Cardiovascular manifestations of primary hyperparathyroidism: a narrative review

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Abstract

Data on cardiovascular disease in primary hyperparathyroidism (PHPT) are controversial; indeed, at present, cardiovascular involvement is not included among the criteria needed for parathyroidectomy. Aim of this narrative review is to analyze the available literature in an effort to better characterize cardiovascular involvement in PHPT. Due to physiological effects of both parathyroid hormone (PTH) and calcium on cardiomyocyte, cardiac conduction system, smooth vascular, endothelial and pancreatic beta cells, a number of data have been published regarding associations between symptomatic and mild PHPT with hypertension, arrhythmias, endothelial dysfunction (an early marker of atherosclerosis), glucose metabolism impairment and metabolic syndrome. However, the results, mainly derived from observational studies, are inconsistent. Furthermore, parathyroidectomy resulted in conflicting outcomes, which may be linked to several potential biases. In particular, differences in the methods utilized for excluding confounding co-existing cardiovascular risk factors together with differences in patient characteristics, with varying degrees of hypercalcemia, may have contributed to these discrepancies. The only meta-analysis carried out in PHPT patients, revealed a positive effect of parathyroidectomy on left ventricular mass index (a predictor of cardiovascular mortality) and more importantly, that the highest pre-operative PTH levels were associated with the greatest improvements. In normocalcemic PHPT, it has been demonstrated that cardiovascular risk factors are almost similar compared to hypercalcemic PHPT, thus strengthening the role of PTH in the cardiovascular involvement. Long-term longitudinal randomized trials are needed to determine the impact of parathyroidectomy on cardiovascular diseases and mortality in PHPT.

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Introduction

Primary hyperparathyroidism (PHPT) is typically characterized by elevated serum calcium associated with elevated or non-suppressed levels of parathyroid hormone (PTH) (1). Renal stones, osteoporosis and symptoms related to hypercalcemia are well-known complications (2). Controversy exists regarding the

cardiovascular involvement in PHPT, as reported by few previous reviews on this topic, with the most recent published in 2008 (3, 4, 5, 6). The latest guidelines on PHPT management do not include cardiovascular symptoms among the criteria utilized to consider parathyroidectomy (PTx), mainly due to discordant

Invited author profile

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evidences regarding the improvement of cardiovascular abnormalities after surgical intervention (2). Since 2008, new emerging data on cardiovascular manifestations have been published, including those in patients with mild PHPT, which is nowadays the most frequent form of PHPT diagnosed (7) and in normocalcemic primary hyperparathyroidism (NC-PHPT); this last is a new entity recognized in 2009, defined by normal serum calcium levels in the presence of elevated PTH (8), without any recognizable cause of increased hormone values. The categorization of these different forms of PHPT could be considered arbitrary, even though it is important for many aspects (i.e. epidemiological, therapeutic and so on); indeed, some authorities in the field consider PHPT disease as continuum from NC-PHPT to hypercalcemic PHPT.

The purpose of this paper is to review the available literature in an effort to better characterize cardiovascular involvement in PHPT patients and to examine controversies concerning this topic. The authors searched Medline for articles published in English language up until April 30, 2017, with special attention to articles published after 2008 also referring to previous older reviews on this topic whenever possible. The following keywords were used in the search strategy: 'primary hyperparathyroidism' and 'cardiovascular', or 'heart', or 'hypertension', or 'glucose metabolism', or 'arrhythmias', or 'metabolic syndrome', or 'cardiovascular mortality' or 'parathyroidectomy'.

Effect of calcium and parathyroid hormone on myocyte, conduction system and endothelial cells in physiological conditions

PTH has been largely recognized as a hormone with vascular and cardiovascular properties and paracrine or autocrine roles in the heart (4). PTH exerts a direct action on cardiac myocytes by activating protein kinase C leading to hypertrophic growth (9). PTH, in animal models, has chronotropic effects (probably due to an increase in the pacemaker current of the sinoatrial node); it influences the coronary blood flow and contractility (10). Calcium also influences the contraction of cardiac myocytes. In normal heart, ionized calcium (Ca^{++}) enters cells through L-type Ca^{++} channels following each action potential, triggering Ca^{++} release from sarcoplasmic reticulum (SR) through type 2 ryanodine receptor channels. During diastole, cytosolic Ca^{++} is removed via reuptake in SR and transmembrane extrusion through sodium (Na^+)- Ca^{++} exchanger. It has been recently

demonstrated that an enhanced SR Ca^{++} leak and an increased exchanger activity may increase the risk of supraventricular arrhythmias (11, 12).

The effect of calcium and PTH is seen not only on cardiac myocytes but also on vascular smooth cells. PTH exerts its vasodilatory effects by a direct vasorelaxant mechanism on vascular smooth muscle cells, caused by an inhibition of L-type calcium channels, while calcium is necessary for cell muscle contraction (13). Both calcium and PTH have effects on endothelial cells. PTH is involved in the expression of endothelial pro-atherosclerotic and pro-inflammatory parameters such as receptor advanced glycation end products (Rage) and interleukin 6 (14). It has been demonstrated that PTH stimulates the VEGF 165 mRNA expression, which is implicated in vascular growth, having the potential to accelerate the formation and the progression of vascular atherosclerosis and remodeling (15). There are data suggesting that PTH modulates endothelial function by increasing the production of endothelial nitric oxide synthase and its activity, which involves availability of nitric oxide, a potent vasodilatory substance (14). Calcium signaling has also a direct role in the regulation of endothelial permeability (16).

Primary hyperparathyroidism and cardiovascular risk factors

Hypertension

PHPT has been associated with an increased risk of hypertension, with a prevalence ranging from 40% to 65% (17, 18, 19, 20). Controversy exists on the exact mechanism, which underlies the possible link between PHPT and hypertension. Potential explanations include altered renin–angiotensin–aldosterone axis (21, 22, 23), dysfunction or structural changes in the resistance of vessels documented by altered vasodilatory response (24, 25) and/or enhanced vascular constriction in response to pressor hormones (26, 27). A univariate correlation between PTH and mean 24-h systolic blood pressure was found (28); however, this observation could not be confirmed in other PHPT cohorts when multivariate analyses were applied (29, 30). Interestingly, a recent paper showed that PHPT independently predicted the risk of hypertension (OR: 1.3, $P < 0.0001$) in a population from a large national database of hospital admissions where PHPT was diagnosed in 0.1% of 37 922 admissions (31).

Several studies demonstrated that following PTx, there was a reduction of blood pressure after six months

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(32), one year (33) and up to 5 years (34) while others did not report significant reduction (35). Tomaschitz *et al.* reported a reduction of blood pressure in PHPT patients followed conservatively with a mineralocorticoid receptor antagonist (eplerenone) with no impact on PTH levels (36).

Due to the variations in published data, which are possibly related to the different criteria used in selecting patients, hypertension is not considered nowadays as a criterion to submit patients to surgery (37). Limited data exist on the effect of PTx on blood pressure in patients with mild PHPT; blood pressure was reduced one year after surgical intervention in one study (38) while it remained stable after 6 months in another investigation (39, 40). It should be noted that the only randomized two-year duration study in mild PHPT patients showed neither benefit after PTx nor a deleterious effect on blood pressure with conservative management (41). A few very small retrospective studies analyzed blood pressures in subjects with NC-PHPT, showing the same prevalence of hypertension, which was not statistically different from that found in hypercalcemic patients (42, 43, 44); however, data on PTx in this last population are lacking.

Glucose metabolism

The prevalence of type 2 diabetes mellitus in PHPT has been estimated to be approximately 8%, while the prevalence of PHPT in patients with type 2 diabetes mellitus is about 1%; these figures are higher than those reported in the general population (45, 46). The high prevalence of type 2 diabetes mellitus in patients with PHPT was not confirmed in a large cohort of patients, even though the prevalence was still high in a subgroup of older patients and in men (47); differences are probably due to the retrospective nature of the investigation and the lack of appropriate controls (47). More subtle alterations of glucose metabolism, such as glucose intolerance and insulin resistance, have also been described in PHPT patient compared to controls by some (48, 49, 50), but not by all authors (35). The exact mechanism underlying this association is still unclear. In the general population, alteration of serum calcium homeostasis is significantly correlated with the abnormality of glucose level, insulin resistance and beta-cell function; in particular, calcium influences the affinity of insulin receptor and sensitivity to insulin (51), and PTH concentration is also an independent determinant of insulin sensitivity (52).

PTx improved glucose metabolism in PHPT patients after 6 months (28, 33, 53, 54) or 12 months (55), while other studies did not report such an improvement (56, 57). Considering mild PHPT patients, an increased insulin resistance (HOMA IR) and lower quantitative insulin sensitivity check index (QUICKI) compared to controls, has been reported by some investigators (54); however, these findings were not confirmed by Gianotti *et al.* (56). PTx in patients with mild PHPT showed no improvement in insulin sensitivity after one year (57, 58, 59) or 2 years (41). In patients with asymptomatic PHPT, a conservative follow-up of 18 months showed no progression of calcium and glucose metabolism abnormalities (60).

Conflicting results have also been reported in NC-PHPT. Hagström *et al.* demonstrated that fasting glucose concentrations were significantly higher in the NC-PHPT group, compared to controls, but within the normal reference range (61). Two studies, found no differences in the prevalence of impaired fasting glucose between NC and hypercalcemic patients with PHPT (19, 42). Ozturk *et al.* showed that NC-PHPT patients had similar prevalence of glucose intolerance compared with hypercalcemic PHPT patients, but found a significantly higher prevalence compared with controls (43). This study reported no statistically significant difference concerning mean fasting serum insulin and glycosylated hemoglobin levels (43), in agreement with the results obtained by Hagstorm *et al.* concerning the last parameter (61). Long-term conservative follow-up of NC-PHPT demonstrated no worsening in glucose metabolism after 4 years, while data on the role of PTx in this setting are missing (62). The heterogeneity of these findings may be a reflection of different parameters utilized to investigate glucose metabolism abnormalities (i.e. insulin resistance, fasting blood glucose or glycosylated hemoglobin).

Atherosclerosis

Several surrogates of early atherosclerosis have been investigated in PHPT; high levels of serum PTH have been related to atherogenesis in the general population possibly via vascular calcification and remodeling, through direct PTH receptor interaction on the vessels as well as indirectly via inflammation and vascular dysfunction (63). Flow-mediated dilatation (FMD) of brachial artery, a 'gold standard' of endothelial dysfunction also considered a surrogate marker of atherosclerosis, has been reported to be impaired in

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PHPT patients improving after PTx (24, 25). FMD has been shown to be negatively correlated with serum calcium levels (64). In contrast, some authors found no improvement in the FMD 3 years after PTx (26).

Concerning patients with mild PHPT, FMD was impaired compared to controls; negatively correlated with calcium and PTH and improved significantly after PTx (65). Contrary to these observations, Carrelli *et al.* demonstrated that FMD was normal in patients with mild PHPT and was unchanged one year after PTx; however, among those who had impaired FMD at baseline, a significant improvement was observed following PTx (66).

Endothelial dysfunction can also directly contribute to vessel stiffening and reduced arterial elasticity; indeed, arterial stiffness is considered an early marker of atherosclerosis. In one study, PHPT patients were characterized by significantly higher mean values of arterial stiffness compared to controls (67, 68), that improved 6 months after PTx (67). However, Rosa *et al.* hypothesized that this effect may be determined primarily by improved blood pressure control after surgery (68). Mild PHPT '*per se*' has been considered a stronger predictor of increased aortic stiffness compared to other traditional cardiovascular risk factors being associated with the degree of PTH elevations (69, 70). However, Barletta *et al.* did not report any difference in aortic stiffness in PHPT patients compared to controls (40). There was a long-term improvement of pulse wave velocity, a marker of aortic stiffness, after PTx in one study (71); however, Cansu *et al.* demonstrated that this was accounted for by changes in blood pressure post-operatively (72). Normocalcemic PHPT seems to be characterized by similar arterial stiffness values compared to hypercalcemic PHPT patients; the effect of PTx in this population has not yet been investigated (19).

Metabolic syndrome

The prevalence of metabolic syndrome (MS) has been shown to increase the risk of cardiovascular disease in the general population (73). In symptomatic PHPT, the prevalence of MS seems to be similar or higher compared to control populations (35, 74), ranging from 8% to 59% (75, 76). These different percentages may arise from the inclusion in the population studied of both female and male subjects of different ages. There are several papers that investigated the change of each component of MS after PTx, but only Ishay *et al.* reported the effect on

MS one year after surgery in patients with PHPT (35). They showed no impact on MS prevalence after PTx, but when adjusted for age and waist circumference, patients with severe PHPT had a 14.2-fold increased risk of MS compared to controls, which decreased to 1.3 following PTx (35).

In mild PHPT, Luboshitzky *et al.* showed that the prevalence of MS was lower (34.3%) compared to symptomatic PHPT (37.5%) (77); however, Procopio *et al.* reported a significantly higher prevalence (47.6%) in asymptomatic PHPT patients, with low-risk of end-organ damage, compared to symptomatic PHPT (8.7%) (50). Moreover, both BMI and the presence of a low-risk asymptomatic PHPT disease predicted MS after adjusting for age and sex (50). In PHPT patients with MS, Delfini *et al.* showed higher mean values of leptin and lower adiponectin serum level compared to controls (78); these findings are interesting because an interaction between adipokines and bone metabolism has been recently suggested in the general population (79).

In asymptomatic PHPT, a significant reduction of MS was seen by Luigi *et al.* (38% vs 28%) 6 months following PTx (28). NC-PHPT patients had similar prevalence of MS, evaluated using International Diabetes Federation (IDF) 2006 criteria, compared to hypercalcemic PHPT, without difference compared to controls (43). Hagström *et al.* reported separately the criteria needed for the diagnosis of MS; they showed that in NC-PHPT, there was an increase in proatherogenic lipoprotein levels, BMI and glucose levels compared to age-matched controls; PTx had positive effects only on proatherogenic lipoprotein levels in contrast with conservative treatment (61).

Primary hyperparathyroidism and cardiovascular abnormalities

Structural heart involvement

Cardiac dysfunction has been reported in patients with PHPT, distinctly involving the diastolic and systolic ventricular function, as illustrated by previous reviews including studies carried out before 2008 (3, 4, 5). After 2008 several studies were published; in particular, in 2010, Farahnk *et al.* reported no significant abnormalities in left ventricular ejection fraction, fractional shortening and left ventricular end-systolic volume (80). Two studies carried out in patients with mild PHPT showed no diastolic dysfunction (81, 82). Persson *et al.* carried out

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the only randomized study to investigate the effect of PTx on these parameters in mild PHPT patients, showing no benefits after surgery (82). A recent study utilizing new methods to detect global ventricular performance (which include both diastolic and systolic function) showed an impaired global ventricular function in PHPT patients when also considering those with the mild form of the disease (83). Left ventricular mass index (LVMI), a well-known risk factor for cardiovascular mortality in the general population (84), has been extensively studied in this glandular disorder, and observed to be increased in some but not all studies, as reported by previous reviews on this topic (3, 4, 5, 81). A recent meta-analysis carried out in PHPT patients by Mc Maohn *et al.*, which included 15 studies for a total of 457 patients enrolled, showed that six months after PTx, there was an average 12.5 LVMI reduction; more importantly, the highest pre-operative PTH levels were related with the greatest improvements (85). However, this meta-analysis included patients of both genders and considered both mild PHPT patients together with those who met surgical criteria. A recent study showed that cardiac remodeling was associated with low-grade inflammation (86); furthermore, bone turnover markers, such as N-terminal propeptide of procollagen type 1 (P1NP), osteocalcin (OC), bone-specific alkaline phosphatase (BALP) or beta-crosslaps (CTX) appeared to be associated with systolic and diastolic function (87). Another peculiar finding documented in PHPT patients is myocardial and valvular calcification, also highlighted in initial reviews on this topic (3, 4, 5).

Interestingly, the only paper published after 2008 on this topic showed that in mild PHPT, aortic calcification was predicted by PTH and not by calcium levels, after corrections for well-known cardiovascular risk factors (88). So far, there are no studies in NC-PHPT regarding structural heart involvement.

Cardiac conduction abnormalities and arrhythmias

It is well known that hypercalcemia may induce electrocardiogram abnormalities such as QT interval shortening, sometimes associated with prolongation of PR interval and QRS duration (89). A short QT is associated with increased risk of arrhythmias and sudden cardiac death (90); furthermore, and more importantly, it has been recently shown that QT interval duration is associated with increased mortality risk, even within the normal reference range in the general population (91). The presence of arrhythmias in PHPT patients has

been reported, so far, mainly as case reports (92, 93). Indeed, it is difficult to ascertain symptoms reported by patients that may arise suddenly and last only a few minutes. Nilsson *et al.* (25) showed an increased incidence of ventricular premature beats (VPBs) during the exercise test, which is an experimental method that physiologically induces a further shortening of QT; however, patients with diabetes or ischemic heart disease were also included. We carried out a study excluding patients with these disorders to avoid potential biases. We found that PHPT was associated with VPBs during stress testing; furthermore, serum calcium level was a predictor of VPBs during peak exercise (94), even if mean QT values were normal in the PHPT group, but significantly shorter compared with controls. It should be noted that in our study only 6 patients out of 30, had serum calcium values 1 mg/dL above the normal range. Nilsson *et al.* evaluating the effect of PTx on VPBs did not find significant changes in prevalence; it is worthy to underline that the investigators enrolled patients with coronary artery disease and diabetes (25). Our randomized study, carried out under strict exclusion criteria to avoid potential biases, showed a reduction of VPBs and a restored physiological QT dynamics, 6 months after PTx, as evaluated by exercise test (95). In this context, Birgander *et al.* demonstrated a previously unknown impairment of catecholamine response to physical stress test in PHPT patients along with changes of heart rate variability, a predictor of arrhythmias, that was reversed 6 months following PTx (96). Similar findings were reported by Curione *et al.*; they evaluated the 24-h Holter ECG, investigating sympatho-vagal balance (heart rate variability and QT parameters) in asymptomatic PHPT patients compared to controls (97). The enhanced sympathetic tone (shorter QTc interval, higher QTc dispersion and lack of physiological adaptation of QT length to R-R interval), was restored 18 months following PT, but not after 4 months (97, 98). There are no studies, so far, regarding arrhythmic risk in NC-PHPT patients.

Primary hyperparathyroidism and large vessel involvement

Mean carotid intima-media thickness (IMT) values, considered a strong predictor of systemic atherosclerosis and cerebrovascular events, have been shown to be elevated by some authors in patients with PHPT (65, 99, 100, 101). However, most authors did not find carotid structural changes in PHPT (24, 25, 40, 49, 102, 103,

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104, 105), nor did PTx seem to have significant effects (24, 25, 40, 104) on this parameter, except in one study (33).

In mild PHPT patients, PTx was found to improve IMT values according to Tuna *et al.* (65), but not to Ring *et al.* (105). Walker *et al.* showed improvement only in patients with abnormal IMT at baseline (106). In NC-PHPT, mean carotid IMT values were significantly higher (regardless of serum calcium values) compared to controls; PTx led to an improvement in IMT only in hypercalcemic patients and not in NC-PHPT (72).

With regards to abdominal aortic calcification, postmenopausal symptomatic PHPT patients had a higher prevalence compared to weight, age- and sex-matched controls, which correlated with higher PTH levels (107). No data on mild and NC-PHPT patients are currently available.

Considering the coronary artery district, Streeten *et al.* did not find significant coronary artery calcification utilizing a computed tomography scan (108) while Osto *et al.* detected microvascular dysfunction using a transthoracic Doppler (109). A recent study evaluating myocardial perfusion, conducted by gated single-photon emission computed tomography, demonstrated that coronary flow reserve is significantly reduced in PHPT patients without coronary artery disease compared to controls and was dependent on disease duration (110).

In symptomatic PHPT patients, six months after PTx, there was no improvement of coronary artery calcification; however, half of the patients studied were affected by hypertension and dyslipidemia (111). In a study carried out with transthoracic Doppler, 6 months following PTx, a reduction in microvascular dysfunction was reported; PTH, age and heart rate were independently associated with microvascular dysfunction and not with disease duration (109). In the only study performed in mild PHPT, by Kepez *et al.*, coronary calcification scores of hypertensive PHPT patients were significantly higher than both normotensive PHPT patients and controls (112). There was no significant difference regarding calcification scores of normotensive PHPT patients vs controls. Coronary artery calcifications have not been studied in NC-PHPT.

Primary hyperparathyroidism and mortality for cardiovascular disease

Studies carried out in cohorts enrolled during the last millennium, showed normal or higher cardiovascular

mortality in PHPT patients compared to general population, with different outcomes related to PTx, as previously reviewed (3, 4, 5). More recently, Clifton-Bligh *et al.* studied PHPT patients between 1961 and 1994 prospectively until 2011. They showed that both surgically treated and non-surgically treated patients have an increased risk of mortality, independently of serum calcium. They also emphasized that other factors had a significant impact on mortality, such as, the presence of diabetes mellitus, coronary heart disease and hypertension (113). Therefore, differences in mortality in studies examining the impact of PHPT on morbidity may be ascribed to different incidence of these conditions in the populations studied. In a retrospective population based observational study of mild PHPT patients (PEARS), selected from a cohort between 1997 and 2006, both cardiovascular morbidity and mortality ratio appeared to be increased (114), contrary to several studies carried out before the '90 (115, 116). These authors, in an effort to identify the best biochemical risk factors alongside other factors for predicting adverse outcomes in untreated PHPT patients showed that calcium was associated with increased risk of all-cause mortality in the short term but had no significant impact on other outcomes, while baseline PTH, rather than calcium, best predicts long-term outcomes (117). Thus, the question remains unresolved as to which of the two, i.e. calcium or PTH, is mainly responsible for higher mortality in PHPT patients. Unfortunately, there are no data in the current literature on mortality in NC-PHPT, which could help to answer this question and to better understand the role of high PTH in the presence of normocalcemia. However, a recent meta-analysis, in the general population, indicates that higher serum levels of PTH are associated with increased risk of fatal cardiovascular disease events (118).

Perspective

The evidence accumulated so far, seems to suggest a high cardiovascular risk in PHPT, through different mechanisms (Fig. 1). However, the vast majority of the studies conducted so far are observational, cross-sectional, single-center studies, not randomized. After 2008, only three randomized trials were carried out: two involving mild PHPT, suggesting neither improvement on both blood pressure and insulin sensitivity (41), nor a significant improvement in cardiac structure (82) after

Figure 1

Proposed mechanisms behind the observed increase in cardiac disease risk associated with primary hyperparathyroidism.

PTx; the third one involving symptomatic PHPT, which demonstrates reduction of arrhythmias following PTx (95). For this reason, further longitudinal randomized studies are needed to determine whether or not cardiovascular involvement should be included among the criteria for recommending PTx; the same could apply to the different nontraditional manifestations of PHPT reported in the literature (119). It would also be important to analyze the possible differences in cardiovascular risk factors related to gender, different countries, hereditary forms of PHPT and effects of drugs such as cinacalcet; indeed, these differences have already been shown to impact the classical manifestation of the diseases (120, 121, 122, 123, 124).

Conclusion

The reasons for discordant prevalence of cardiovascular risk factors in PHPT, discussed in this review, are not fully understood. Differences in the methods employed for excluding the influence of co-existing cardiovascular risk factors as well as differences in patient characteristics with varying degrees of hypercalcemia may have contributed to discrepancies. It could be hypothesized that PHPT might induce structural abnormalities during the course of the disease; therefore, parathyroidectomy could be effective only if performed in the early phase of disease. The extent and the nature of cardiovascular involvement in those with symptomatic PHPT have been better characterized compared to mild PHPT and NC-PHPT patients; in the latter conditions, there are too limited data to provide a comprehensive picture. However, if we consider NC-PHPT an early stage

of hypercalcemic PHPT, research should mainly focused on this population. If a cardiovascular examination becomes a standard evaluation of PHPT patients, it would be possible to obtain a definitive prevalence of cardiovascular risks and consequently discover more subtle impairment, as it has been the case for kidney and skeletal involvement. Indeed, the adoption of a routine imaging examination as part of the standard management of PHPT patients, even in the asymptomatic cases (37, 125), has changed the prevalence of the classical complications.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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