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Concise Review

Neuronal-Hematopoietic Cell Fusion in Diabetic Neuropathy

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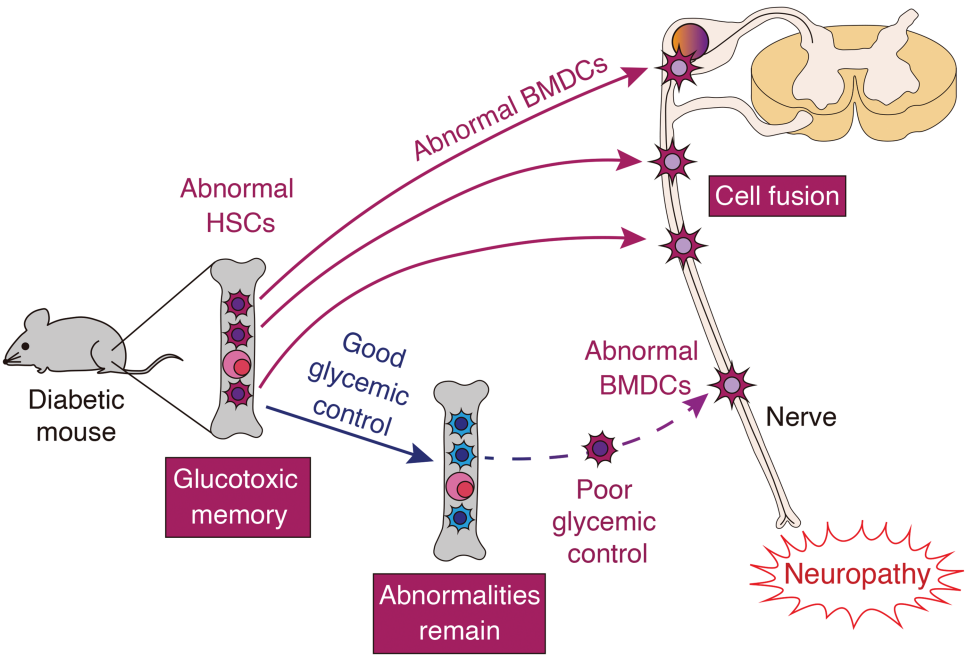
Abstract

Diabetic neuropathy is a major complication of diabetes mellitus that occurs during the early stages of the disease. Many pathogenic mechanisms are related and induced by hyperglycemia. However, even if these factors improve, diabetic neuropathy cannot go into remission and progresses slowly. Furthermore, diabetic neuropathy often progresses even with proper glycemic control. Recently, bone marrow-derived cells (BMDCs) were reported to be involved in the pathogenesis of diabetic neuropathy. BMDCs expressing proinsulin and TNFα migrate to the dorsal root ganglion and fuse with neurons, and this neuronal-hematopoietic cell fusion induces neuronal dysfunction and apoptosis. The CD106-positive lineage$^-$sca1$^+$c-kit$^+$ (LSK) stem cell fraction in the bone marrow is strongly involved in cell fusion with neurons, leading to diabetic neuropathy. Surprisingly, when CD106-positive LSK stem cells obtained from diabetic mice were transplanted into nondiabetic mice, they fused with dorsal root ganglion neurons and induced neuropathy in non-hyperglycemic normal mice. The transplanted CD106-positive LSK fraction inherited the trait even after transplantation; this "progeny effect" may explain the irreversibility of diabetic neuropathy and is a significant finding for determining the target of radical treatments and provides new directions for developing therapeutic methods for diabetic neuropathy.

Key words: bone marrow; diabetes; hematopoietic stem cell; neuropathy; Sca-1+c-Kit+Lin.

Graphical Abstract



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Significance Statement

The involvement of bone marrow cells has recently attracted a great deal of attention as a pathogenesis of diabetic neuropathy. Especially, the most remarkable discovery is the contribution of neuronal-hematopoietic cell fusion. Here, it is summarized what populations of abnormal hematopoietic stem cells are involved in cell fusion and how they fuse with neurons to cause neuropathy. Once programmed, the cells irreversibly show abnormalities and remain in the bone marrow even with good glycemic control. Moreover, they have a progeny effect that induces neuropathy even in normal mice. Therefore, it will be necessary to target these cells for radical remission in diabetic neuropathy.

Introduction

Diabetic neuropathy is one of the major complications of diabetes mellitus (DM) and is induced at an early stage compared to other complications such as cardio-cerebrovascular disease, nephropathy, and retinopathy.[1-4] Many pathogenic mechanisms are induced by hyperglycemia, which leads to gangrene and non-traumatic lower-limb amputations.[3,5,6] The major pathogenesis is oxidative stress, abnormalities in the polyol pathway, increased advanced glycation end products, and activation of protein kinase C and mitogen-activated protein kinases.[3,6] However, even if these factors improve, diabetic neuropathy cannot be remitted and gradually progresses even when glycemic control is good. Therefore, there is "a point of no return" in diabetic neuropathy,[7] and it is believed that there should be an unknown pathogenesis that may explain this irreversibility. Detailed observations of peripheral nerves include elevated cytokines such as IL-6 and tumor necrosis factor (TNF)α, and the infiltration and accumulation of numerous blood cells.[8-12] In this review, we focused on blood cells that migrate to the peripheral nervous system, as they might be pivotal players in elucidating the novel mechanism of diabetic neuropathy.

Neuronal Inflammation in the Peripheral Nervous System and Circulating Bone Marrow Cells Under Diabetic State

Classically, immune responses and inflammation have been reported to be related to the pathogenesis of diabetic neuropathy. In particular, the contribution of macrophages has been well described in terms of their features, which induce inflammation in peripheral nerves by the expression of cytokines such as TNFα, iNOS, and IL-1β.[13,14] In addition, $CD8^+$ T lymphocytes can infiltrate into the sural nerve and are involved in the development of diabetic neuropathy by affecting cytotoxicity in Schwann cells in the peripheral nerve.[10] In addition bone marrow-derived endothelial progenitor cells (EPCs) can repopulate the vasculature, a non-hematopoietic tissue.[15-17] EPCs show phenotypes overlapping with hematopoietic cells, and are thought to originate in the bone marrow. In diabetic patients, circulating EPCs are reduced and exhibit dysfunction.[15] Diabetic complications are related to micro- and macroangiopathy and may affect the microcirculation in the peripheral nerves. In addition, bone marrow-derived hematopoietic stem/progenitor cells (HSPCs) and $CD34^+$ cells contribute to the pathogenesis of bone marrow autonomic neuropathy by bone marrow denervation and stem cell trafficking.[18-20] Nociceptive receptors for sensory nerves in the bone marrow decrease in diabetic mice and lead to dysfunction in the appropriate trafficking of bone marrow cells to peripheral tissues and dysfunction in the stabilization of hematopoietic stem cells (HSCs).[21] Many studies have described a relationship between bone marrow-derived cells (BMDCs) and diabetic neuropathy (Table 1),[13,18-27] suggesting that BMDCs are involved in diabetic complications.

Neuronal Cell Fusion with Hematopoietic Cells

The streptozotocin (STZ) mouse as an insulin-deficient diabetic model due to β-cell death specifically induced by STZ injection and the high-fat diet (HFD) mouse as an insulin-resistant diabetic model induced by HFD are widely used as diabetic mouse models in animal experiments.[28,29] In both STZ and HFD diabetic mice, bone marrow transplantation was performed to determine the pathogenesis and the contribution of bone marrow cells to neuropathy under diabetic conditions, and the presence of hyperglycemia-induced abnormal HSCs was discovered.[24,27] These cells are positive for proinsulin (expressed as a marker of this cell) and TNFα in animal models, migrate to the dorsal root ganglion (DRG) as BMDCs, and undergo fusion with neurons (Fig. 1).[24,27] Neuronal-hematopoietic cell fusion has been shown to induce neuronal dysfunction and apoptosis.[27] Specifically, DRG neurons fused with proinsulin-positive BMDCs induced by hyperglycemia selectively exhibit the abnormal cell excitability upon KCL stimulation, high TNFα expression, and TUNEL positivity.[27] To the question of why BMDCs migrate to DRG and fuse with neurons under disease conditions, it has been reported that circulating BMDCs contribute to repairing damaged tissues through cell fusion.[30,31] In addition, other studies have shown that transplanting HSCs into mice with retinal degeneration or Parkinson's disease rescues the disease condition by reprogramming through cell fusion with glial cells or neurons.[32-34] Hence, the neuronal-hematopoietic cell fusion in diabetes might be interpreted as an effect of BMDCs trying to protect neurons from glucotoxic damage due to hyperglycemia. However, this results in cell damage rather than the support or rescue of neurons. Therefore, abnormal HSCs and BMDCs should be targeted for therapy in the case of diabetic neuropathy. In an investigation using TNFα conditional knockout mice, the presence or absence of neuropathy was examined in diabetic mice after transplantation of bone marrow in which TNFα was knocked out only in insulin-positive cells.[13] Results revealed that the development of diabetic neuropathy was significantly suppressed by knocking out TNFα in abnormal BMDCs.[13] This finding suggests that hyperglycemia-induced abnormal BMDCs are involved in the onset of neuropathy. The presence of diabetes-induced abnormal BMDCs may represent a novel pathogenesis of diabetic neuropathy and help determine why diabetic neuropathy is irreversible (Fig. 1).

Features of Abnormal Hematopoietic Cells in Diabetic Condition

To identify the original population of abnormal BMDCs, various fractions of the bone marrow including polynuclear

Table 1. Summary of the contribution of bone marrow-derived cells in the pathogenesis of diabetic neuropathy.

Cell type of BMDCs	Neuropathy type	Contribution to the pathogenesis	Model (reference), year
BMDCs expressing TNFα and proinsulin	Peripheral neuropathy	Neuronal apoptosis, cell fusion with neuron	Mouse, rat,[27] 2005
BMDCs expressing TNFα and proinsulin	Peripheral neuropathy	Oxidative stress, neuronal apoptosis, cell fusion with neuron	Mouse,[26] 2012
LSK HSCs	Peripheral neuropathy	Neuronal apoptosis, cell fusion with neuron, progeny effect	Mouse,[24] 2014
$CD34^+Flk^+$cells, LSK HSCs	Bone marrow autonomic neuropathy	Trafficking of BMSCs	Mouse, human,[18] 2014
$Thy1^+$BMDCs	Bone marrow autonomic neuropathy	Proinflammation	Rat,[19] 2015
BMDCs expressing TNFα and proinsulin	Peripheral neuropathy	Neuronal apoptosis	Mouse,[13] 2015
$NK1R^+$LSK HSCs	Bone marrow autonomic neuropathy Peripheral neuropathy in bone marrow	Trafficking and mobilization of BMDCs	Mouse, human,[21] 2015
BMDCs expressing TNFα and proinsulin	Peripheral neuropathy	Neuronal apoptosis	Mouse,[22] 2015
$CD106^+$LSK HSCs	Peripheral neuropathy	Cell fusion with neuron, progeny effect	Mouse,[23] 2021
BM-MSCs	Peripheral neuropathy	Apoptosis, proinflammation	Rat,[25] 2021
HSPCs	Bone marrow autonomic neuropathy	Denervation in bone marrow	Mouse,[20] 2022

Abbreviations: BMDCs, bone marrow-derived cells; BM-MSCs, bone marrow-derived mesenchymal stem cells; HSCs, hematopoietic stem cells; HSPCs, hematopoietic stem and progenitor cells; LSK, lineage-sca1+c-kit+; NK1R, neurokinin 1 receptor; TNF, tumor necrosis factor.

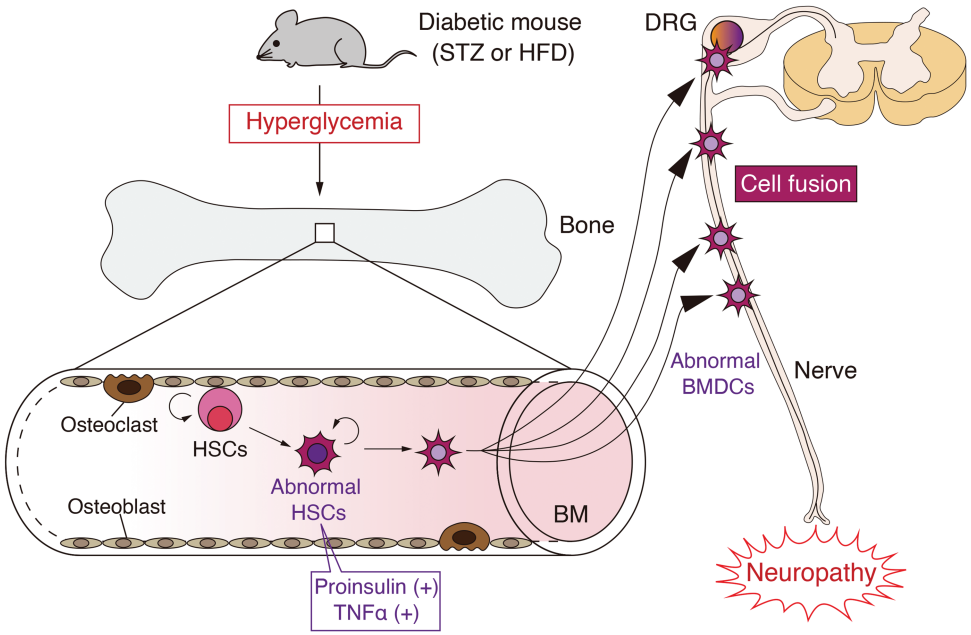

Figure 1. Mechanism of the onset in diabetic neuropathy by neuronal-hematopoietic stem cell fusion. Abnormal HSCs expressing TNFα and proinsulin appear in the bone marrow of diabetic mice induced by STZ or HFD. Abnormal HSCs proliferate and differentiate in the bone marrow and migrate to systemic tissues through the bloodstream. Abnormal BMDCs that reach peripheral nerves fuse with nerve fibers and dorsal root ganglion neurons, causing neuropathy. BM, bone marrow; BMDCs, bone marrow-derived cells; DRG, dorsal root ganglion; HFD, high-fat diet; HSCs, hematopoietic stem cells; STZ, streptozotocin; TNFα, tumor necrosis factor α.

cells, mononuclear cells, lymphocytes, monocytic cells, mesenchymal stem cells, and HSCs were examined. The $lineage^-sca1^+c\text{-}kit^+$ (LSK) fractions showed significant differences in proinsulin and TNFα expression between diabetic and nondiabetic cells.[24] Further analysis revealed that CD106 (Vcam1)-positive cells in the LSK fractions showed abnormalities under hyperglycemic conditions and migrated to the peripheral nervous system through the sinusoid in the bone marrow (Fig. 2) and fused with DRG neurons or nerve cells, leading to peripheral neuropathy in diabetic mice.[23] Additionally, the trafficking and stabilization of HSCs were impaired by the dysfunction of sympathetic nerves in the bone marrow (Fig. 2). The phenotypic features of $CD106^+$ cells in the LSK fraction were different under diabetic and nondiabetic conditions (Fig. 2); however, there was no difference in the phenotypic features of $CD106^+$ cells in the non-LSK fraction between diabetic and nondiabetic condition, similar to that in $CD106^-$ cells in the LSK fraction.[23] These

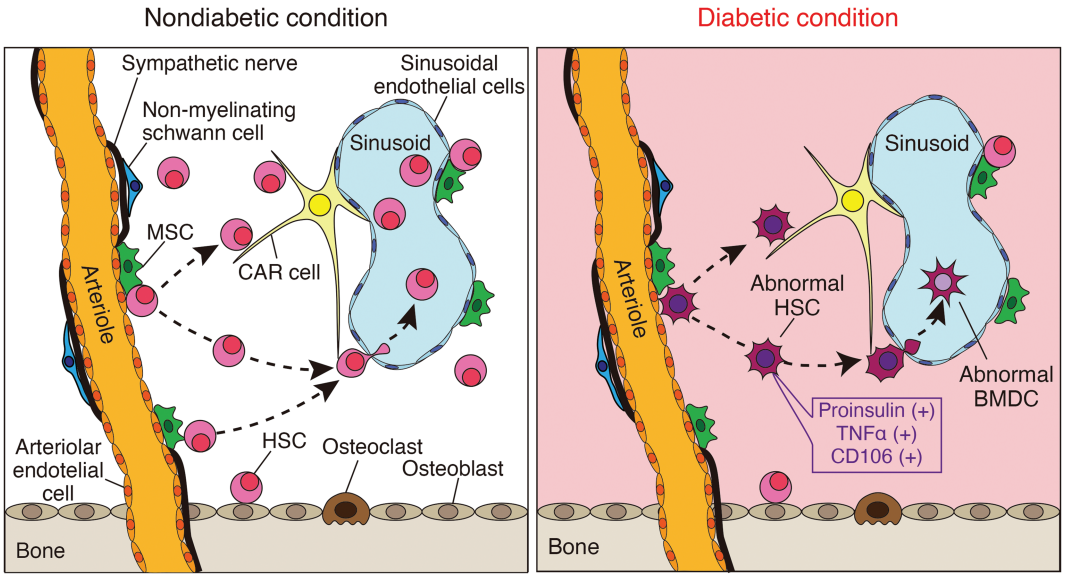

Figure 2. Abnormal homeostasis in bone marrow tissues under diabetic conditions. In physiological conditions (left panel; nondiabetic condition), HSCs retained in MSCs that constitute the vascular niche are released upon sympathetic nerve stimulation and migrate from CAR cells to sinusoids with proliferation and differentiation. Once these cells reach the sinusoids, they migrate through the sinusoidal endothelium to systemic tissues. In the diabetic condition (right panel), normal HSCs are reduced; they are released into the bone marrow upon sympathetic nerve stimulation under hyperglycemia from the condition of retaining in MSCs and migrate to the sinusoids with the help of CAR cells while differentiating to abnormal HSCs expressing proinsulin, TNFα, and CD106. The abnormal HSCs enter into the sinusoids through the sinusoidal endothelium and migrate into systemic tissues as BMDCs, but this mobilization of HSCs exhibits abnormality under the diabetic condition. BMDCs, bone marrow-derived cells; CAR, CXCL12 abundant reticular; HSCs, hematopoietic stem cells; MSCs, mesenchymal stem cells; TNFα, tumor necrosis factor α.

results suggest that the CD106⁺ LSK fraction is strongly involved in cell fusion with neurons and causes diabetic neuropathy.

Abnormal Programming in Hematopoietic Stem Cells Under Diabetic Conditions

When bone marrow LSK fractions obtained from diabetic mice were transplanted into nondiabetic mice, they fused with DRG neurons and induced neuropathy in non-hyperglycemic normal mice.[24] The transplanted LSK fraction inherited the trait even after transplantation,[24] this is called the "progeny effect".[24] The cause of the "progeny effect" may be glucose toxicity or glucotoxic memory, leading to an abnormal direction of differentiation or abnormal programming in HSCs (Fig. 3). Furthermore, the transplantation of only the CD106⁺ LSK fraction induces neuronal-hematopoietic cell fusion and diabetic neuropathy.[23] CD106⁺ LSK fractions also showed the "progeny effect" (Fig. 3).[23] Therefore, this fraction is the most important contributor to diabetic neuropathy and is expected to be an optimal therapeutic target. Although this "progeny effect" may be a key factor in explaining the irreversibility of diabetic neuropathy, the molecular mechanism of this phenomenon remains to be clarified and is a subject for future research.

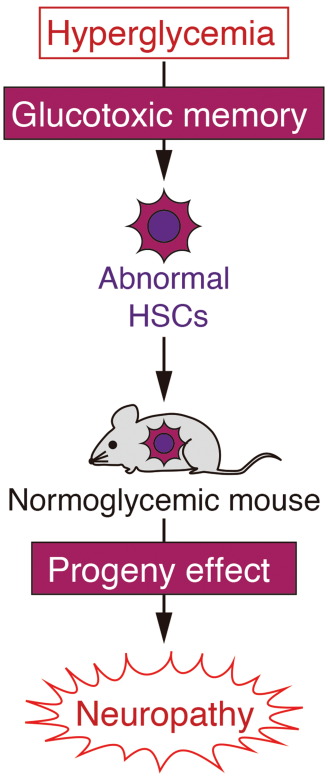

Figure 3. Abnormal HSCs induced by hyperglycemia have the "progeny effect." Hyperglycemia induces abnormal HSCs with aberrant programming such as glucotoxic memory. Once programmed with the abnormal features, the HSCs show irreversibility of phenotype and can lead to neuropathy in normal mice, also called the "progeny effect." HSCs, hematopoietic stem cells.

Possibility of Development of Radical Therapy for Diabetic Neuropathy

Abnormal BMDCs that are positive for insulin and TNFα are deeply involved in the pathogenesis of neuropathy and could be novel therapeutic targets for the amelioration of the disease condition. Focusing on the features of abnormal

BMDCs expressing TNFα, an inflammation-related molecule, animal experiments were performed using TNFα knockout mice and bone marrow cells derived from them.[13] These studies demonstrated that knocking out TNFα only in BMDCs in a diabetic mouse model significantly suppressed the onset of diabetic neuropathy, similar to the results in TNFα knockout mice.[13] Next, the elimination of abnormal BMDCs was investigated to determine whether the onset of diabetic neuropathy was suppressed.[13] To remove these cells, a genetic experimental system was used in transgenic mice. A transgenic mouse in which Cre recombinase was induced by the rat insulin promoter and a transgenic mouse with an inducible diphtheria toxin receptor gene downstream of the stop codon flanked by loxP sites were prepared and crossed.[22] Mice expressing the diphtheria toxin receptor only in insulin-expressing cells were obtained. Bone marrow transplantation from these transgenic mice to wild-type mice was performed and STZ was administered to induce diabetes. Diabetic mice were injected with diphtheria toxin every 3 days to selectively kill insulin-expressing abnormal bone marrow cells with diphtheria toxin receptors. The onset of neuropathy was completely suppressed.[22] This suggests that suppressing the appearance of abnormal BMDCs is a potential radical treatment for neuropathy.

In addition, to compare the direct effects of hyperglycemia on the peripheral nervous system and the effects of BMDCs in diabetic neuropathy, bone marrow transplantation from poly ADP-ribose polymerase (PARP) knockout mice have been performed in diabetic model mice.[26] The PARP pathway has been implicated in the pathogenesis of diabetic neuropathy and inhibition of PARP reduced its progression.[26] Bone marrow transplantation was performed from either PARP knockout mice or wild-type mice to either wild-type mice or PARP knockout mice.[26] Diabetes was induced by STZ injection, and its therapeutic effect on neuropathy was evaluated. PARP knockout in BMDCs suppressed cell fusion and neuronal cell death. Furthermore, the therapeutic effects of PARP knockout were effective in both BMDCs and the peripheral nervous system. Abnormal BMDCs are also involved in the widely recognized pathogenesis of diabetic neuropathy, such as the PARP pathway. PARP is involved in the regulation of DNA methylation in bone marrow cells and may have therapeutic effects through epigenetic alterations in BMDCs under diabetic conditions. A signature finding also showed that these abnormal bone marrow cells in diabetic conditions were observed in the bone marrow tissues even when treated with PARP inhibitors or insulin.[26,27] Therefore, once programmed to express TNFα and proinsulin upon hyperglycemic stimulation, abnormal HSCs become irreversible and remain in the bone marrow even when the blood glucose level is normalized. And, they migrate to peripheral tissues when exposed to hyperglycemia again.

Challenges Ahead and Future Direction: Development of Reprogramming Technology

Abnormal BMDCs appear due to hyperglycemia, cause cell fusion in peripheral nerve tissue, and impair nerve function.[23,27] Considering that diabetic peripheral neuropathy is irreversible, it is possible that program abnormalities in HSCs caused by hyperglycemia stimulation are converted into memory and remain latent in the bone marrow. Hyperglycemia may imprint an abnormal program such as metabolic memory or glycemic legacy on bone marrow stem cells and determine the fate of HSCs. It has been found to cause neuropathy even in non-hyperglycemic conditions due to the "progeny effect," making it necessary to reprogram abnormal HSCs to their normal condition in order to treat diabetic neuropathy. Normalizing abnormal HSCs may suppress the progression of neuropathy and repair damaged neurons through the direct contribution of normalized HSCs, as seen in the case of regeneration effects for the retina and Parkinson's disease by reprogramming.[32-34] It has the potential to be a curative treatment as a disease-modifying therapy (Fig. 3). Eliminating abnormal memory in HSCs and control of blood glucose levels at the same time would be necessary for a complete cure for diabetic neuropathy.

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Conflict of Interest

The authors indicated no potential conflicts of interest.

Author Contributions

T.T.: conception and design, manuscript writing, final approval of the manuscript. M.K.: artwork and illustrations, final approval of the manuscript. N.O.: collection of data, preparation of table, final approval of the manuscript.

Data Availability

Data sharing was not applicable for this article because no new data was shown in this study.

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