The role of autophagy/lipophagy in the response of osteoblastic cells to hyperlipidemia (Review)

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Abstract. There has been interest in the connection between cardiovascular diseases and osteoporosis, both of which share hyperlipidemia as a common pathological basis. Osteoporosis is a progressive metabolic bone disease characterized by reduced bone mass, deteriorated bone microstructure, increased bone fragility and heightened risk of bone fractures. Dysfunction of osteoblastic cells, vital for bone formation, is induced by excessive internalization of lipids under hyperlipidemic conditions, forming the crux of hyperlipidemia-associated osteoporosis. Autophagy, a process fundamental to cell self-regulation, serves a critical role in osteoblastic cell function and bone formation. When activated by lipids, lipophagy inhibits osteoblastic cell differentiation in response to elevated lipid concentrations, resulting in reduced bone mass and osteoporosis. However, an in-depth understanding of the precise roles and mechanisms of lipophagy in the regulation of osteoblastic cell function is required. Study of the molecular mechanisms governing osteoblastic cell response to excessive lipids can result in a clearer understanding of osteoporosis; therefore, potential strategies for preventing hyperlipidemia-induced osteoporosis can be developed. The present review discusses recent progress in elucidating the molecular mechanisms of lipophagy in the regulation of osteoblastic cell function, offering insights into hyperlipidemia-induced osteoporosis.

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1. Introduction

Osteoporosis has become a significant health concern worldwide as a number of countries develop aging populations (1-3). Previous studies have focused on the relationship between cardiovascular diseases (CVDs) and osteoporosis, and have reported that hyperlipidemia forms the common pathophysiological basis of the two disorders (4-7). Under hyperlipidemia, excessive lipids in the serum are delivered to the bone marrow, changing the microenvironment and dysregulating bone cell function. Osteoblastic cells are the major functional cells during osteogenic differentiation and bone formation, and their dysfunction results in insufficient bone formation and bone loss (8). At the cellular level, excessive lipids accumulate in osteoblastic cells and further impair their function as reported by Kim *et al* (9). This previous study investigated the biodistribution of lipids by administering radiolabeled fatty acid tracers (^{3}H-bromopalmitate and ^{14}C-oleate) through gavage to C57BL/6 mice, and found significant uptake of both tracers in the femur, tibia and calvaria, which indicated that except for the heart and liver, bone was the main organ of lipid uptake. A similar study was conducted by injecting ^{125}I-tyramine cellobiose chylomicron remnants (CR) into C57BL/6 mice, with radioactivity measured to assess internalized CR particles 20 min after injection. The results showed that CR uptake by bone was ~17% of uptake by the liver, and was higher than uptake by the lung, muscle, heart and kidney. Further study indicated that CR uptake by apolipoprotein E (ApoE)-deficient osteoblasts was ~50% that of wild-type osteoblasts (10). The aforementioned results illustrate that osteoblasts possess a high lipoprotein uptake capacity and that endogenous ApoE is necessary for efficient lipid internalization for osteoblasts.

However, how lipids taken up by osteoblastic cells affect cell function is not entirely clear.

Autophagy serves an essential role in the homeostasis of osteoblastic cells and impaired autophagy leads to decreased bone mass (11-13). Autophagy of lipids, termed lipophagy, is an important lipid catabolism event that degrades triglycerides (TGs) and cholesterol (CH) in lipid droplets (LDs) via the autophagy-lysosome system (14,15). During lipophagy, the LD coat proteins are identified and selectively removed, inducing the release of free fatty acids (FFAs) (16,17). The generated FFAs improve the rate of mitochondrial β-oxidation, to produce ATP to meet the need for nutrients in cells (18). Therefore, lipophagy is required for mediating lipid content, preventing the formation of potentially toxic lipids and maintaining cellular energy homeostasis (19). Impaired lipophagy leads to excessive tissue lipid accumulation (20,21). A previous study reported high-fat environments suppress osteoblast mineralization and activate lipophagy (22). However, the role of lipophagy in regulating bone metabolism and the mechanism by which lipophagy affects osteoblastic cell function remain largely unknown.

In the present review, current knowledge of the role of autophagy/lipophagy in osteoblastic cell dysfunction is summarized. This is expected to provide insight into the mechanism of hyperlipidemia-induced osteoporosis, providing a theoretical foundation and potential therapeutic targets for the disorder.

2. Adverse effects of hyperlipidemia on bone metabolism

Lipids are stored in LDs, which are primarily found in the cytoplasm; however, in certain cell types such as Huh7 cells, LDs are also located in the nucleus (23). These LDs form, expand, shrink and dissolve in response to changes in the cell energy status. In the case of energy demand, FAs escaping from LDs are substrates for β-oxidation and ultimately generate ATP to meet the energy requirements for cell survival. On a whole organism level, the degradation of LDs in white adipose tissue is important to supply fuel during nutrient insufficiency (24). It has previously been reported that the accumulation of excess LDs in cells may be the cause of osteoporosis (24). Pirih *et al* (25) reported that a high-fat diet (HFD) significantly decreased the cortical bone volume fraction (BV/TV), and, reduced femoral bone strength and stiffness while increasing cortical porosity. It was also observed that the serum levels of parathyroid hormone, calcium, phosphorus and TNF-α were markedly increased, whereas procollagen type I N-terminal pro-peptide, a serum marker of bone formation, was decreased in a $Ldlr^{-/-}$ mouse model but not in the wild-type mice, which indicated that hyperlipidemia impaired bone regeneration and mechanical strength, and induced secondary hyperparathyroidism. Further study showed that the adverse effects of hyperlipidemia on bone tissue were regulated by oxidized lipids and could be blunted after administration of D-4F, an ApoA-I mimetic peptide. Almeida *et al* (26) also reported that HFD-fed $Ldlr^{-/-}$ mice had significantly different collagen orientations and decreased volumetric tissue mineral density assessed using micro-computed tomography, which suggested that hyperlipidemia affected bone microstructure and density. Similarly, C57BL/6 mice fed a high-CH diet (40% of calories from fat, 1.25% of calories from CH) exhibited an osteoporotic bone phenotype, including trabeculae loss, and thinning of the trabeculae and cortex (27). Female mice fed a Western diet (1.1 mg CH/g) or high-CH diet demonstrated a notable decrease in bone mass, and reduced bone mineral content and bone mineral density (BMD) in the femur compared with mice fed a meat-supplemented diet (28,29). As expected, a high-CH diet also led to decreased bone formation and reduced BMD in rats (30). Previous studies reported that the loss of lysosomal acid lipase (LAL), the only known essential CH ester (CE) hydrolysis enzyme, increased CE and TG accumulation in numerous cells and tissues (31,32). A further study reported that global $Lal^{-/-}$ mice exhibited lower cortical bone thickness and strength along with fewer osteoblasts, which resulted in altered lipid metabolism and was connected with the Wnt, Notch and bone morphogenetic protein (BMP) signaling pathways, which indicated that hyperlipidemia had adverse effects on bone metabolism and induced osteoporosis via another mechanism (33). However, although the mechanisms in other tissues, such as the liver and heart, have been extensively illustrated, the mechanisms underlying the impact of hyperlipidemia on bone metabolism are inadequately understood (18,34,35).

3. Hyperlipidemia leads to the dysfunction of osteoblastic cells

Hyperlipidemia leads to abnormal accumulation of lipids in bone tissue compartments, which has a wide range of effects on bone cell function through varied mechanisms, causing bone loss (36-38). Hyperlipidemia causes osteogenic cell dysfunction through certain pathways, which eventually induce bone loss and osteoporosis. Marrow stromal cells (MSCs) isolated from C57BL/6 mice fed a HFD were reported to have failed to undergo osteogenic differentiation *in vitro*. In addition, the osteogenic differentiation of the murine MSCs, M2-10B4, was inhibited after treatment with minimally oxidized LDL (MM-LDL), along with decreased alkaline phosphatase (ALP) activity, decreased levels of collagen I (Col I) and suppressed mineralization, which were all related to the MAPK pathway (39). In addition, MM-LDL, but not native LDL, promoted the adipogenic differentiation of M2-10B4 and 3T3-L1 preadipocytes by activating PPARα (39). These observations indicate that LDL oxidation products induce osteoporotic loss of bone by directing osteoprogenitor cells to undergo adipogenic rather than osteogenic differentiation. Moreover, it has been reported that CH inhibited osteoblastic differentiation by downregulating osteogenic differentiation marker genes, such as Bmp2, Cbfa1, Alp and Col I, and inhibiting matrix calcium deposition, which is regulated by intracellular reactive oxygen species (ROS) (40,41). CH serves a dual role in mediating osteoblastic cell function because it is not only the structural component of the cell membrane but also possesses the ability to regulate cellular function. A previous study reported that exogenous CH inhibited osteoblast differentiation, whereas endogenous CH at physiological levels was essential for bone marrow stem cell (BMSC) osteogenesis (42). Zhang *et al* (43) reported that CH retarded BMSC senescence in a dose-dependent manner when cells were treated with H_2O_2 for 30 h, which was associated with

enhanced autophagy regulated by the ROS/p53/p21Cip1/Waf1 signaling pathway. These observations indicate that the effect of CH on osteoblastic cell function is more complex than that of either 'bad' or 'good' (42).

However, accumulated lipids indirectly influence osteogenic cell function by altering the microenvironment of the bone marrow (44,45). One of the major functions of bone marrow is to provide mature blood cells to the circulation, where they are involved in blood clotting and innate immunity. As well as the close association of hyperlipidemia with CVD, CH content is closely associated with the bone marrow microenvironment and influences hematopoiesis (46). LDL, which accumulates in the subendothelial matrices of arteries, undergoes oxidation and produces modified forms, such as MM-LDL and oxidized-LDL. Modified LDL further induces potent inflammatory responses, such as the induction of chemotactic factors in endothelial cells, recruitment of monocytes to the arterial wall and adhesion of monocytes to endothelial cells (47). In chronic inflammatory conditions, such as certain rheumatological diseases, systemic bone loss has been observed in both patients and experimental models (48-51). Chronic inflammatory diseases weaken the function of osteogenic cells in maintaining the balance of bone remodeling, inducing the occurrence of osteoporosis. Redlich *et al* (51) reported that osteogenic cells were present at local erosion sites in rheumatoid arthritis, but their number and activity were too low to counteract osteoclast action owing to the role of proinflammatory cytokines. TNF, for example, inhibits osteoblast differentiation through the p55 TNF receptor by inhibiting Runx2, which is regulated in part by inducing Runx2 ubiquitylation (52-54). Other pro-inflammatory cytokines, such as IL-1 and IL-6, lead to osteogenic cell dysfunction and inhibit osteoblastogenesis (55,56). Moreover, a number of cytokines negatively affect osteoblast function by activating the NF-κB signaling pathway, thought to be via inhibition of the JUN N-terminal kinase 1 and thus decreasing the transcription factor AP1 (57). In addition, the negative effects of proinflammatory cytokines on osteogenic cells can be further regulated byDickkopf-1, an inhibitor of the Wnt signaling pathway and induced by Tnf32. Sclerostin, another inhibitor of the Wnt signaling pathway, can bind to and antagonize BMPs to suppress osteogenesis (58-60). The aforementioned studies indicate that an inflammatory environment impairs osteogenic cell function, which strongly suggests that the inflammatory response induced by hyperlipidemia in the bone marrow leads to osteogenic cell dysfunction and bone loss. However, the mechanism by which hyperlipidemia impairs osteogenic cell function has not been clearly elucidated.

4. Autophagy/lipophagy is a pivotal mechanism of osteoblastic cell dysfunction induced by hyperlipidemia

Autophagy regulates bone metabolism. Autophagy is a highly conserved cellular self-degradative and dynamic energy recycling process, mediated by a series of autophagy-related genes (ATGs), that provides energy and basic substances for cell survival and homeostasis maintenance (61,62). Three primary types of autophagy, including microautophagy, macroautophagy and chaperone-mediated autophagy, are found in mammalian cells, through which cytoplasmic materials are delivered to the lysosome for degradation and recycling (63). In the early stages of autophagy, cells sequester a portion of their cytoplasm and organelles into autophagosomes, double-membraned vesicles that subsequently fuse with lysosomes to degrade the enclosed materials (62). Autophagosome formation is mediated by a series of protein complexes that act sequentially. For example, the ULK1-ATG13-RB1CC1/FIP200-C12orf44/ATG101 complex regulates autophagy induction, the class III phosphatidylinositol 3-kinase complex, containing BECN1, PIK3R4/VPS15, PIK3C3/VPS34, ATG14/ATG14L/Barkor and AMBRA1, regulates autophagosome initiation, and the ATG12-ATG5-ATG16L1 complex and the MAP1LC3A/LC3 (ATG8 homolog)-phosphatidylethanolamine complex regulates autophagosome double membrane extension and closure (64,65). Autophagy can be induced by numerous intrinsic and extrinsic cellular stress conditions, such as ROS accumulation, bacterial infections, endoplasmic reticulum stress and abnormal lipid accumulation. Dysfunctions of autophagy have been reported to be associated with numerous serious diseases, including inflammatory bowel diseases and neurodegenerative diseases (66,67). For example, the accumulation of ubiquitinated protein aggregates (or inclusion bodies) is normally cleared by autophagy, which results in cellular defects, a hallmark of neurodegenerative diseases (68-70). In cancer, defective autophagy increases DNA damage and gene mutations, which leads to increased tumorigenesis, and reduced tumor cell proliferation during cancer progression and metastasis (71,72).

Previous studies have indicated that abnormal autophagy can lead to imbalances in bone metabolism and serve a critical role in bone metabolism disorders (73,74). Piemontese *et al* (75) reported that the autophagy level in primary osteoblasts from $Atg7^{-/-}$ mice was inhibited, which caused the accumulation of endoplasmic reticulum stress, and resulted in low bone mass and a greater number of fractures compared with wild-type mice. Further study indicated that the effect of Atg7 deficiency on bone tissue might be associated with a decreased number of osteoblasts. Another study reported that 17 β-estradiol could induce autophagy to protect osteoblast function in women with postmenopausal osteoporosis through the G protein-coupled receptor 30 (GPR30) and extracellular-regulated protein kinases 1/2 signaling pathway (76). However, this protective effect could be abolished by G15, a selective GPR30 antagonist (77). In a type 2 diabetes mouse model, the acceleration of autophagy in osteoblasts protected their ability to survive and differentiate by increasing ROS and protein oxidation induced by the high glucose environment (78). Autophagy was also reported to regulate MSC function to control the development of postmenopausal osteoporosis, which was mediated by the mTOR signaling pathway (79). Moreover, numerous studies have reported that autophagy is significantly enhanced during osteoblast differentiation and mineralization, and its inhibition rapidly causes dysfunction of osteoblasts *in vitro* (80-83). The aforementioned studies demonstrate that autophagy serves a key role in osteoporosis by regulating osteoblastic cell function and differentiation.

Lipophagy is a type of selective autophagy. Autophagy can be activated in osteoblastic cells by LDs in a high-fat environment (84). Putative links between autophagy and LDs were

identified following the observation that mutations in LAL, a lipase responsible for lysosomal LD degradation, caused LD accumulation in certain organs (17). However, the contribution of lipophagy to LD accumulation is unknown. Singh *et al* (15) clearly demonstrated that, in hepatocytes, autophagy was termed the 'lipophagy' when it was linked to LD degradation, which suggested new avenues of study of the role of the regulation of lipid metabolism in cellular physiology and pathophysiology. Lipophagy is a type of selective autophagy that can occur via both macro- and micro-based mechanisms. Macrolipophagy refers to the classical autophagosome-mediated manner in which LD budding occurs and LDs are sequestered for subsequent delivery to autolysosomes. Microlipohagy refers to the transient and direct interactions between LDs and lysosomes as a means of degrading LD-derived lipids (17).

Lipophagy is regulated by certain proteins and pathways. ATGs that mediate membrane fusion and the subsequent degradation processes have been identified in recent studies. Lipophagy is reported to begin with the identification of cargo by the autophagosomal membrane through interaction with LC3 (85,86). LC3 promotes the movement of cytoplasmic ATGL, another important protein during lipophagy, to LDs by interacting with ATGL to induce lipophagy. In the liver, ATGL accelerates lipophagy to mediate catabolism of hepatic LDs via SIRT1 activity (87). Small regulatory Rab GTPase (Rab) molecular switch families are indispensable in lipophagy (88). Rab7 serves an essential role in the regulation of autolysosome-mediated lipid degradation in adipocytes (89). Moreover, Rab7 can be activated to enhance the recruitment of lysosomes and multi-vesicular bodies to the surface of LDs during lipophagy under nutrient deprivation conditions (89). The deficiency of Rab7 leads to morphological alterations of multi-vesicular bodies, lysosomes and autophagosomes, resulting in decreased lipophagy in hepatocellular lysosomes (90). Rab10 forms a complex with EH domain-binding protein 1 and EH domain-containing 2 to promote LC3-positive autophagic membrane migration to the LD surface. Deletion of Rab10 causes lipophagy dysfunction and LD accumulation (91). Lipases, such as patatin-like phospholipase domain-containing enzyme (PNPLA)5 have been reported to contribute to lipophagy and autophagic proteolysis (92). These lipases serve key roles in the initial stage of lipophagy by recruiting triglycerides and sterol esters, resulting in the formation of autophagosomes (93,94). PNPLA8 regulates SREBP-2 to drive lipophagy by interacting with LC3 in the hepatocytes of HFD-fed mice (95). In energy-deprived conditions, PNPLA3 mediates the formation of autophagosomes during the lipophagy process in human hepatocytes, (96). Moreover, perilipin, which exists on the surface of LDs, is removed before degradation by lipophagy, which is mediated by chaperones through AMP-activated protein kinase (AMPK) (97). Under nutrient deprivation conditions, lipophagy is regulated by falconoid X receptor, cAMP response element-binding protein, mTOR or AMPK (98-101). To meet the energy requirements of cells, lipophagy is activated, leading to the breakdown of triglycerides in LDs under fasting conditions. During this process, LDs are targeted by autophagosomes, captured and broken down by LAL (15,102,103). Lysosomal lipase expression is mediated by the lysosomal biogenesis transcription factor EB in mouse hepatocytes and *Caenorhabditis elegans* (104). Furthermore, fork head homeobox transcription factor1 is associated with lysosomal lipase and induces lipophagy in adipocytes under dietary restriction (105). A recent study reported that spartin, as a receptor localized to the LD surface, interacts with the core autophagy machinery, and that spartin is required for the delivery of LDs to lysosomes and spartin-deficiency in neurons leads to LD accumulation in cultured human neurons or the murine brain (106). Numerous functions of lipophagy have been reported in different cellular processes ranging from transdifferentiation to resistance to apoptosis (Fig. 1). However, the role of lipophagy in bone cells remains unclear.

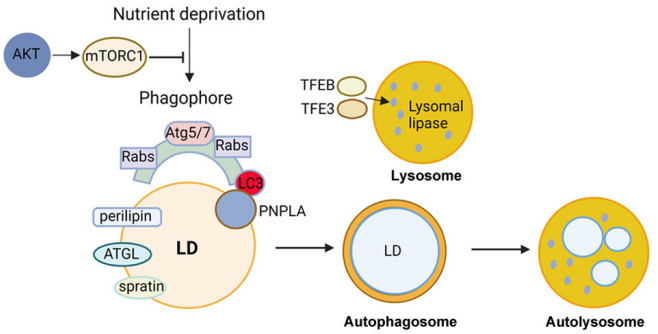

Figure 1. Overview of core proteins involved in lipophagy. Under nutrient deprivation, lipophagy begins as a selective autophagy process, which degrades LDs. This process involves the formation of phagophores, which are composed of families of proteins including LC3, Atg5, Atg7 and Rab. The PNPLA family possess specific molecular motifs related to LDs and are essential in facilitating LD breakdown. During lipophagy, autophagosomes engulf LDs and subsequently fuse with lysosomes, giving rise to autolysosomes. At this stage, the neutral lipids in LDs are hydrolyzed by lysosomal lipases, a process that is regulated by TFEB. LD, lipid droplets; ATG, autophagy-related gene; TFEB, transcription factor EB; TFE3, transcription factor E3; Rab, Rab GTPase; PNPLA, patatin-like phospholipase domain-containing enzyme.

Role of lipophagy in osteoblastic cells and bone metabolism. Previous studies have reported that lipophagy is one of the pivotal mechanisms by which patients experience lipotoxic effects on cells in bone tissue, inducing osteoblastic cell dysfunction (107,108). Autophagy/lipophagy in osteoblastic cells has previously been verified by co-administration of rapamycin (RAP), an autophagy promoter, and 3-MA, an autophagy inhibitor, with different concentrations of high-lipid medium. In moderately-high lipid conditions, RAP promoted the co-localization of LDs and autophagy-associated proteins, which contributed to a reduction in lipid deposition in osteoblasts and relieved the adverse effects of high-lipid conditions on the proliferation and osteogenic differentiation of osteoblasts, accompanied by increased activity of ALP, mineralization of nodules and high expression of osteogenic-associated proteins. Treatment with 3-MA decreased lipophagy, weakened lipolysis and produced inverted oil-red granules, and further suppressed osteoblast proliferation and osteogenesis. However, at high-lipid concentrations, RAP inhibited both osteoblast proliferation and osteogenic differentiation, and 3-MA improved the inhibitory effect of high-lipid conditions on proliferation and osteogenesis by suppressing autophagy/lipophagy, although the change in lipid deposition was reported to not be significant (22). Subsequent *in vivo*

studies reported that autophagy/lipophagy was activated in the bone tissue defect of a mouse model of hyperlipidemia and in osteoblasts cultured in high-fat medium. Specifically, a defect created on the femurs of mice fed a HFD was assessed after 2 weeks of healing; the results showed that BV/TV and BMD were decreased, and the number of new bones was significantly reduced in the hyperlipidemia mouse model compared with in wild-type mice. Although bone healing was promoted in hyperlipidemic mice when RAP was used to enhance autophagy/lipophagy, new bone was further reduced in hyperlipidemic mice treated with 3-MA to inhibit autophagy/lipophagy (22). This study illustrates that local promotion of autophagy/lipophagy reduces osteogenesis in hyperlipidemia and provides a potential therapeutic strategy for patients with poor bone metabolism induced by acquired hyperlipidemia. A similar study reported that CH retarded senescence in BMSCs in a dose-dependent manner by altering autophagy and regulating LC3 expression (43). Furthermore, palmitate (PA) induced normal human osteoblast apoptosis, which led to decreased osteoblastogenesis and bone mineralization, whereas 3-MA-induced inhibition of autophagy reduced apoptosis. These studies indicated that lipophagy could be activated by lipids, such as CH and PA, in osteoblastic cells and regulate cell function (109). These contradictory findings indicate the need for more comprehensive and systematic studies on the influence of lipophagy on the function of osteoblastic cells and bone metabolism. Elucidating the role of lipophagy in bone metabolism under hyperlipidemia conditions and the mechanism of hyperlipidemia-induced dysfunction of osteoblastic cells is challenging because of the complexity of cross-talk between multiple organs.

5. Conclusions and future perspectives

Hyperlipidemia affects the function of osteoblastic cells, the major functional cell of bone formation, by inducing an inflammatory response in the bone cavity and osteoblastic cell dysfunction by internalizing lipids. However, how lipids affect osteoblastic cell function remains unknown. The present review described the research progress on hyperlipidemia-induced osteoporosis and discussed the possible mechanisms. Lipophagy in osteoblastic cells can be activated by excessive lipid levels under hyperlipidemia conditions to regulate lipid metabolism, and mediate osteoblastic cell differentiation and bone formation, which would be a novel mechanism for hyperlipidemia-induced bone disorders in the future, although Pirih *et al* (25) preliminarily illustrated the role of lipophagy in the disease. However, there are numerous issues that need to be addressed during future investigation of the role of lipophagy in regulating osteoblastic cell function. Firstly, the types of lipids which affect osteoblastic cell function need to be elucidated. Secondly, how osteoblastic cells respond to hyperlipidemia conditions, and which molecules or pathways mediate osteoblastic cell differentiation under hyperlipidemia conditions need to be identified. Lastly, the potential for the use of lipophagy as a therapeutic target for bone metabolism disorder needs to be further assessed. Clarification of these points would provide insight into the mechanism of hyperlipidemia-induced osteoporosis, and provide references for the prevention and treatment of osteoporosis for patients with hyperlipidemia.

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Authors' contributions

YH and PS wrote the manuscript. YL and QY wrote the outline of the manuscript. YH, XC and RL collected and prepared the related references. YH and AX drafted the manuscript. YH and PS drew the figure. YH, XC and RL made substantial contributions to data interpretation and analysis. Data authentication is not applicable. All authors contributed to the article, and read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

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Competing interests

The authors declare that they have no competing interests.

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