|| Print ISSN: 2589-7837 || Online ISSN: 2581-3935 ||
International Journal of Medical Science and Diagnosis Research (IJMSDR)
Available Online at www.ijmsdr.com
NLM (National Library of Medicine ID: 101738824)
Review Article
Volume 9, Issue 01; January-March: 2025; Page No. 01-05

Diabetic Myopathy and Diabetic Cardiomyopathy: The Negative Influence of Diabetes on Skeletal and Striated Muscle Health

Soumik Chatterjee[1], Papiya Majumdar[2]

[1] Department of Endocrinology, Suraksha Diagnostics, Garia, Kolkata, WB.

[2] Department of Pathology, KPC Medical College & Hospital, Jadavpur, Kolkata, WB

Received: 11-01-2025 / Revised: 30-01-2025 / Accepted: 11-02-2025
Conflicts of Interest: Nil
Corresponding author: Dr Soumik Chatterjee
DOI: https://doi.org/10.32553/ijmsdr.v9i1.1048

Abstract

Diabetes mellitus, an alarming global health concern, is a group of metabolic diseases that are associated with the presence of a hyperglycemic state with impairment in insulin signalling, which can occur due to either a deficiency or resistance to insulin. Furthermore, a variety of additional elements contribute to the complex progression of complications linked to diabetes.

Introduction

Myopathies encompasses a diverse group of diseases that predominantly the skeletal muscle structure, metabolism, or channel function [1]. Myopathies are often characterized by disruptions in muscle tissue integrity and metabolic stability, which can be triggered by a variety of etiological agents ranging from genetic disorders, certain drugs and toxins, infections, to endocrinopathy like diabetes mellitus [1]. Diabetic myopathy, like other long-term consequences, is thought to be caused by a microvascular pathology that causes inflammation, ischemia, and infarction in the afflicted muscles. In 1965, Anger-vall and Stener identified diabetic muscle infarction as tumoriform localized muscular degeneration [2]. Diabetic myopathy most frequently affects the thigh and calf, although there is apparent relative sparing of some of the smaller muscles of the thigh [3–6].

Diabetic cardiomyopathy (DbCM) is a form of Stage B Heart Failure defined by the occurrence of myocardial dysfunction in patients with diabetes mellitus, occurring independently of other cardiac conditions, including coronary artery disease, valvular heart disease, or advanced arterial hypertension [7]. DbCM, first identified in postmortem examinations conducted by Rubler et al. in 1972 [8], is a complication of long-standing diabetes that is gaining recognition yet remains inadequately researched, potentially progressing to heart failure [7,9].

Pathophysiology of Diabetic Myopathy & Diabetic Cardiomyopathy

Skeletal muscle in individuals diagnosed with Diabetes Mellitus exhibits distinct characteristics, including an increased count of glycolytic fibers, pronounced muscle atrophy, and a diminished capillary density [6, 10–13]. These individuals frequently experience disruptions in muscle metabolism, which contribute to a decline in intermyofibrillar mitochondrial content and the abnormal accumulation of lipids [14]. These adverse changes culminate in a condition referred to as "metabolic inflexibility," hindering the muscle's capability to effectively alternate between the oxidation of fats and carbohydrates in response to insulin [10,15]. Furthermore, functional deficits are evident, as indicated by a notable decrease in muscle strength, which correlates significantly with the buildup of intramuscular fat [16]. Chronic low-grade inflammation, oxidative stress, and disrupted extracellular matrix remodeling are proposed as fundamental factors contributing to the deterioration of muscle health in diabetes mellitus [15].

The pathophysiology of diabetic cardiomyopathy encompasses a variety of interconnected mechanisms, such as metabolic disturbances, oxidative stress, inflammation, and the development of fibrosis [17]. Modifications in cardiac metabolic processes, including increased fatty acid usage and diminished glucose oxidation, play a significant role in the onset of myocardial lipotoxicity. The over-accumulation of lipids within cardiomyocytes results in mitochondrial dysfunction, an elevation in the production of reactive oxygen species and a reduction in contractile performance [17,18]. Lipotoxicity has the potential to negatively influence the function of cardiomyocytes. This effect is likely attributable not merely to elevated levels of triglycerides and fatty acids in the bloodstream, but also to the increased presence of intermediate lipid species such as oxidized phospholipids and ceramides. The generation of these intermediates, specifically diacylglycerol, is associated with a nitric oxide synthase-mediated mechanism that diminishes the hypertrophic response of muscle cells, simultaneously impacting the microcirculatory system [19, 20].

Diabetes leads to a persistent inflammatory condition within the body, characterized by elevated levels of the nucleotide-binding oligomerization domain-like receptor family, pyrin domain-containing-3 (NLRP3) inflammasome. It is believed that NLRP3 plays a crucial role in the progression of DbCM [21]. Chronic hyperglycemia plays a significant role in the development of diabetic cardiomyopathy. Increased glucose concentrations lead to the synthesis of advanced glycation end-products, which foster oxidative stress and inflammatory responses. These glycation end-products engage with their receptors located on cardiomyocytes and cardiac fibroblasts, initiating intracellular signaling cascades that enhance fibrosis, hypertrophy, and eventually, apoptosis [17, 22].

Evaluation and Workup

Elaborative history alongside physical examination and nutritional assessment is mandatory to identify and diagnose diabetic myopathy. They usually present with

abrupt onset of pain and progressive swelling of the affected muscles, interfering in daily life activities. Bilateral involvement and multiple discontinuous sites of muscle involvement are often characteristics of diabetic myopathy [6]. While laboratory testing can be beneficial, it is often not tailored to the situation. Creatine kinase levels and ESR are high in nearly half of the reported cases [3, 4]. Creatine kinase levels indicate active muscle breakdown and are typically higher during the acute stages of disease, followed by early normalisation [6, 23]. Electrodiagnostic testing is useful to confirm the myopathic nature of the process if there is an identifiable pattern and to stratify the severity of the disease. Needle Electromyography is the most sensitive examination for myopathy [1]. Anti-nuclear antigen (ANA) and myositis associated antibody panels should be checked. Diffuse subcutaneous edema with poor delineation of fascial planes and focal-to-diffuse low-signal subcutaneous fluid may be seen in Axial T1-weighted MRI [6]. Biopsies should be avoided if the clinical presentation and imaging findings are consistent, since conservative treatment is usually sufficient to resolve symptoms. Biopsy is recommended for atypical clinical scenarios or when treatment does not yield a clinical response [6].

A conclusive diagnosis of DbCM necessitates advanced invasive hemodynamic evaluation, myocardial biopsy, and non-invasive imaging modalities, including echocardiography and cardiovascular magnetic resonance [17]. These methods constitute the most suitable, practical, and risk-benefit-optimized strategy for identifying both functional and structural changes in diabetics [17]. Histopathologically, DbCM is distinguished by a non-specific pattern of hypertrophy in cardiomyocytes, alongside interstitial inflammation and fibrosis [7, 8]. Additionally, DbCM may be associated with cardiovascular autonomic neuropathy [7, 24].

Management

The mainstay of treatment for diabetic myopathy consists of exercises with a combination of analgesics—anti inflammatory and antiplatelet medication along with strict glycemic control, optimized nutrition, and physical therapies. Combining aerobic exercise with strength training seems to be effective in enhancing submaximal endurance capacity [25]. The primary care physician may initially suspect the patient's diagnosis; however, the involvement of various specialities, including endocrinologists, is essential for crafting effective treatment plans. Maintaining interprofessional communication among all members of the treatment team is crucial for mitigating the progression of diabetic myopathy and delaying the emergence of associated complications.

The management of DbCM necessitates a multifaceted strategy that encompasses lifestyle changes, regulation of blood glucose levels, and specific cardiovascular treatments. Metformin, a widely prescribed oral hypoglycemic medication, has demonstrated positive effects on DbCM through the activation of the PK2/PKR signaling pathway [17, 26]. This pathway is integral to the cellular response to stress and inflammation, contributing to a decrease in oxidative stress, inflammation, and fibrosis within the diabetic heart [17].

Empagliflozin, an inhibitor of the sodium glucose co-transporter-2, exhibited significant cardioprotective properties, as evidenced by a reduction in cardiovascular event rates among high-risk patients with diabetes mellitus, thereby enhancing clinical outcomes. Empagliflozin has been linked to a decrease in left ventricular mass and enhancements in diastolic function, as evidenced by echocardiographic evaluations [27]. Additionally, it is associated with a reduction in myocardial fibrosis, an improvement in left ventricular ejection fraction and a decrease in left ventricular end-diastolic volume. Moreover, Empagliflozin optimizes cardiac glucose metabolism by promoting myocardial glucose utilization.

Conclusion

Diabetic myopathy and Diabetic Cardiomyopathy represents a burgeoning field of research that, while still in its infant stages, offers a compelling opportunity for additional therapeutic exploration aimed at preserving muscle integrity and, in turn, mitigating various complications associated with diabetes.

Conflict of Interest Statement

The authors declare that the manuscript was drafted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

References

1. Nagy H, Veerapaneni KD. Myopathy. [Updated 2023 Aug 14]. In: StatPearls [Internet].
2. Angervall L, Stener B. Tumoriform focal muscu- lar degeneration in two diabetic patients. Diabeto- logia 1965; 1:39–42

3. Kapur S, Brunet JA, McKendry RJ. Diabetic mus- cle infarction: case report and review. J Rheuma- tol 2004; 31:190–194
4. Trujillo-Santos AJ. Diabetic muscle infarction: an underdiagnosed complication of long-standing diabetes. Diabetes Care 2003; 26:211–215
5. Jelinek JS, Murphey MD, Aboulafia AJ, Dussault RG, Kaplan PA, Snearly WN. Muscle infarction in patients with diabetes mellitus: MR imaging findings. Radiology 1999; 211:241–247
6. Huang BK, Monu JUV, Doumanian J. Diabetic Myopathy: MRI Patterns and Current Trends. American Journal of Roentgenology 2010;195:198–204.
7. Januzzi JL, Del Prato S, Rosenstock J, Butler J, Ezekowitz J, Ibrahim NE, et al. Characterizing diabetic cardiomyopathy: baseline results from the ARISE-HF trial. Cardiovasc Diabetol 2024;23.
8. Rubler S, Dlugash J, Yuceoglu YZ, Kumral T, Branwood AW, Grishman A. New type of cardiomyopathy associated with diabetic glomerulosclerosis. Am J Cardiol. 1972;30(6):595–602.
9. Tan Y, Zhang Z, Zheng C, Wintergerst KA, Keller BB, Cai L. Mechanisms of diabetic cardiomyopathy and potential therapeutic strategies: preclinical and clinical evidence. Nat Rev Cardiol. 2020;17(9):585–607.
10. D'Souza DM, Al-Sajee D and Hawke TJ (2013) Diabetic myopathy: impact of diabetes mellitus on skeletal muscle progenitor cells. Front. Physiol. 4:379.
11. Mårin, P., Andersson, B., Krotkiewski, M., and Björntorp, P. (1994). Muscle fiber composition and capillary density in women and men with NIDDM. Diabetes Care 17, 382–386
12. Nyholm, B., Qu, Z., Kaal, A., Pedersen, S. B., Gravholt, C. H., Andersen, J. L., et al. (1997). Evidence of an increased number of Type Ilb muscle fibers in insulin resistant first-degree relatives of patients with NIDDM. Diabetes 46, 1822-1828.
13. Nguyen, M.-H., Cheng, M., and Koh, I. J. (2011). Impaired muscle regeneration in Ob/ob and Db/db mice. ScientificWorldJournal 11, 1525-1535.
14. Nielsen, J., Mogensen, M., Vind, B. F., Sahlin, K., Højlund, K., Schrøder, H. D., et al. (2010). Increased subsarcolemmal lipids in Type 2 diabetes: effect of training on localization of lipids, mitochondria, and glycogen in sedentary human skeletal muscle. Am. J. Physiol. Endocrinol. Metab. 298, E706–E713.
15. Kelley, D. E., and Mandarino, L. J. (2000). Fuel selection in human skeletal muscle in insulin resistance: a reexamination. Diabetes 49, 677–683.
16. Park, S. W., Goodpaster, B. H., Strotmeyer, E. S., de Rekeneire, N., Harris, T. B., Schwartz, A. V., et al. (2006). Decreased muscle strength and quality in older adults with Type 2 diabetes: the health, aging, and body composition study. Diabetes 55, 1813–1818.
17. Rizza V, Tondi L, Patti AM, Cecchi D, Lombardi M, Perone F, et al. Diabetic cardiomyopathy: pathophysiology, imaging assessment and therapeutical strategies. International Journal of Cardiology Cardiovascular Risk and Prevention 2024;23:200338.
18. S. Boudina, E.D. Abel, Diabetic cardiomyopathy revisited, Circulation 115 (25) (2007) 3213–3223.
19. Radzioch, E.; Da̧bek, B.; Balcerczyk-Lis, M.; Fra̧k, W.; Fularski, P.; Młynarska, E.; Rysz, J.; Franczyk, B. Diabetic Cardiomyopathy—From Basics through Diagnosis to Treatment. Biomedicines 2024, 12, 765.
20. Bugger, H.; Abel, E.D. Molecular mechanisms of diabetic cardiomyopathy. Diabetologia 2014, 57, 660–671.
21. Nakamura, K.; Miyoshi, T.; Yoshida, M.; Akagi, S.; Saito, Y.; Ejiri, K.; Matsuo, N.;

Ichikawa, K.; Iwasaki, K.; Naito, T.; et al. Pathophysiology and Treatment of Diabetic Cardiomyopathy and Heart Failure in Patients with Diabetes Mellitus. Int. J. Mol. Sci. 2022, 23, 3587.

22. W.C. Stanley, F.A. Recchia, G.D. Lopaschuk, Myocardial substrate metabolism in the normal and failing heart, Physiol. Rev. 85 (3) (2005) 1093–1129.
23. Khoury NJ, El-Khoury GY, Kathol MH. MRI di- agnosis of diabetic muscle infarction: report of two cases. Skeletal Radiol 1997; 26:122–127
24. Fang ZY, Prins JB, Marwick TH. Diabetic cardiomyopathy: evidence, mecha- nisms, and therapeutic implications. Endocr Rev. 2004;25(4):543–67.
25. Voet NB, van der Kooi EL, Riphagen II, Lindeman E, van Engelen BG, Geurts ACh. Strength training and aerobic exercise training for muscle disease. Cochrane Database Syst Rev. 2010 Jan 20;(1):CD003907.
26. B. Zinman, C. Wanner, J.M. Lachin, et al., EMPA-REG OUTCOME investigators. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes, N. Engl. J. Med. 373 (22):2117–2128.
27. S. Verma, A. Garg, A.T. Yan, et al., Effect of empagliflozin on left ventricular mass and diastolic function in individuals with diabetes: an important clue to the EMPA-REG OUTCOME trial? Diabetes Care 39 (12):e212–e213.