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Review

Why Does Inflammation Result in Resorptive Bone Loss?

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Abstract: Burn injury serves as an example of a condition with a robust systemic inflammatory response. The elevation of circulating interleukins (IL)-1β and -6 in children and adolescents with severe burn injury up-regulate the parathyroid calcium sensing receptor (CaSR), resulting in hypocalcemic hypoparathyroidism accompanied by urinary calcium wasting. This effect protects the body from the hypercalcemia that results from bone resorption liberating calcium into the circulation. Extracellular calcium can exacerbate and prolong the inflammatory response by stimulating mononuclear cell chemokine production as well as the NLRP3 inflammasome of the innate immune system, resulting in increased IL-1 production by monocytes and macrophages. Interestingly, the CaSR up-regulation in response to inflammatory cytokines disappears with age, potentially trapping calcium from bone resorption in the circulation, allowing it to contribute to increased inflammation and possibly increased calcium deposition in small arteries, such as the coronaries, as conditions with increased chronic inflammation, such as spinal cord injury, osteoarthritis, and rheumatoid arthritis have an incidence of cardiovascular disease and coronary artery calcium deposition significantly higher than the unaffected age-matched population.

Keywords: inflammation; calcium-sensing receptor; burns; chemokines; NLRP3 inflammasome

1. Introduction

Inflammation results in the release of various cytokines from the body's immune cells, most notably interleukin (IL)-6, IL-1 β, and tumor necrosis factor (TNF)-α. In addition, various immune cells produce chemoattractant cytokines, called chemokines. These substances attract immune cells to a site of inflammation within the body increasing the intensity and/or duration of the inflammatory response.

Burn injury is an example of a condition in which a robust systemic inflammatory response is manifested with circulating concentrations of IL-1 β and IL-6 elevated three-fold and one hundred-fold respectively (1). In conjunction with relative immobilization and elevated endogenous glucocorticoids (2), resorptive bone loss is observed in children burned over 40% total body surface area. The result is a loss of 7% of total trabecular bone density of the lumbar spine over the first six weeks following burn injury and a 3% loss of total body bone mineral density, mainly cortical bone, over the first six months post-burn.

In the laboratory, in vitro studies of bovine parathyroid cells (3) and equine parathyroid cells (4) incubated with IL-1 β and IL-6 (5) up-regulate the parathyroid calcium sensing receptor (CaSR). This up-regulation has the effect of lowering the amount of circulating calcium necessary to suppress parathyroid hormone (PTH) secretion, leading to hypocalcemic hypoparathyroidism. This is what we have observed in a sheep model of burn injury (6) as well as in the pediatric patients with injury of ≥40% total body surface area burn (7).

Another observation in the same sheep model of burn injury and over the same time frame, i.e., the first five days following burns, was that backscatter scanning electron microscopic study of iliac crest demonstrated that biochemical markers of bone resorption, namely urine C-telopeptide of type I collagen (CTx), a biomarker of bone resorption, was

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elevated on day one post-burn with histologic scalloping, a hallmark of resorption, plainly visible by day 5(8). Note that the coincidence of cytokine-mediated up-regulation of the parathyroid CaSR and the onset of bone resorption, stimulated by inflammation, immobilization, and increased endogenous steroid production, likely serves as a way to facilitate the excretion of excess calcium entering the circulation following acute bone resorption. Concomitantly, the inflammation-induced up-regulation of the CaSR suppresses PTH secretion, allowing increased urinary calcium excretion, thus protecting the body from hypercalcemia. So what does this have to do with inflammatory cytokines causing resorptive bone loss?

2. Extracellular Calcium and Inflammation

In an unrelated in vitro study we performed, we isolated peripheral blood mononuclear cells from normal adult volunteers and incubated them in media containing varying amounts of calcium (9). We found very tight direct and inverse correlations between various chemokines produced by these mononuclear cells and the amount of calcium in the medium. It is not clear why chemokines such as RANTES and MIP-1 α were strongly stimulated whereas Monocyte Chemotactic Protein (MCP-1) was equally strongly inhibited by extracellular calcium, although it is possible that the sequence and timing of appearance in the blood of the various chemokines is important to the inflammatory response. The implication of these findings is that extracellular calcium stimulates or suppresses certain chemokines, which can serve to attract more inflammatory cells to the areas of existing inflammation, thus intensifying and possibly prolonging the inflammatory response in burn patients. These observations were reinforced by the work of Rossol et al (10) who demonstrated that extracellular calcium could stimulate the nod-like receptor (NLR)-P3 inflammasome of the innate immune system via the CaSR on monocyte membranes to stimulate monocytes and macrophages to produce more IL-1, further intensifying the inflammatory process. Subsequently, this group also demonstrated that circulating calcium and phosphate are converted by the serum protein Fetuin A to colloidal calciprotein particles in order to prevent ectopic calcification. These undergo pinocytosis by monocytes, a function of increased circulating calcium triggering monocyte CaSR up-regulation prior to the pinocytosis. This action triggers activation of the NLRP3 inflammasome resulting in the production of IL-1β (11). Thus, it would appear that the calcium entering the circulation following bone resorption is capable of intensifying and prolonging the inflammatory response to burn injury and perhaps other conditions. Furthermore, Olszak et al (12) demonstrated in vitro that extracellular calcium could increase monocyte expression of various chemokine receptors, thus building even a stronger case for extracellular calcium stimulating various components of the inflammatory response. Further evidence implicating calcium in the inflammatory response comes from Michalick and Kuebler (13) Front Immunol 2020), who point out that transient receptor potential vanilloid (TRPV)-type 4, or TRPV4, a mechanosensitive calcium channel, is involved in neutrophil activation and chemotaxis.TRPV4 has also been implicated in macrophage activation leading to lung injury following mechanical ventilation. These issues have also been reported in a rat model of immobilization and mechanical ventilation (14) in which it was shown that pharmacologic immobilization of rats was accompanied by marked trabecular bone loss, thus liberating calcium into the circulation and possibly contributing to the inflammation described by Michalick and Kuebler (13).

3. Preservation of the Hypocalcemic Response in Small Burns

The data on the longitudinal decrease in bone density following burns was originally published in 1995 (15) and was applicable to children with burns of ≥ 40% total body surface area. In that same publication we studied a cohort of children with burns of approximately 20% total body surface area. Those children did not suffer significant resorptive bone loss and had no reduction in their bone mineral density. From these data we can

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infer that the additional amount of calcium entering the circulation from bone resorption was negligible. Therefore, we attempted to find out whether blood ionized calcium levels remained normal in children with small burns. Accordingly, we obtained blood ionized calcium concentrations from the records of 190 anonymized children with burns ranging from 1-20% total body surface area. Throughout hospitalization their mean ionized calcium concentration was 1.04 ± 0.08 (SD) mM, range 0.73-1.31, normal range 1.12-1.37. The mean values were 8% below the lower limits of normal for age, while only 16.8 % of the 190 pediatric patients with small burns had mean circulating ionized calcium concentrations within the normal range. Therefore, since burn size plays a role in resorptive bone loss and reduced bone density, the hypocalcemic response to burns as small as 1% total body surface area suggests that up-regulation of the parathyroid CaSR in response to acute inflammation is the prime purpose of the reactive hypocalcemia rather than this response being uniquely related to resorptive bone loss induced by inflammation, immobilization, or endogenous glucocorticoid production. Unfortunately, neither serum PTH concentrations nor quantitative urinary calcium data were available in this anonymized population.

4. Developmental Disappearance of Calcium-Sensing Receptor Response to Inflammatory Cytokines

Despite the apparent uniformity of findings in burn patients under the age of 19, studies in adults yield an entirely different picture of ionized calcium and PTH response to severe burn injury. In our patients (16) and in the adult burns literature (17), severely burned adult patients were normo- or mildly hypercalcemic and euparathyroid or mildly hyperparathyroid. In our patients, the mean blood ionized calcium concentration was 1.08± 0.03 (SD) mM in children with normal range being 1.12 to 1.37 (7) while in adults with similar size burns, the blood ionized calcium concentration was 1.15 ±0.06 mM , normal range 1.00 to 1.15 mM. Similarly, serum PTH concentration in burned children was 7±3 pg/ml, normal range 15 to 55, whereas in adults the mean PTH for similar sized burns was 114 ± 96 pg/ml, normal range 10 to 65. The mechanism explaining this difference is not apparent. However, it would appear likely that the ability of the parathyroid calcium-sensing receptor to respond to inflammatory cytokines by up-regulation and consequent development of hypocalcemic hypoparathyroidism is lost with age, sometime after the onset of puberty. By age 19, there is still no change in the childhood response pattern of parathyroid CaSR up-regulation in response to inflammatory cytokines, thus likely making the age at loss of response of the parathyroid CaSR to inflammatory cytokines at least into the early 20's. This age approximates the time of acquisition of peak bone mass and the relationship between these two developmental milestones requires further investigation. Likewise, sexual dimorphism was not apparent in analysis of the results of circulating ionized calcium and PTH concentrations in children and adolescents past the onset of puberty, up through ages 18-19.

5. Potential Implications of the Disappearance of Calcium-Sensing Receptor Response to Inflammatory Cytokines

The implications of the disappearance of the parathyroid CaSR response to inflammatory cytokines with age are at least two-fold. The first is that children and adults with similar body surface area burns have different clinical outcomes. Thus children are able to respond to inflammatory cytokines by up-regulating the calcium-sensing receptor, resulting in hypocalcemic hypoparathyroidism and accompanying increased urinary calcium excretion. The excess calcium lost from the skeleton and entering the circulation is excreted in the urine and therefore will not build up in the circulation and cause intensified or prolonged inflammation. In contrast, adults cannot up-regulate the parathyroid CaSR in response to inflammatory cytokines, resulting in failure to excrete the excess

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calcium introduced into the circulation in response to bone resorption, leading to intensified and/or prolonged inflammation. This difference is documented by the difference in mortality between children and adults experiencing severe burn injury. In a large multicenter study by Jeschke et al (18) involving 226 children and 347 adults, children burned greater than 60% total body surface area were at greater risk for burn mortality while adults burned greater than 40% total body surface area were at greater risk for burn mortality, an extent of burn injury 20% lower than in children.

In addition, long-term cardiac dysfunction complicates severe burn injury in children (19), including reduced left ventricular ejection fraction, systolic and diastolic dysfunction, and myocardial fibrosis, all possibly due to a putative effect of transforming growth factor (TGF)-β release from resorbing bone matrix adversely affecting cardiac smooth muscle as well as skeletal muscle catabolism (20-22) and fibrosis (23). However, there is also in adults the possibility of excess calcium from resorbing bone entering the circulation and remaining there as opposed to being excreted in urine in significant quantities, leading to accumulation in end arteries, such as in coronary blood vessels, thus contributing to plaque formation. Alexander et al (24) documented increased troponin levels in adults with burn injury of greater than 15% total body surface area.

Campos-Obando et al reported correlations between osteoporosis and heart disease, in aging adults (25) potentially involving mechanisms related to bone resorption. While the changes due to aging are clearly confounding variables, bone resorption and consequent release of calcium into a circulation that cannot adequately eliminate it could equally be a contributing factor.

6. Other Clinical Conditions

The bulk of this review has focused on the body's response to burn injury as a model for understanding why bone resorption occurs with inflammation. However, there are many other conditions in which resorptive bone loss can play a role in exacerbating the systemic inflammatory response. Among them are spinal cord injury, rheumatoid and osteoarthritis, as well as hyperresorptive conditions such as hyperparathyroidism to name a few.

Of note, spinal cord injury bears many similarities to burn injury, including an increased inflammatory response, robust bone loss of up to one percent per week (26), and skeletal muscle wasting, an increased incidence of cardiovascular disease and congestive heart failure (27), and suppression of PTH and FGF-23 in the case of burns(28), and increased tubular threshold for the excretion of phosphate in spinal cord injury, indicating the body's conservation of phosphate, possibly for a role in muscle metabolism. Del Rivero and Bethea (29) studied a mouse model of spinal cord injury and found acute and chronic bone loss associated with normal levels of PTH at one week post-injury, but a significant decrease in serum PTH concentration at 4 weeks, along with a rise in circulating calcium. These findings suggest that PTH does not induce a rise in bone resorption but is suppressed by the acute and continuous loss of bone. The progressive rise in serum calcium can be explained by the low PTH. Additionally, as Bauman and Spungen (30) have noted, there is an increased risk of coronary heart disease in patients with spinal cord injury, currently attributed to immobilization and increased abnormalities in carbohydrate and lipid metabolism. However, the role of calcium retention in the body due to bone resorption has not been investigated as a contributing factor to coronary artery disease. In addition, Lieberman et al (31)J Spinal Cord Med 2011) in a study of spinal cord-injured men, aged 45-70 yr, found correlations of coronary calcium score with the Framingham Risk Score and age, but there was a divergence of agreement of cardiovascular risk assessment for lipid lowering treatments between Framingham Risk Scores and coronary calcium scores. Of the 20 of 38 patients who qualified for lipid lowering treatment by either the Framingham Risk Score or the coronary calcium score, only 4 of the 20 patients, 20%, qualified by both assessments. While the numbers are small, the divergence

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leaves room for other factors, such as circulating calcium, to serve as a contributor to cardiovascular disease in this population.

Rheumatoid arthritis is another condition with a marked inflammatory response contributing to loss of bone. In this condition, Karpouzas et al (32) Arthritis &Rheumatology 2020) report that cumulative inflammation in this chronic disease contributes to progressive coronary artery calcium accumulation.

Osteoarthritis, another chronic inflammatory disease of joints associated with bone loss, has been shown in meta-analysis studies of Macedo et al (33) who demonstrated that patients with osteoarthritis were three times as likely to have atherosclerotic heart disease compared with non-osteoarthritic cohorts. Wang et al (34) in another meta-analysis concluded that patients with osteoarthritis had a 24% increase in risk for cardiovascular disease than unaffected age-matched populations. Additionally, Hall et al (35) in yet another meta-analysis found that patients with osteoarthritis were nearly three times more likely to develop either heart failure or ischemic heart disease than unaffected matched cohorts.

Calcium has been implicated as well in generating inflammation through combining with calmodulin to activate the enzyme, Ca^{2+}/calmodulin regulated kinase δ in response to pressure overload. This enzyme then stimulates inflammatory gene expression and activation of the NLRP3 inflammasome, which results in increased production of IL-1β and IL-18 by the innate immune system. This has been demonstrated in cardiomyocytes (36). A similar mechanism has been described for the initiation of inflammation in mechanical ventilation (14), and a related mechanism has been implicated following cardiac ischemia, also involving a Ca^{2+}/calmodulin regulated kinase (37). It is unclear how much circulating Ca is necessary to trigger these latter effects or if there is a threshold for circulating Ca to contribute to these effects. Nonetheless they are also potential ways in which Ca can trigger an inflammatory response.

7. Conclusion

In summary, release of calcium into the circulation following bone resorption is capable of contributing to the inflammatory response by affecting peripheral blood mononuclear cell production of chemokines and stimulating the NLRP3 inflammasome, thus increasing the production of IL-1 by monocytes and macrophages of the innate immune system. In addition, extracellular calcium can play a role in the expression of inflammatory genes which activate the NLRP3 inflammasome under conditions of ischemia or increased pressure. Children and adolescents may be capable of responding to systemic inflammation by dumping the excess calcium entering the circulation via bone resorption into the urine by means of cytokine-stimulated up-regulation of the parathyroid calcium-sensing receptor, a mechanism which developmentally disappears in adults at a time possibly coinciding with the acquisition of peak bone mass. The inability of adults to reduce their circulating load of calcium may contribute to increased mortality from burn injury and coronary heart disease among other conditions. The expanded use of bisphosphonates and other anti-resorptive agents in patients with severe inflammatory responses to illness may modify the effects caused by inflammation.

It is therefore incumbent upon us to investigate these potential effects of extracellular calcium in relation to the generation of inflammatory responses in adult populations and to determine if reducing bone resorption in these and other inflammatory conditions can modify their outcomes or prognoses.

References

1. Klein GL. Herndon DN, Goodman WG, Langman CB, Phillips WA, Dickson IR et al Histomorphometric and biochemical characterization of bone following acute severe burns in children. Bone 1995; 17: 455-60.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 20 May 2022 doi:10.20944/preprints202205.0269.v1

2. Klein GL, Bi LX, Sherrard DJ, Beavan SR, Ireland D, Compston JE et al Evidence supporting a role of glucocorticoids in short-term bone loss in burned children. Osteoporos Int 2004; 15: 468-74.
3. Nielsen PK, Rasmussen AK, Butters R, Feldt-Rasmussen U, Bendtzen K, Diaz R, et al Inhibition of PTH secretion by interleukin-1 beta in bovine parathyroid glands in vitro is associated with an up-regulation of the calcium-sensing receptor mRNA. Biochem Biophys Res Commun 1997; 238: 880-5.
4. Toribio RE, Kohn CW, Capen CC, Rosol TJ Parathyroid hormone (PTH) secretion, PTH mRNA and calcium-sensing receptor mRNA expression in equine parathyroid cells and effects of interleukin (IL)-1, IL-6 and tumor necrosis factor alpha on equine parathyroid cell function. J Mol Endocrinol2003; 31: 609-20.
5. Canaff L, Zhou X, Hendy GN The proinflammatory cytokine, interleukin-6, up-regulates calcium-sensing receptor gene transcription via Stat1/3 and Sp 1/3 J Biol Chem 2008; 283: 13586-600.
6. Murphey ED, Chattopadhyay N, Bai M, Kifor O, Harper D, Traber DL, et al. Up-regulation of the parathyroid calcium-sensing receptor after burn injury in sheep: a potential contributory factor to postburn hypocalcemia. Crit Care Med 2000; 28: 3885-90.
7. Klein GL, Nicolai M, Langman CB, Cuneo BF, Sailer DE, Herndon DN Dysregulation of calcium homeostasis after burn injury in children: possible role of magnesium depletion. J Pediatr 1997; 131: 246-51.
8. Klein GL, Xie Y, Qin Y-X, Lin L, Hu M, Enkhbaatar P, Bonewald LF Preliminary evidence of bone resorption in a sheep model of acute burn injury: an observational study. J Bone Miner Metab 2014; 32: 136-41.
9. Klein GL, Castro SM, Garofalo RP The calcium-sensing receptor as a mediator of inflammation. Semin Cell Dev Biol 2016; 49: 52-6.
10. Rossol M, Pierer M, Raulien N, Quandt D, Meusch U, Rothe K et al Extracellular Ca2+ is a danger signal activating NLRP3 inflammasome through G protein-coupled calcium sensing receptors Nat Commun 2012; 3: 1329.
11. Jager E, Murthy S, Schmidt C, Hahn M, Strobel S, Peters A et al Calcium-sensing-receptor-mediated NLRP3 inflammasome response to calciprotein particles drives inflammation in rheumatoid arthritis. Nat Commun 2020; 11: 4243.

12. Olszak IT, Poznansky MC, Evans RH, Olson D, Kos C, Pollak MR, et al Extracellular calcium elicits a chemokinetic response from monocytes in vitro and in vivo. J Clin Invest 2000; 105: 1299-305.
13. Michalick L, Kuebler WM TRPV$_4$- a missing link between mechanosensation and immunity. Front Immunol 2020; 11:413.
14. Gugala Z, Cacciani N, Klein GL, Larsson L J Orthop Res 2022; 40: 1293-1300.
15. Klein GL, Herndon DN, Langman CB, Rutan TC, Young WE, Pembleton G et al Long-term reduction in bone mass after severe burn injury in children. J Pediatr 1995; 126: 252-6/
16. Klein GL, Herndon DN, Rutan TC, Sherrard DJ, Coburn JW, Langman CB et al Bone disease in burn patients. J Bone Miner Res 1993; 8: 337-45.
17. Klein GL, Benjamin DA, Herndon DN Calcemic response to burns differs between adults and children: A review of the literature. Osteoporos Sarcopenia 2017; 3: 170-3.
18. Jeschke MG, Pinto P, Kraft R, Nathens AB, Finnerty CC, Gamelli RL et al Morbidity and survival probability in burn patients in modern burn care. Crit Care Med 2015; 43: 808-15.
19. Hundeshagen G, Herndon DN, Clayton RP, Wurzer P, McQuitty A, Jennings K et al Long-term effect of critical illness after burn injury on cardiac function in adolescent survivors: an observational study. Lancet Child Adolesc Health 2017; 1: 293-301.
20. Pin F, Bonetto A, Bonewald LF, Klein GL Molecular mechanisms responsible for the rescue effects of pamidronate on muscle atrophy in pediatric burn patients. Front Endocrinol (Lausanne) 2019 Aug 7 10: 543.
21. Borsheim E, Herndon DN, Hawkins HK, Suman OE, Cotter M, Klein GL Pamidronate attenuates muscle loss after pediatric burn injury. J Bone Miner Res 2014; 29: 1369-72.
22. Waning DL, Mohammad KS, Reiken S, Xie W, Andersson DC, John S et al Excess TGF-β mediates muscle weakness associated with bone metastases in mice. Nat Med 2015; 21: 1262-71.
23. Abrigo J, Simon F, Cabrera D, Cordova G, Trollet C, Cabello-Verrugio C Central role of transforming growth factor-beta 1 in skeletal muscle dysfunctions: an update on therapeutic strategies. Curr Protein Pept Sci 2018; 19: 1189-1200.

24. Alexander W, Schneider H-G, Smith C, Cleland H The incidence and significance of raised troponin levels in acute burns. J Burn Care Res 2018; 39: 729-35.
25. Campos-Obando N, Kavousi M, Roeters van Lennep JE, Rivadeneira F, Hofman A, Uitterlinden AG et al Bone health and coronary artery calcification: The Rotterdam Study. Atherosclerosis 2015; 241: 278-83.
26. Qin W, Bauman WA, Cardozo C Bone and muscle loss after spinal cord injury: organ interactions. Ann NY Acad Sci 2010; 1211: 66-84.
27. Peterson MD, Berri M, Lin P, Kamdar N, Rodriguez G, Mahmoudi E et al Cardiovascular and metabolic morbidity following spinal cord injury. Spine J 2021; 21: 1520-7.
28. Porter C, Sousse LE, Irick R, Schryver E, Klein GL Interactions of phosphate with serious injury including burns. JBMR Plus 2017; 1: 59-65.
29. Del Rivero T, Bethea J The effects of spinal cord injury on bone loss and dysregulation of the calcium/parathyroid hormone loop in mice. Osteoporos Sarcopenia 2016; 2: 164-9.
30. Bauman WA, Spungeon AM Coronary artery disease in individuals with spinal cord injury: assessment of risk factors. Spinal Cord 2008; 46: 466-76.
31. Lieberman JA, Hammond FM, Barringer TA, Norton HJ, Goff DC Jr, Bockenek WL et al Comparison of coronary artery calcification scores and National Cholesterol Education program guidelines for coronary heart disease assessment and treatment paradigms in individuals with chronic traumatic spinal cord injury. J Spinal Cord Med 2011; 34: 233-40.
32. Karpouzas GA. Ormseth SR, Hernandez E, Budoff MJ Impact of cumulative inflammation, cardiac risk factors and medication exposure on coronary atherosclerosis progression in rheumatoid arthritis. Arthritis Rheumatol 2020; 72: 400-08.
33. Macedo MB, Ostrovski Sousa Santos VM, Rodrigues Pereira RM, Fuller R Association between osteoarthritis and atherosclerosis: A systematic review and meta-analysis. Exp Gerontol 2022 May; 161: 111734.
34. Wang H, Bai J, He B, Hu X, Liu D Osteoarthritis and the risk of cardiovascular disease: a meta-analysis of observational studies. Sci Rep 2016 Dec 22; 6: 39672.

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35. Hall AJ, Stubbs B, Mamas MA, Myint PK, Smith TO Association between osteoarthritis and cardiovascular disease: systematic review and meta-analysis. Eur J Prev Cardiol 2016; 23: 938-46.
36. Suetomi T, Willeford A, Brand CS, Cho Y, Ross RS, Miyamoto S, Brown JH. Inflammation and NLRP3 inflammasome activation initiated in response to pressure overload by Ca^{2+}/calmodulin-dependent protein kinase II δ signaling in cardiomyocytes are essential for adverse cardiac remodeling. Circulation 2018; 138: 2530-44.
37. Yu J, Chen Y, Xu M, Sun L, Luo H, Bao X et al Ca2+/Calmodulin-dependent protein kinase II regulation by Inhibitor 1 of Protein Phosphatase 1 protects against ischemia-reperfusion injury. J Cardiovasc Pharmacol Ther 2019; 24: 460-73