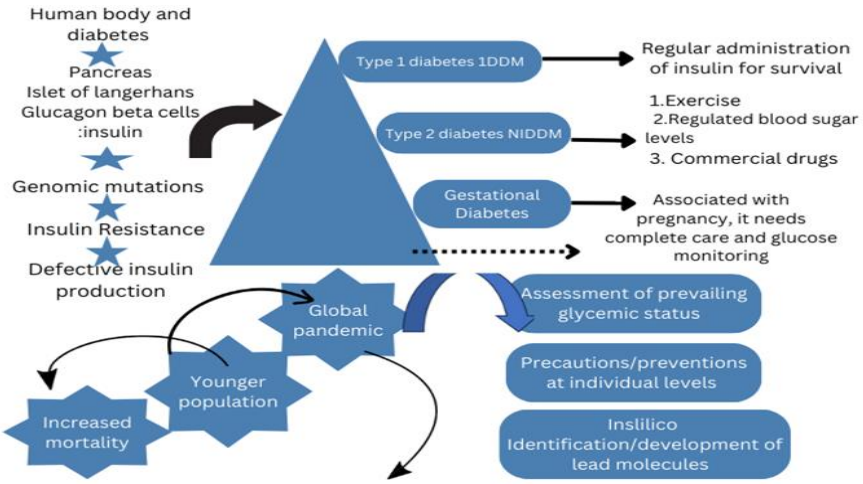

Fig. 5: A visual representation of the common incidence and methods used to control diabetes.

The following genes are linked to JDM: phospholipase B1, tyrosine hydroxylase, CD 6 molecule, perforin 1, dynein axonemal heavy chain 2, and cystic fibrosis transmembrane conductance regulator. Based on their research, it is plausible to suggest that individuals who have a genetic predisposition to both JDM and T1D may experience the development of either illness [29], which may be caused by a variety of genetic or epigenetic variables [30].

As may be assumed, there are certain common genetic risk factors in this metabolic pathway, such as IFN-α signalling, which plays a significant role in the development of several autoimmune illnesses, including JDM. By investigating genetic correlations with JDM patients' elevated IFN-α characteristic [31]. Data from 308 children with documented definite or probable JDM were included in the study, which followed Bohan and Peter's criteria at the Children's Memorial Hospital in Chicago. Adopted children were not included since they lacked a history of biological relationships. The study involves 304 children. During the initial clinic visit, a three-generational approach was used to collect family histories from the patients. Following that, the same individual was interviewed every 36 months, which included information from all JDM patients seen between 1971 and 2008 (Table 1, [30]).

Table 1: Prevalence of autoimmune disorders in JDM families with specific symptoms

Autoimmune disease in family history	Percentage of JDM families	Estimated percentage of JDM relatives affected %	Reported population prevalence%	Estimated risk in JDM relatives compared with general population	P
Rheumatoid arthritis	15.79	0.94	1.0	0.93(0.67-1.33)	72
Type 1diabetes	15.69	0.85	0.15	5.74(2.92-11.3)	$8.6*10^{-9}$
Lupus(SLE)	13.73	0.77	0.10	5.89(2.64-13.1)	$1.0*10^{-7}$
Inflammatory bowel disease	11.51	0.61	0.39	0.77(0.43-1.38)	38
Multiple sclerosis	3.62	0.30	0.08	2.40(0.85-6.82)	14
Celiac disease	1.97	0.18	0.75	0.14(0.06-0.31)	$1.1*10^{-8}$
Dermatomyosistis	0.99	0.10	0.02	3.00(0.31-28.9)	.62

Scleroderma	0.66	0.04	0.03	1.00(0.14-7.10)	1.0
Myasthenia gravis	0.66	0.03	0.01	2.00(0.18-22.1)	1.0
Vasculitis	0.33	0.01	0.002	N/A	N/A
Polymyositis	0	0	0.004	N/A	N/A
Psoriasis	13.73	0.77	2.2	0.35(0.25-0.48)	$8.0*10^{-12}$

4. GENES AND METABOLIC PATHWAYS:

4.1. Diabetes

An important genetic component contributes to the complexity of type 1 diabetes (T1D), an autoimmune illness. These are a few important genes and genetic indicators linked to type 1 diabetes (Fig. 6).

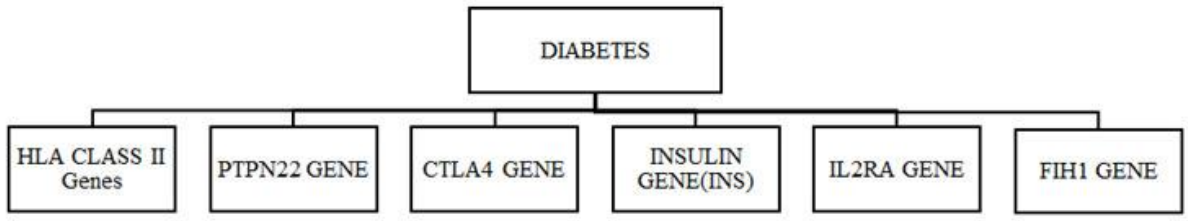

Fig 6: Genes and Pathways involved in Diabetes

4.1.1. HLA Class II Genes:

T1D's key susceptibility locus is on chromosome 6p21, among the HLA class II genes. These genes contribute for between 30% and 50% of the hereditary risk for T1D. Specific alleles, such as HLA DR3/DR4-DQ8, have been related to an increased risk of illness development.

4.1.2. Insulin Gene (INS):

on chromosome 11p15 accounts for approximately 10% of the hereditary vulnerability to type 1 diabetes. Variations in this gene, namely polymorphisms and tandem repeats, have been linked to the condition. Shorter alleles of the variable number of tandem repeats are associated with greater risk, whereas longer alleles are protective.

4.1.3. PTPN22 gene:

This gene, found on chromosome 1p13, is another significant non-HLA locus related with T1D. It helps regulate the immune system and has been linked to the illness.

4.1.4. CTLA4 gene:

The CTLA4 gene, located on chromosome 2q33, has a role in immune response and is linked to T1D risk.

4.1.5. IL2RA gene:

The interleukin 2 receptor alpha gene, found on chromosome 10p15, is another genetic marker associated with T1D risk. It regulates T cells and contributes to immunological response.

4.1.6. Gene FIH1:

Genome-wide association studies (GWAS) have linked this gene, which is found on chromosome 2q24, to an increased risk of developing type 1 diabetes.

4.1.7. Non-HLA Locations:

More than 40 more loci have been found in recent research that increase the risk of T1D, however their individual effects are often less significant than those of the HLA genes.

The multifaceted aspect of T1D, where environmental circumstances and genetic predisposition combine to impact disease development, is highlighted by these genetic markers and loci [32].

4.2. Myositis

Recent studies have focused on the genetics of idiopathic inflammatory myopathies (IIM), this is linked to immune-related genetic variations, such as TYK2 [33]. There are some important genes and genetic variables have been linked to myositis (Fig. 7).

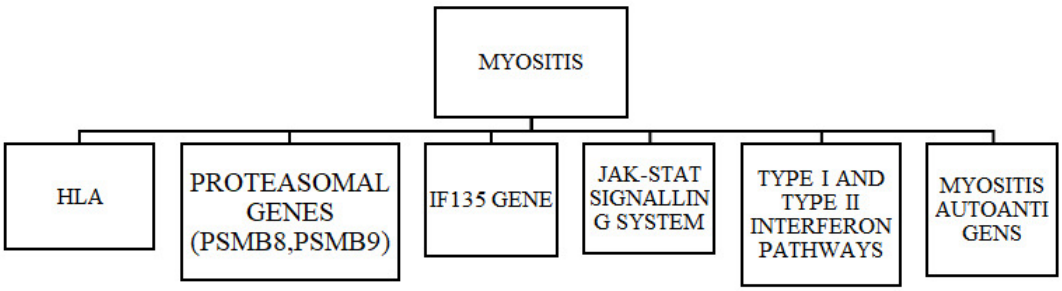

Fig. 7: Genes and Pathways involved in Myositis

4.2.1. HLA:

The HLA area is the genetic region in IIM that is most significantly related, according to genome-wide association studies. Different correlations between clinically defined subgroups suggest that particular HLA genes may affect a person's vulnerability to different myositis manifestations.

4.2.2. Proteasomal genes:

Anti-synthetase syndrome (ASS) has been linked to variations in proteasomal genes, particularly PSMB8 and PSMB9 (proteasome 20S subunit beta 8/9). These genes may contribute to the pathophysiology of IIM since they are involved in immunological response and protein breakdown.

4.2.3. IF135 gene:

One important new genetic risk locus for IIM has been found to be Interferon-Induced Protein 35 (IFI35). It implies that type I interferon activation might have a role in the illness by influencing the production of other genes unique to muscles, such as PTGES3L (prostaglandin E synthase 3 like).

4.2.4. JAK-STAT Signalling pathway:

Regardless of the myositis subtype, people with IIM have been found to have a higher burden of uncommon non-coding variations and synonymous variants in genes linked to the JAK-STAT signalling system. This route is essential for immune response mediation.

4.2.5. Type I and Type II Interferon Pathways:

While type II interferon-inducible genes have significant expression in DM, sporadic inclusion body myositis (sIBM), and ASS, type I interferon-inducible genes are highly expressed in DM and marginally in ASS,

according to gene expression studies. This suggests that various myositis subtypes have varying levels of interferon pathway activation.

4.2.6. Myositis Autoantigens& Autoantibodies:

These autoantigens are extensively expressed during muscle regeneration, indicating their involvement in the disease process, even if the production of myositis-specific autoantibodies does not correlate with the expression of their corresponding autoantigens in muscle biopsies. These results demonstrate the intricate genetic makeup of myositis and the significance of particular genes and pathways in comprehending the pathophysiology of the condition [34]. Autoantibodies directed against proteins such as TRIM72 interfere with muscle regeneration, which accelerates the development of myositis and may be connected to immunological dysregulation brought on by diabetes [10]. The Anti-Jo-1 autoantibodies and elevated blood BAFF levels in myositis patients are associated with SNPs in the BAFF gene, indicating a hereditary susceptibility to autoimmune reactions [35]

5. GENETIC LINKAGE BETWEEN DIABETES AND MYOSITIS:

The overlapping immune dysregulation processes between Type 1 Diabetes (T1D) and Idiopathic Inflammatory Myopathies (IIM) are highlighted by the genetic overlap between the two conditions (Fig. 8). These mechanisms include the HLA area, proteasomal genes, interferon pathways, and immune control genes such as CTLA4 and PTPN22. These hereditary variables imply that immunological tolerance is compromised in both disorders, causing the immune system to wrongly attack self-tissues (pancreatic β-cells in T1D and muscles in IIM). Potential targets for treatments that might alter the immune response in both conditions are provided by the involvement of shared pathways such the JAK-STAT and interferon signalling. Understanding these genetic connections might lead to better diagnostic tools for people at risk of developing certain autoimmune diseases as well as more individualized and efficient therapies.

Many genes linked to energy metabolism pathways, such as PGM1, GYG1, and RBCK1, have been linked to metabolic myopathies in recent research. Their regulatory implications in muscle metabolism, affecting insulin signalling and energy balance, are suggested by the altered expression of long non-coding RNAs (lncRNAs) and microRNAs (miRNAs) in diabetic muscle tissues [36], [37]. Diabetic myonecrosis has been linked to dysregulation of the insulin signalling and AMP-activated protein kinase (AMPK) pathways, which impairs muscle metabolism. Excessive lipid buildup, or lipotoxicity, has been connected to mitochondrial dysfunction in diabetes circumstances, which exacerbates muscle damage [37], [38].

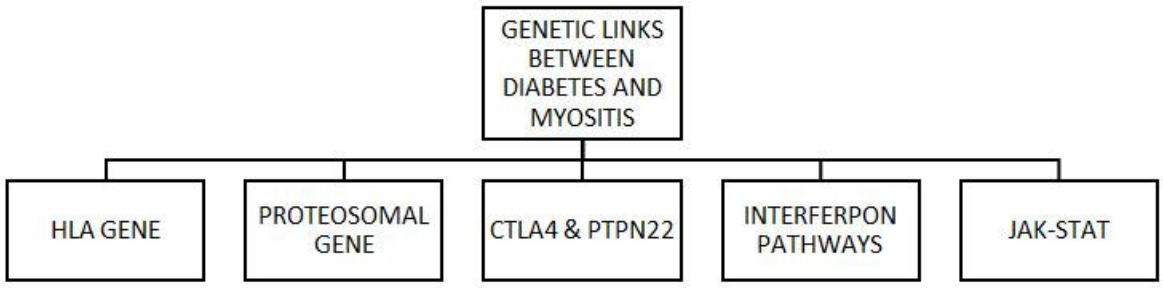

Fig. 8: Genetic Linkage Between Diabetes Between Diabetes and Myositis

6. DETECTION AND DIAGNOSIS

Advanced imaging techniques are used in the detection of myositis illnesses associated with diabetes such as hybrid image processing model, FDG- PET imagining and MRI scaning which improves the precision and effectiveness of diagnosis. To find underlying disorders linked to diabetes and myositis, these techniques combine conventional and novel methodologies [9]. Diabetic myonecrosis is detected by a combination of imaging investigations, clinical examination, and occasionally biopsy. Myositis and diabetes have a complicated association; diabetes can cause diseases that resemble or exacerbate myositis. It might be difficult to diagnose diabetic myonecrosis, a rare consequence of poorly managed diabetes, because it can exhibit symptoms that are similar to those of idiopathic inflammatory myositis (IIM) [39].

The following are the main techniques employed in the detecting process,

6.1. Clinical Presentation

Patients usually arrive with excruciating leg pain, especially in the thigh, and frequently do not have any concomitant infection symptoms like oedema or erythema. Finding symptoms and risk factors requires a comprehensive history and physical examination, particularly in those with poorly managed diabetes.

6.1.1. Imaging Techniques

MRI: Instead of computed tomographic imaging, magnetic resonance imaging is the preferred imaging modality for diabetic foot disease [40]. MRI is the recommended diagnostic test for diabetic myonecrosis. It is non-invasive and yields good anatomical detail. On T2-weighted images, an elevated signal suggests muscular oedema, which is characteristic of the syndrome. MRI can also assist to rule out other disorders, such as deep venous thrombosis.

CT SCAN: CT scans are useful for guiding biopsy operations and detecting muscle necrosis.Initial imaging information can be obtained via a CT scan, which reveals asymmetrical, enhancing space-occupying lesions in the afflicted muscles. Additionally, it can show widespread fat stranding and a muscle's heterogeneous look [3]. US: Ultrasound can detect deep venous thrombosis and may reveal a localised mass in the muscle.

BIOPSY: Although MRI is frequently enough to make a diagnosis, biopsy is regarded as the "gold standard." Despite the dangers of infection and delayed recovery, it can verify the existence of inflammation and necrosis in muscle tissue.

6.2. Laboratory Tests

Blood tests can be used to evaluate a patient's general health and diabetes management. Glycosylated hemoglobin and elevated blood glucose levels can be signs of inadequate diabetes care, which is a major risk factor for myonecrosis. It's critical to distinguish diabetic myonecrosis from other illnesses such infections, tumours, and deep vein thrombosis that might manifest similarly. To make the right diagnosis, a thorough assessment of the symptoms and imaging data is required [41].

6.3. Treatment Methods

Diabetic muscle necrosis is primarily treated conservatively. To alleviate symptoms and prevent complications, bed rest, analgesics, and avoiding weight bearing on the afflicted limb are essential. Early ambulation will lengthen hospital stays and increase the risk of muscle haemorrhage. Since physical treatment might prolong myocardial infarction, it should be avoided. Excisional biopsy of the afflicted muscle should ideally be avoided because some cases showed the development of muscle haemorrhage after an exercise program. Antiplatelet and anti-inflammatory medications taken together may shorten the healing period from eight to five weeks. It is also advised to maintain optimal glycaemic management. For individuals with compartment syndrome, decompression requires surgery [42]. Individualized therapies are necessary to effectively address the distinct lifestyle problems faced by patients with diabetes and myositis. With an emphasis on dietary modifications, exercise, and self-management education, lifestyle treatment is essential for the control of diabetes. In addition to helping with glucose management, this strategy treats related issues, such as musculoskeletal diseases that are common in diabetic patients [43].

Long-term immunosuppressive medication is common for autoimmune disorders including myositis. Prednisolone is often administered at a high dose (0.75 mg/kg per day) for 1-2 months, then gradually reduced monthly. Immunosuppressive medication is commonly used with corticosteroids to improve disease management and minimise overall steroid dosage. Personal experience and medication toxicity have a role in selecting the appropriate agent. Treatment options include methotrexate, azathioprine, cyclosporine, mycophenolate mofetil, and hydroxychloroquine. Intravenous immunoglobulin is typically reserved for refractory patients [18].

The primary focus of treatment is supportive care, including as pain management and glucose control, with surgical procedures infrequent. The following sections discuss the most important components of DMN treatment:

7. SUPPORTIVE CARE

Pain management: Etoricoxib and other nonsteroidal anti-inflammatory medicines (NSAIDs) are frequently used to reduce pain [44], [45].Physiotherapy: To enhance muscular strength and function and facilitate recovery, early physiotherapy is advised [44], [46]. Control of Glycaemic Strict Glycaemic Control: Since inadequate glycaemic management is a major risk factor for DMN, blood sugar optimisation is essential [2], [46]. Examining the diagnostic: Non-invasive Imaging: Magnetic resonance imaging (MRI), which shows distinctively hyper intense signals in afflicted muscles, is the favoured diagnostic method [44], [46]. Although DMN is usually benign and treatable, its symptoms might be mistaken for more serious illnesses, resulting in incorrect diagnoses and ineffective treatments [26].

8. CONCLUSION

The connection between diabetes mellitus and myositis highlights common genetic and immune processes, with both conditions showing overlaps in pathways such as the HLA region and immune-regulating genes like CTLA4 and PTPN22. Inadequately managed diabetes raises the likelihood of musculoskeletal issues, such as diabetic myonecrosis, while myositis, marked by muscle inflammation and weakness, is affected by various genetic factors. The treatment of these disorders includes a mix of controlling blood sugar levels, managing pain, and using immunosuppressive therapies. Prompt recognition and individualized treatment approaches, informed by genetic studies, are crucial for enhancing patient outcomes, emphasizing the significance of comprehending the genetic connection between these autoimmune diseases for more effective treatments.

The future of addressing the genetic relationship between diabetes mellitus and myositis is tied to progress in genomics and precision medicine. As our comprehension of shared genetic pathways and immune processes improves, tailored treatments and enhanced diagnostics will facilitate earlier identification, individualized therapies, and more effective management of both diseases. Innovations in immune-modulating treatments and gene editing may offer new therapeutic options, potentially decreasing disease severity and enhancing patient outcomes. Merging genetic discoveries with clinical application holds promise for improving care and the quality of life for those affected.

9. ACKNOWLEDGEMENT

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