

## Review Article

# Vascular and Valvular Calcification in Chronic Peritoneal Dialysis Patients

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Cardiovascular disease accounts over half of the total mortality in peritoneal dialysis (PD) patients. In addition, there is an increasing recognition of a high prevalence of vascular and valvular calcification that may contribute to the increased all-cause and cardiovascular mortality in the PD patients. Disturbed mineral metabolism in association with chronic kidney disease has been suggested as one of the major contributing factors to the increased vascular/valvular calcification in this population. In this paper, we provide an overview of the prevalence and importance of this complication in the PD patients. In addition, we review the contributing factors and some emerging mechanisms for this complication. Furthermore, we discuss some therapeutic strategies that may be useful in limiting the progression of vascular/valvular calcification in the PD population.

## 1. Introduction

Cardiovascular disease is the leading cause of death in end-stage renal disease (ESRD) patients receiving long-term peritoneal dialysis (PD) therapy. Data from the Canada and United States (CANUSA) Peritoneal Dialysis Study showed that nearly half of the mortality in PD patients was due to cardiovascular disease [1]. According to data from the United State Renal Data System (USRDS), this trend has remained more or less the same in the recent years [2]. Vascular/valvular calcifications are important and highly prevalent complications in ESRD patients including those receiving PD therapy and very much contributed to the exceedingly high cardiovascular mortality in this population. Numerous observational cohort studies demonstrated the prognostic importance of vascular/valvular calcification in ESRD patients. Using plain radiographs to estimate number of arterial sites with calcification including carotid artery, abdominal aorta, and iliofemoral axis, both the presence and extent of vascular calcifications are strong predictors of cardiovascular and all-cause mortality in the ESRD patients [3]. Abdominal aortic calcification detected nonquantitatively using plain lateral abdominal radiographs has also been shown to be an independent predictor of all-cause mortality and cardiovascular death in hemodialysis patients [4]. Using

multislice computed tomography (MSCT) that enables quantification of calcification, Block et al. demonstrated a significant mortality effect of the severity of coronary artery calcium score in incident hemodialysis patients [5]. Cardiac valvular calcification, detected using echocardiography, also predicts all-cause mortality and cardiovascular death in chronic PD patients. Notably, patients with both aortic and mitral valvular calcification showed the highest risk of mortality and cardiovascular death compared to those with either heart valve calcification or no valve calcification [6]. These data suggest that the presence of vascular or valvular calcification, irrespective of the sites involved, is indicative of a poor prognosis in the dialysis population including patients on PD. In this paper, we reviewed the prevalence, significance, contributing factors, and emerging mechanisms for this important complication in the PD population. Furthermore, we discussed therapeutic strategies that may be useful in retarding calcification burden in the PD patients.

## 2. Prevalence of Vascular and Valvular Calcification in PD Patients

The reported prevalence of coronary artery calcification in the ESRD patients ranged from 40% to nearly 100% [7–14]. So far, a majority of the studies were done in hemodialysis

patients. There are very little data in PD patients but the available evidence suggest that vascular and valvular calcification is an equally highly prevalent complication in the PD population. In two small surveys, at least 60% to 80% of the PD patients, were complicated with coronary artery calcification [15, 16]. The prevalence of cardiac valvular calcification ranges from 32% to 47% in PD patients [17, 18], in contrast to 19% to 84% in hemodialysis patients [19–24].

### 3. Significance of Vascular/Valvular Calcification in PD Patients

In the general population, coronary artery calcium score provides a quantitative estimate of total atherosclerotic plaque burden and correlates with obstructive coronary artery disease [25]. In nondialysis chronic kidney disease (CKD) patients, similar association was observed between the severity of coronary artery calcium score and obstructive coronary artery disease [26]. Study in hemodialysis patients demonstrated a close relation between the severity of coronary artery calcification and prevalence of atherosclerotic vascular disease [10]. This is in keeping with recent similar analysis in PD patients showing that the severity of coronary artery calcium score was associated with the prevalence of atherosclerotic vascular disease (unpublished observation). On the other hand, the severity of coronary artery calcium score is predictive of arterial stiffening in patients with CKD [27] and is associated with increased risk of left ventricular hypertrophy [28]. Unlike in the general population, where calcification occurs mainly in the intimal layer and reflects atherosclerotic disease burden, vascular calcification in ESRD patients typically occurs both in the intimal and medial layer [29]. The medial calcification, known as Monckeberg's medial calcinosis is also prominent in patients with diabetes. Medial calcification promotes arterial stiffening and is associated with increased risk of left ventricular hypertrophy and impaired coronary perfusion [30]. While both medial and intimal type of calcifications predict mortality and cardiovascular death in ESRD patients, intimal calcification was associated with worse survival compared to medial calcification [14]. On the other hand, cardiac valvular calcification is a marker reflecting generalized atherosclerosis and calcification in the PD patients [31].

### 4. Clinical Course of Vascular/Valvular Calcification in Long-Term PD Patients

Vascular calcification is a progressive and actively mediated disease. Goodman et al. showed in a cohort of young hemodialysis adults of rapid progression in coronary artery calcification over a mean follow-up period of 20 months [8]. In the subsequent study by Block et al., patients who had baseline coronary artery calcifications showed significant progression in coronary calcification while those without baseline calcification remained free from calcification during follow-up [32]. These data suggest that preexisting coronary artery calcification is one of the key factors predicting further progression of vascular calcification in ESRD patients. Our

recent analysis also reported similar finding in PD patients (unpublished observation) in that PD patients without significant baseline vascular calcification remained relatively free of calcification with time on dialysis. These data raised the possibility of some protective mechanisms or genetic factors in play that prevent patients from developing vascular calcification.

### 5. Contributing Factors to Vascular/Valvular Calcification in PD Patients

The high incidence of vascular/valvular calcification in PD patients is contributed by both traditional and so-called nontraditional or kidney disease-related risk factors. Age is one of the major clinical factors associated with vascular/valvular calcification in dialysis patients [7, 10, 17, 33]. Some studies showed that the degree of coronary or valvular calcification increased with increasing duration of dialysis [7, 8, 17]. Disturbed mineral metabolism with resulting hyperphosphatemia has been suggested to play a major contributing role for vascular/valvular calcification in ESRD patients [8, 10, 12, 17]. According to a retrospective analysis from the USRDS, an elevated serum phosphorus or an elevated calcium  $\times$  phosphorus product predicts all-cause mortality as well as cardiovascular mortality in hemodialysis patients [34]. Notably, patients with a high serum phosphorus  $\geq 6.5$  mg/dL was associated with an increased risk of death from coronary artery disease, sudden death, infection or other causes, compared with the low phosphorus group [34]. The Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD) study compared hemodialysis and PD patients and showed that hyperphosphatemia with resulting high calcium  $\times$  phosphorus product had similar predictive value for mortality in PD and hemodialysis patients [35]. Having a serum phosphorus level  $>1.78$  mmol/L was associated with a time-dependent adjusted hazard ratios of 1.6 and 1.4 for all-cause mortality in PD and hemodialysis patients, respectively. These data clearly indicated that optimizing phosphorus control is equally important in PD as in hemodialysis patients.

In vitro study showed that inorganic phosphate induced an osteoblastic phenotypic change in vascular smooth muscle cells which led to the deposition of calcium and phosphate-containing apatite crystals [36]. This is in keeping with cross-sectional studies demonstrating an association between hyperphosphatemia and vascular calcification in ESRD patients [8, 10, 12, 33]. Hyperphosphatemia is also associated with an increased risk of valvular calcification in patients on PD [17]. Previous longitudinal study showed a significant association between serum phosphorus and calcium  $\times$  phosphorus product with changes in coronary artery calcification over 1 year in PD patients [37], providing further evidence to support the involvement of hyperphosphatemia in vascular/valvular calcification in PD patients.

As in hemodialysis patients, PD patients have a high prevalence of hyperphosphatemia. According to the NECOSAD study, around 40% of the long-term PD patients had serum phosphorus level above the Kidney Disease Outcome Quality Initiative (K/DOQI) target of 1.78 mmol/L

and was similar to that of hemodialysis patients (50%) [35]. This is very similar to our survey showing that around 40% of Chinese PD patients had serum phosphorus level above the K/DOQI target [38]. One of the major clinical factors associated with hyperphosphatemia in PD patients was dietary protein intake. Residual renal function is the other significant factor associated with serum phosphorus control in PD patients. Its importance outweighed that of PD clearance among those with preserved residual kidney function. On the other hand, among anuric PD patients, serum phosphorus showed the strongest correlation with PD clearance followed by normalized dietary protein intake [38]. Additionally, a total urea clearance of at least 2.0 and creatinine clearance of at least 60 L/wk per 1.73 m<sup>2</sup> appeared to be optimal clearance targets that maintain serum phosphorus below 5 mg/dL in continuous ambulatory PD patients. Given that it is extremely difficult to achieve a total weekly creatinine clearance of over 60 L with PD alone, these data suggest potential limitation of PD alone to achieve adequate phosphorus control in anuric PD patients. In keeping with these observations, our recent study demonstrated an increased prevalence of valvular calcification among anuric PD patients and was partly mediated via an increased calcium \* phosphorus product [39].

Apart from alterations in phosphorus metabolism, some of the therapeutic strategies for abnormal mineral metabolism and renal bone disease have been suggested to have the potential of worsening vascular calcification in ESRD patients [8, 40]. The use of very high doses of calcium-based binders for phosphorus control [8] as well as the administration of large doses of vitamin D analogs for control of secondary hyperparathyroidism [40] may contribute to episodes of hypercalcemia and/or hyperphosphatemia and may thus aggravate vascular calcification. Chertow and coworkers have shown in a longitudinal study that calcium-based phosphate binders are especially associated with progressive coronary artery and aortic calcification in hemodialysis patients when mineral metabolism is poorly controlled [41]. Patients with low bone activity appeared to be particularly susceptible to worsening of vascular calcification and stiffening when exposed to an excess calcium load [42]. This may be due to the inability of adynamic bone to incorporate extra calcium load and thus increases the risk of extraskeletal calcification.

## 6. Pathogenesis of Vascular/Valvular Calcification

Vascular/valvular calcification is now recognized to be an active, cellular-mediated process involving an osteogenic phenotypic change of vascular smooth muscle cells along with the dynamic interactions between calcification inducers and inhibitors. Inflammation may act as one of the potential stimulus for calcification. This is first evident by the accumulation of macrophages and T-lymphocytes other than low-density lipoprotein and Lp(a) lipoprotein in early aortic valve calcification [43, 44]. Subsequent study from our group showed an important link between inflammation and valvular calcification in PD patients [17]. Among patients

with high calcium \* phosphorus product, the presence of both inflammation and malnutrition increased the prevalence of valvular calcification as compared to those with no evidence of inflammation and malnutrition. Notably, even among patients with normal calcium \* phosphorus product, the presence of inflammation and malnutrition was associated with at least twofold increase in the prevalence of valvular calcification as compared to those with no inflammation or malnutrition at all [17]. These data suggest that inflammation is predictive of an increased risk of valvular calcification independent of calcium \* phosphorus product. The presence of inflammation also predicts a more adverse clinical outcome among PD patients with valvular calcification [45]. Histopathological study showed markedly increased expression of C-reactive protein messenger ribonucleic acid (mRNA) in the coronary vessels of renal patients compared to nonrenal patients in both calcified and noncalcified parts of arteries [29], suggesting that uremia itself was associated with increased vascular inflammation and that may mediate the development of vascular calcification. This is further supported by *in vitro* data showing that pooled uremic serum can induce accelerated calcification of vascular smooth muscle cells, regardless of the level of phosphorus. However, the exact uremic toxins that increase vascular calcification are currently not clear. In hemodialysis patients, C-reactive protein showed similar association with annualized change in coronary artery calcium score [46] and has been associated with progression of abdominal calcification [47]. Inflammation has also been inversely related to circulating fetuin-A or alpha-Heremans-Schmid glycoprotein (AHSG) in both hemodialysis and PD patients [48, 49]. These data add circumstantial evidence to support possible causal link between inflammation and calcification and warrant further investigation.

Circulating calcification inhibitors are increasingly recognized to play an important role in modifying the calcification risk of ESRD patients. The presence of extensive calcification in various organs including the kidneys, lungs, myocardium, skin, and blood vessels in AHSG or fetuin-A deficient mice being fed a mineral and vitamin D rich diet provides novel evidence to support a crucial role of fetuin-A in inhibiting ectopic calcification [50]. Even though some studies suggested higher fetuin-A levels in PD than hemodialysis patients [51], lower serum fetuin-A was linked to an increased risk of all-cause mortality and cardiovascular death in both hemodialysis [48] and PD patients [49]. Lower fetuin-A was associated with more inflammation and valvular calcification in PD patients [49] and was inversely related to more aortic calcification in pediatric dialysis patients [52]. All these data lent supporting evidence that fetuin-A may be involved in inhibiting vascular and valvular calcification.

Other circulating inhibitor such as pyrophosphate has recently been shown to be inversely related to the severity of coronary artery calcification [53] and its circulating level did not seem to be affected by the severity of kidney disease, the modality of dialysis or inflammatory activity [53]. Matrix gla-protein (MGP) belongs to a family of the N-terminal  $\gamma$ -carboxylated (Gla) proteins that require a vitamin

K-dependent  $\gamma$ -carboxylation for their biological activation. The development of spontaneous vascular calcification in MGP-deficient mice was novel evidence to support a key role of MGP in inhibiting vascular calcification [54]. A study in the general population indicated an inverse correlation between blood MGP levels and coronary artery calcification [55]. However, the assay measured total blood levels of MGP without differentiating between undercarboxylated (uc) and carboxylated (cMGP) and without taking into account of tissue deposition. More recently, study showed that serum total uc-MGP was significantly reduced in hemodialysis patients compared to nonrenal failure population and markedly reduced in patients with calciphylaxis [56]. Serum total uc-MGP level was inversely correlated with serum phosphate but positively associated with serum fetuin-A [57]. In a very recent study, lower circulating levels of dephosphorylated-carboxylated MGP (de-cMGP) was associated with more inflammation and was predictive of higher mortality in hemodialysis patients. Patients with lower dp-cMGP level were also associated with more calcifications as denoted by a composite semiquantitative calcification score [58]. However, it remains further elucidation whether circulating MGP directly reflects the biologically active MGP in the vasculature and may play a causative role in vascular calcification.

Osteoprotegerin (OPG) belongs to the tumor necrosis factor-receptor gene superfamily and serves as a soluble decoy receptor for the receptor activator of NF- $\kappa$ B-ligand (RANKL). It inhibits osteoclast activation and promotes osteoclast apoptosis *in vitro*. The demonstration of medial calcification of the aorta and renal arteries in OPG knockout animal suggests OPG and its signaling pathway may play a role in medial arterial calcification [59]. In the general population, serum OPG was positively related to the extent and severity of coronary artery disease [60]. Serum OPG was higher in dialysis patients than healthy controls [52] and was independently associated with the severity of abdominal aortic calcification in hemodialysis patients [61]. Furthermore, both serum C-reactive protein and OPG were higher among rapid progressors of abdominal calcification compared to slow progressors [62]. Further study will be required to investigate the exact role of OPG in vascular calcification in ESRD patients.

Other potential mechanisms of vascular calcification include vascular smooth muscle cells apoptosis and FGF-23 and Klotho activity. There is *in vitro* evidence that chronic mineral dysregulation is capable of triggering vascular smooth muscle adaptation and release of matrix vesicles and that ultimately culminates in vascular smooth muscle cell apoptosis and vascular calcification [63, 64]. The fibroblast growth factor-23 (FGF-23)—klotho activity plays an important role in the systemic regulation of phosphate homeostasis [65, 66]. Studies have shown that both FGF-23 and klotho knockout mice develop extensive vascular and soft tissue calcification [67, 68]. Serum calcium and 1,25 hydroxyvitamin D levels are also elevated in both Fgf23 and klotho ablated mice [69]. Moreover, increased sodium phosphate cotransporter activity in both Fgf23 and klotho ablated mice increases renal phosphate reabsorption

which in turn can facilitate calcification [68]. Very recent study showed that Klotho may exert direct effects on vascular smooth muscle cells and its deficiency may directly induce vascular calcification in uremia [70], suggesting that Klotho may act as a novel circulating inhibitor of vascular calcification.

## 7. Limiting the Progression of Vascular or Valvular Calcification in PD Patients

Current therapeutic strategies for vascular/valvular calcification in the ESRD population are largely linked to management of mineral bone disorder associated with CKD such as control of hyperphosphatemia, avoiding, hypercalcemia and control of secondary hyperparathyroidism. A recent prospective analysis comparing 3555 patients who began treatment with phosphorus binders during the first 90 days after initiating hemodialysis versus 5055 patients who remained untreated clearly showed that the early use of phosphorus binders was independently associated with better survival [71]. So far, there are no data as to whether the type of phosphorus binders may affect progression of vascular calcification in PD patients. Study in PD patients showed that sevelamer hydrochloride provides a similar reduction in serum phosphorus compared to calcium-based binders as in hemodialysis patients [72]. A number of prospective open-label randomized controlled trials in hemodialysis patients including the Treat to Goal study [11], and the Renagel in New Dialysis Patients (RIND) study [32], comparing sevelamer versus calcium-based binders suggested a slower progression of coronary artery calcification with sevelamer hydrochloride as compared to calcium-based binders. Notably, in both studies [11, 32], sevelamer and calcium-based binders-treated patients achieved comparable serum phosphorus control, but serum calcium was significantly lower in calcium-based binder-treated patients versus sevelamer-treated patients. The reduced calcium load with resulting lower serum calcium may partly contribute to the slower progression of vascular calcification in sevelamer-treated patients. In the extended followup of the RIND study, a significant survival benefit was observed in the sevelamer-treated patients as compared to patients treated with calcium-based binder [5]. On the other hand, the Calcium Acetate Renagel Evaluation-2 (CARE 2) study reported similar progression of coronary artery calcification with sevelamer and calcium acetate when statins were used to achieve a similar serum LDL-cholesterol in hemodialysis patients [73]. In the Dialysis Clinical Outcomes Revisited (DCOR) study, no significant difference was observed in the overall all-cause mortality between sevelamer and calcium-based binder treated hemodialysis patients. However, there is some suggestion that sevelamer treatment may be associated with lower overall mortality but not cardiovascular-related mortality among elderly patients [74]. There is no data on the effect of lanthanum carbonate or other newer phosphorus binders on the progression of vascular calcification as compared to calcium-based binders in dialysis patients. Given the current available evidence, the Kidney Disease Improving Global Outcome (KDIGO) guideline suggests

restricting the dose of calcium-based binders in patients with stage 5D CKD including those on PD, in the presence of persistent or recurrent hypercalcemia, arterial calcification, adynamic bone disease, and persistently low parathyroid hormone [75].

Vitamin D receptor activator (VDRA) has been the standard treatment for secondary hyperparathyroidism in patients with CKD. There is animal data to suggest that different VDRA have differential effects on vascular calcification in uremia [40]. In the study by Mizobuchi et al., paricalcitol, a selective VDRA, showed no effects on serum calcium, phosphorus and aortic calcium content in uremic animals in contrast to other VDRA such as calcitriol or doxercalciferol which increased serum calcium, phosphorus, and aortic calcium content. In addition, doxercalciferol treatment increased mRNA and protein expression of bone-related markers Runx2 and osteocalcin in the aorta, while paricalcitol did not [40]. Similar data suggest differential effects of paricalcitol and calcitriol on aortic wall remodeling in uninephrectomized Apo-E knockout animals [76]. There are observational data to suggest that use of paricalcitol was associated with survival advantage over calcitriol in hemodialysis patients [77]. Randomized controlled trials will be required to determine whether paricalcitol may be associated with less progression of vascular calcification compared to other VDRA in the dialysis population.

Cinacalcet hydrochloride is a calcimimetic agent that inhibits parathyroid hormone secretion from the parathyroid cells by activation of the Ca receptor and emerges as a novel therapeutic agent for the treatment of secondary hyperparathyroidism in patients with CKD [78]. Previous double-blind randomized placebo-controlled trial showed that cinacalcet had comparable efficacy in both hemodialysis and PD patients and effectively reduced calcium, phosphorus, and parathyroid hormone [79]. In the more recent 33-week ACHIEVE study that randomized hemodialysis patients to receive either cinacalcet and low-dose vitamin D analog or flexible vitamin D analog, a more significant reduction in parathyroid hormone (PTH) (median percent change,  $-47\%$  versus  $-11\%$ ), calcium, and phosphorus was observed in the cinacalcet and low-dose vitamin D analog treatment group as compared to flexible vitamin D analog group [80]. Studies in uremic animal models showed that calcimimetic is capable of inhibiting vascular calcification in contrast to calcitriol which induces vascular calcification [81, 82]. In the ADVANCE trial, a prospective, randomized, controlled trial that evaluated the progression of vascular and cardiac valve calcification in 360 prevalent adult hemodialysis patients with secondary hyperparathyroidism after receiving treatment with cinacalcet plus low-dose vitamin D sterols versus flexible doses of vitamin D sterols alone, a trend towards less progression of coronary artery Agatston calcium score was observed in the cinacalcet-treated group after 52 weeks versus the flexible vitamin D sterol group but did not reach statistical significance. The difference in the corresponding changes in volume scores between the two groups were, however, of statistical significance. Furthermore, increases in calcium scores were consistently less in the aorta, aortic valve and mitral valve

among subjects treated with cinacalcet plus low-dose vitamin D sterols versus the flexible vitamin D sterol group, and the differences were significant at the aortic valve [83]. These data suggest that the use of cinacalcet may be associated with slower progression of vascular/valvular calcification as compared to flexible vitamin D sterol-treated patients. We await the results of another randomized trial, namely, the EVOLVE (evaluation of cinacalcet HCl therapy to lower cardiovascular events) study to investigate whether cinacalcet treatment may confer survival benefit in hemodialysis patients with secondary hyperparathyroidism. There is so far no randomized controlled study in PD population that addresses the issue of vascular/valvular calcification and clinical outcomes in relation to VDRA or cinacalcet. Thus, we can only lend support from data in hemodialysis patients.

Studies in *in vitro* cell culture model or *ex vivo* model suggested that aortic calcification requires the elevation of both calcium and phosphorus and that calcium rather than phosphate appears to have a more profound effect on aortic calcification [63, 84]. However, in PD patients, a low calcium PD fluid may be associated with exacerbation of secondary hyperparathyroidism [85]. Thus, to help reduce calcium loads yet without exacerbating secondary hyperparathyroidism, the previous K/DOQI guideline suggested that the dialysate calcium concentration in hemodialysis or PD should be maintained at 2.5 meq/L (1.25 mmol/L) [86]. The more recent 2009 KDIGO guideline suggested that the dialysate calcium concentration in hemodialysis or PD patients should be between 2.5 (1.25 mmol/L) and 3 mEq/L (1.5 mmol/L) [75]. A dialysate calcium concentration above 3 meq/L (1.5 mmol/L) is not recommended in dialysis patients as it results in positive calcium balance and increased risk of hypercalcemia [87]. Therefore, maintaining a neutral calcium balance appeared a reasonable goal in managing PD patients. There is so far very little data on the effect of dialysate calcium concentration on vascular calcification in PD patients. A small nonrandomized study suggested that patients receiving PD fluid of high calcium concentration, namely 1.75 mmol/L showed an increase in arterial stiffening as compared to those using low calcium concentration PD fluid which showed no change [88]. These preliminary data suggest that high calcium exposure through PD solution may play a role in progressive arterial stiffening through an increase in vascular calcification and warrant further investigation.

## 8. Conclusions

Vascular and valvular calcifications are equally highly prevalent in ESRD patients receiving PD treatment as in hemodialysis patients and are predictive of an increased mortality and adverse cardiovascular outcomes. Current therapeutic strategies that may be of use in limiting progressive vascular/valvular calcification in PD patients are largely linked to management of mineral bone disorder associated with CKD including control of hyperphosphatemia, avoiding hypercalcemia, and control of secondary hyperparathyroidism. Randomized controlled trials will be required to determine

whether these strategies may reduce calcification burden and clinical outcomes in the PD population.

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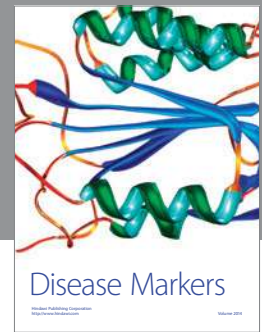
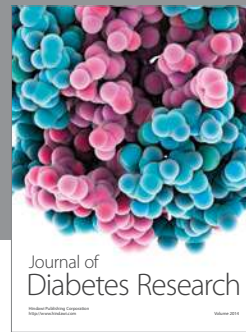
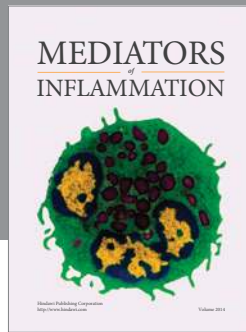
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