OPEN ACCESS

Journal of Orthopedic Research and Therapy

Lecka-Czernik B, et al. J Orthop Res Ther 9: 1353.

www.doi.org/10.29011/2575-8241.001353

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Short Communication

Spinal Fusion Complications in Diabetes

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Citation: Lecka-Czernik B, Elgafy H, Czernik PJ (2024) Spinal Fusion Complications in Diabetes. J Orthop Res Ther 9: 1353. https://doi.org/10.29011/2575-8241.001353

Received Date: 20 July, 2024; **Accepted Date:** 25 July, 2024; **Published Date:** 26 July, 2024

Introduction

Diabetes is a chronic metabolic disorder that affects millions of people worldwide, with a significant portion of them likely to become orthopaedic patients at some point in their lives. It is estimated that over 38.4 million Americans live with diabetes (11.6% of U.S. population), including 13.8 million of 65 and older individuals (https://www.cdc.gov/diabetes). Diabetes is associated with a variety of complications with cardiovascular, kidney, and vision disabilities among the most recognized.

One of the lesser-known effects of diabetes is its impact on bone health and fracture healing. Historically, the focus on skeletal complications in diabetes was limited to the pathologies developed in the lower extremities due to neuropathy and impairment in vascular function. However, recent studies have shown that diabetes is associated with increased risk of fracture despite often normal or even higher bone mineral density (BMD) [1,2]. Detailed clinical studies have documented that diabetic bone disease is characterized by low bone turnover, as evidenced by decreased bone turnover markers such as CTX and P1NP in circulation, and structural abnormalities that contribute to the overall decrease in bone quality and increased fragility. These, corroborated with animal studies, led to a consensus that diabetic bone disease is a pathology of low bone material quality due to changes in bone metabolism and derangement of bone at the molecular and structural level [3]. Disruption in the diabetic bone microenvironment predisposes to fractures and impairs healing by affecting different stages of the process including hematoma and callus formation, and their resolution during bone remodelling phase [4]. In addition, hyperglycaemia and chronic inflammation lead to increased formation of advanced glycation end products (AGEs) and generation of reactive oxygen species (ROS), which in turn contribute to the disruption in osteoblast and osteoclast balance leading to decreased bone formation and heightening the risk of non-union or delayed union of fracture.

Degenerative Spine Disorders in Diabetes

Diabetes predisposes to development of spine degenerative conditions including degenerative disc, degenerative spondylolisthesis, lumbar facet arthropathy, degenerative scoliosis, and spinal stenosis [5-8]. In respect to the disc degeneration, recent studies on obese diabetic rats showed that biomechanical properties of annulus fibrosus are impaired because stiffening of collagen fibrils due to introduction of nonenzymatic cross-links by highly reactive AGEs [9].

Spinal Fusion Complications in Diabetes

It is estimated that 300,000 lumbar spinal fusions are performed in U.S. annually with a success rate of 70% to 90%. Recent retrospective observational study on patients residing in the same community and receiving care at the same health care facility, showed that diabetes increased risk ratio of revision surgery almost 3-fold due to non-union and more than 2-fold due to development of degenerative processes in the spine segments adjacent to the fused vertebrae [8]. This study also showed, for the first time, that a newly formed bone needed for fusion stabilization is of decreased quality in diabetic as compared to nondiabetic patients. This amounts to underdeveloped bone microstructure which is essential for integrity of biomechanical properties suggesting that even if the fusion is successful the quality of newly formed bone in diabetes is compromised which may cause additional complications in the future. Based on the aforementioned evidence on molecular basis of diabetic bone disease, one can suspect that differentiation of bone forming osteoblast and their activity can

be compromised, which together with increased proinflammatory signaling and AGEs may result in defective bone formation.

To follow up on this hypothesis, we have analyzed differentiation potential of mesenchymal. Cells residing in the paravertebral tissue isolated from fusion site of patients undergoing revision, in response to osteoblastic and adipocytic stimuli. Preliminary findings suggested that in contrast to nondiabetic, the cells isolated from diabetic patients had compromised response to differentiation stimuli, however the rigor of this analysis was confounded by the low number of analyzed specimens and complex composition of isolated tissues, which were a mixture of bony, fatty and connective tissue components. Nevertheless, these results were consistent with findings in diabetic rat model of spinal fusion indicating that newly formed bone was less mineralized despite no difference in availability of growth factors at the site of fusion surgery between diabetic and non-diabetic rats suggesting altered response of mesenchymal progenitors to pro-osteoblastic signaling [10]. An understanding of cellular mechanisms behind poor bone formation in diabetes may aid development of intervention to increase rate of spinal fusion success.

Potential Risk of Anti-Diabetic Therapies on Success of Spinal Fusion Surgery

The evidence on the effects of anti-diabetic therapies on spine health and success of fusion surgeries are not available, as yet. However, there is ample evidence on the effect of these therapies on bone mass, fracture risk, and fracture healing. Anti-diabetic therapies target different aspects of glucose metabolism including insulin sensitization (metformin and TZDs), insulin secretion and bioactivity (sulfonylurea, GLP-1 receptor agonists, DPP-4 inhibitors, and insulin analogues), and modulation of blood glucose levels by either increased glucose excretion (SGLT2 inhibitors) or slower digestion (GLP-1 receptor agonists, alpha-glucosidase inhibitors, and amylin). In general, these therapies are relatively safe for bone with some exceptions. TZDs, the full agonists of PPARG nuclear receptor, cause bone loss, increase fracture rate in older diabetic women, and significantly affect bone healing as shown in animal studies [11-13]. There is some evidence that biguanide, sulfonylurea and insulin have a negative effect on fracture healing by delaying either callus formation, cortical bridging or new bone formation resulting in increased risk of non-union [14]. Most recent study showed that semaglutide, which belongs to the family of GLP-1 receptor agonist and has become a blockbuster drug for weight loss, has a negative effect on BMD in obese adults with increased fracture risk [15]. Although, this study concluded that decrease in bone mineral density was secondary to the weight loss and involved increased bone resorption but not bone formation, however emerging new evidence indicate more complex skeletal effects of this drug. The study by Khalid et al. recently presented at the American Association of Neurological Surgeons has indicated that lumbar spine fusion patients taking semaglutide were 12-times more likely to have an additional lumbar surgery within one year than those who did not use semaglutide [16]. This finding underscores a need for a vigilance in the use of anti-diabetic and weight loss therapies in patients undergoing spinal fusion.

Therapeutical Perspectives

In the last two decades, researchers and surgeons focused on improving surgical techniques, as well as hardware used in spine surgery and fixing bone. Further, multiple biological substances used to stimulate bone formation have been developed and used to improve bone healing. Recently, the focus has shifted to bone health, how do we improve bone health before we take patients to surgery? It's an important question as we look to improve surgical outcomes and avoid patients having a second or third surgery. Improving bone health such as better diabetes and renal function control as well as any nutritional deficiency in particular Vitamin D. Further, to mitigate the high risks of failure of bone healing in diabetic patients, the use of patient's own bone (autograft), as well as biologics that help bone healing may improve the surgical outcome. As for postoperative care, nutrition supplement, extended antibiotic coverage, and wound care are used to mitigate the increased risks of wound infection.

Simultaneously, more preclinical research needs to be done to define molecular and cellular mechanisms underlying bone formation at the fusion site. Specifically, we have to understand whether defective new bone formation in diabetes is due to either osteoblast progenitors not responding to the signaling, or defective signaling, or proinflammatory and oxidative stress environment which have a negative effect on osteoblast activity. In addition, more research should be done on the possibility to use of already approved systemic bone anabolic therapies, including anti-sclerostin therapy, to improve new bone formation.

Interestingly, sclerostin protein levels in circulation are increased in diabetic individuals potentially inhibiting osteoblast differentiation and contributing to defective bone formation at the fusion site [17-19].

Acknowledgments

This work was supported by grant to B.L-C. from the National Institute of Health R01AG071332.

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