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An Overview on Mutations of *MEN1* Gene and its Role in Orthopedic Pathology

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About the Study

Menin is a highly conserved protein encoded by the *MEN1* gene, which is widely expressed. It is involved in a variety of intracellular functions, including transcription, genomic integrity, proliferation, and intracellular signalling. Multiple Endocrine Neoplasia type 1 (*MEN1*) syndrome is caused by mutations in the menin gene. The growth of numerous tumours, mostly in the endocrine glands, is a hallmark of this autosomal dominant disorder. The parathyroid gland lesions have the highest penetrance in *MEN1* and appear as Primary Hyperparathyroidism (PHPT). PHPT, on the other hand, is a potent etiological factor that can cause bone abnormalities such as a considerable reduction in Bone Mineral Density (BMD) and repeated low-energy fractures.

Bone abnormalities in people with PHPT with multiple endocrine neoplasias (*PHPT/MEN1*) are more severe than in those with sporadic PHPT. Clinical evidence has shown that individuals with menin gene mutations have more severe bone and mineral disorders: bone mineral densities in the lumbar spine and at the femoral neck in *PHPT/MEN1* patients are much lower than in spontaneous PHPT patients. Up to 77.8% of people have bone demineralization, which can lead to osteoporosis. Furthermore, after parathyroidectomy, the rate of bone formation in *PHPT/MEN1* individuals is much lower than in sporadic PHPT patients.

There are also some discrepancies in the structure of the modifications. Both cortical and trabecular bone tissues are demineralized in *PHPT/MEN1*, but only cortical bone tissue is damaged in sporadic *PHPT*.

At the same time, the quality of the published clinical research is inadequate, owing to the orphan nature of the condition and the wide range of probable comorbidities. It is impossible to interpret these research without ambiguity, necessitating the development of a proper experimental model.

In the absence of human cell-based models, mice were used to investigate menin's role in bone metabolism *in vitro* and *in vivo*. Menin is directly involved in the regulation of osteoblastogenesis, differentiation, and function of osteoblasts, as well as the osteocyte-osteoclast interaction, according to a number of recent studies. Menin's effects have been shown to be mediated by a variety of potential mechanisms, including interactions with the Runx2 transcription factor, molecules involved in the -catenin pathway, BMP, and Smad3, Smad1/5, and JunD signalling molecules. Menin influences osteoclastogenesis, as well as the formation and function of osteoblasts, via these mechanisms.

Bone remodelling is a continuous process that occurs throughout a person's life. It entails the removal of old bone tissue and the replacement of it with a newly formed bone matrix. Osteoblasts (bone-forming cells) and osteoclasts are the primary cells involved in bone remodelling (cells that degrade bone tissue). The combined action of these cells results in the resorption of old bone and the formation of new bone. Menin plays an important role in bone remodelling, which is a continuous dynamic interaction of bone-forming cells (osteoblasts) and bone-resorbing cells (osteoclasts). Models that use transformed cell lines and/or *MEN1*-knockout animals, on the other hand, are unable to fully reproduce the extremely variable clinical presentation of *MEN1* in humans and do not account for the possible influence of individual genetic and epigenetic changes on the course of bone disorders. An in vitro isogenic model based on MEN1 patients' cells, created through cell reprogramming and genome editing, would be a promising approach to understanding the mechanisms underlying menin's role in bone metabolism while taking individual genetic and epigenetic features into account. Aside from the advantages of personalization, this model can be used to identify specific therapeutic targets and develop modern effective therapeutic algorithms for *MEN1*. However, transforming induced pluripotent stem cells, Mesenchymal Stem Cells (MSCs), or fibroblasts into osteoblasts is a difficult task. Stem cells, in particular, can form teratomas, are collected in a traumatic manner, and lose their ability to differentiate after five passages. Dermal fibroblasts can go through 15 passages, but they are differentiated cells that are difficult to direct toward specific lineages.