



OPEN Increased arterial stiffness in normotensive individuals with hypoparathyroidism

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Hypoparathyroidism is the inability of parathyroid hormone (PTH) to maintain calcium homeostasis. Patients with post-surgical hypoparathyroidism may have an increased risk of mortality; there is clinical and molecular evidence of the effects of this condition on the cardiovascular system. The aim of this study was to evaluate arterial stiffness by measuring the carotid-femoral pulse wave velocity (PWV) in post-surgical hypoparathyroidism patients. A cross-sectional study was conducted with 30 post-surgical hypoparathyroidism patients and 25 volunteers from the Endocrinology Outpatient Clinic of the Medical School. The SphygmoCor system was used to evaluate arterial stiffness by analyzing the PWV. The mean ages of the hypoparathyroidism (50.4 years) and control individuals (49.6 years) were similar. The mean PWVs were 8.7 and 7.5 m/s in the Hypoparathyroidism and Control groups, respectively (p -value = 0.084). Considering only normotensive patients, PWV was statistically higher in the Hypoparathyroidism Group (7.6 versus 6.5 m/s; p -value = 0.039). For this group, serum ionized calcium, phosphorus, and the calcium x phosphorus product levels were positively associated to PWV. Hypoparathyroidism increases arterial stiffness as assessed by PWV. Serum ionized calcium, phosphorus, and the calcium x phosphorus product are affected. A more effective investigative and therapeutic approach for patients with hypoparathyroidism can help control cardiovascular risk.

Keywords Hypoparathyroidism, Vascular stiffness, Hypocalcemia, Pulse wave velocity

Abbreviations

AS	Arterial stiffness
PWV	Pulse wave velocity
BP	Blood pressure
PTH	Parathormone
HIV	Human immunodeficiency virus
CKD	Chronic kidney disease
CPP	Calciprotein particles
Ca x P product	Calcium x phosphorus product
25-OHD	25-hydroxyvitamin D
CT	Computer tomography
CVD	Cardiovascular disease
TSH	Thyroid stimulating hormone
SBP	Systolic blood pressure
DBP	Diastolic blood pressure
AIx75%	Augmentation index adjusted for a 75 pulse/min heart rate

Hypoparathyroidism is an endocrine disease characterized by decreased levels of parathormone (PTH), hypocalcemia and high plasma levels of phosphorus. Insufficient hormone synthesis, accidental damage, or removal of the parathyroid glands during surgery are reported as the origin of hypoparathyroidism. In adults, surgical procedures of the neck, particularly thyroidectomy, are the most common cause of the disease; other

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causes include autoimmune diseases, genetic diseases, infiltration, radiation, and human immunodeficiency virus (HIV)^{1–4}. The incidence rate of permanent post-surgical hypoparathyroidism is 0.4–33%.²

The effects of PTH on calcium and phosphorus levels have been described in respect to the cardiovascular system. PTH receptors in endothelial and myocardial cells and direct hypertrophic effects of PTH on myocardial cells have been reported⁵. Although the mechanism is uncertain, hypocalcemia is believed to reduce myocardial contractility; QT prolongation and arrhythmias may occur due to hypocalcemia⁶. Moreover, persistent hyperphosphatemia has been associated to vascular calcification in patients with chronic kidney disease (CKD)⁷. As hyperphosphatemia is a characteristic of hypoparathyroidism, increased cardiovascular risk has been described in patients with this metabolic disorder⁸.

In turn, arterial stiffness (AS) is cited as an independent risk marker for cardiovascular disease (CVD)^{9,10}. As it is a practical and reliable non-invasive method, pulse wave velocity (PWV) is considered the gold standard to evaluate AS^{11,12}.

There are few studies that describe the effect of hypoparathyroidism on AS^{13,14}. One study reported that PWV values were higher in patients with hypoparathyroidism compared to apparently healthy subjects (6.2 versus 5.9 m/s; p -value = 0.02).¹³ Other researchers enrolled 56 non-surgical hypoparathyroidism patients and found that PWV was higher in this group compared to patients with pseudohypoparathyroidism¹⁴. Although both studies demonstrated increased AS, only the first study found an association between ionized calcium (Ca^{2+}), phosphorus (P) and the calcium x phosphorus product (Ca x P product) with PWV¹³.

The aim of the present research was to evaluate whether central hemodynamic parameters, particularly AS, are altered in post-surgical hypoparathyroidism patients and investigate any association between calcium metabolism parameters and AS.

Subjects and methods

Study population

This was a cross-sectional study performed in patients with permanent post-surgical hypoparathyroidism (≥ 12 months) compared to individuals without any parathyroid gland or systemic disease. The inclusion criteria were adult asymptomatic women (≥ 18 years), receiving adequate treatment with levothyroxine for permanent post-surgical hypoparathyroidism (≥ 12 months) and with serum calcium (Ca) ≥ 7 mg/dL. The exclusion criteria were patients with a glomerular filtration rate < 30 mL/min/1.73 m² calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) Eq.¹⁵, presence of diabetes, uncontrolled hypothyroidism (thyroid stimulating hormone - TSH > 10 mU/L) and other endocrine disorders. The study enrolled 30 women with hypoparathyroidism (Study Group) and 25 women without any history of surgical procedures of the neck or clinical evidence of thyroid dysfunction (Control Group). Both groups were age matched. All hypoparathyroidism patients had been treated with adequate doses of oral calcium and calcitriol over the previous three months. This study was approved by the Research Ethics Committee of the Medical School according to national and international guidelines (CAAE: 11934919.5.0000.5415: #3.314.696) and followed the ethical principles of the Declaration of Helsinki. All individuals read and signed an informed consent form.

Firstly, systolic (SBP) and diastolic (DBP) blood pressures (BPs) were measured at least three times for each individual with an automatic sphygmomanometer (OMROM-Automatic, Digital Blood Pressure Monitor, HEM-705CP), which uses a cuff-based oscillometric method to measure the brachial artery BP. The mean of three BP measurements was considered. AS was evaluated according to the PWV using an AtCor SphygmoCor-XCEL (Atcor Medical Pty Ltd, Sydney, NSW, Australia). This method has previously been validated for AS assessments¹⁶. The augmentation pressure and augmentation index (AI) adjusted for a 75 pulse/min heart rate (AIx75%) were also evaluated.

Anthropometric data were collected for patients and the body mass index (BMI) was calculated. Moreover, the PWV, electrocardiogram and laboratorial tests were performed. According to the VII Hypertension Brazilian Guidelines, a PWV ≥ 10 m per second (m/s) is indicative of AS¹⁷. Laboratory tests of the hypoparathyroidism group were recovered from the hospital computer database including fasting plasma glucose after eight hours of fasting (reference range: 74–100 mg/dL), serum creatinine (range: 0.57–1.11 mg/dL), TSH (range: 0.55–4 mIU/mL), free thyroxine (fT4 - range: 0.90–1.80 ng/mL), total Ca (range: 8.4–10.2 mg/dL), phosphorus (range: 2.5–4.5 mg/dL), magnesium (range: 1.8–2.4 mg/dL), 25-hydroxyvitamin D (25-OHD - range: 25–80 ng/mL), PTH (range: 15–65 pg/mL) and 24-hour urine calcium. The Ca x P product was calculated by multiplying the calcium and phosphorus levels. The exams of the Control Group were serum creatinine and fasting glucose.

Statistical analysis

Descriptive statistics together with the Kolmogorov-Smirnov test were used to analyze the trend of continuous variables. Student's t -test was used to compare independent groups. Correlation analyses were achieved by Spearman's and Pearson's correlation tests. A multivariate regression analysis was performed to detect independent variables predicting hemodynamic parameters and PWV. The sample size was chosen considering the numbers of patients treated with hypoparathyroidism in the health service.

Statistical analyses were performed using the IBM Statistical Package for Social Sciences (SPSS) software, version 27 (IBM Corporation, NY, USA). P -values < 0.05 were considered significant.

Results

This study included 30 hypoparathyroidism patients and 25 control subjects. There was no significant difference in age between the two groups. However, the BMI and waist circumference were statistically greater in the Study Group. (Table 1). Hypertension was present in nine patients of each group, resulting in prevalences of 30% in the Study Group and 36% in the Control Group. BMI greater than 30 was found in 40% and 16% of the Study and

	Control group (n = 25)	Study group (n = 30)	p-value
Age (years)	49.56 ± 14.17	50.43 ± 13.51	NS
BMI (kg/m ²)	25.92 ± 3.90	30.42 ± 6.64	< 0.05
WC (cm)	85.24 ± 10.34	95.82 ± 11.12	< 0.05
Hypertension	9 (36%)	9 (30%)	*

Table 1. Demographic and anthropometric data of the control and study groups. BMI: Body mass index; WC: Waist circumference. *Nominal qualitative value.

Variable	Study group (n = 30) Mean (range)
Free T4 (ng/dL)	1.56 (1.04–1.98)
Thyroid stimulating hormone (mU/L)	2.38 (0.07–10.00)
Ionized Calcium (mg/dL)	1.08 (0.80–1.24)
Total Calcium (mg/dL)	8.31 (7.10–10.30)
Magnesium (mg/dL)	1.96 (1.30–2.30)
Phosphorus (mg/dL)	4.58 (3.10–6.50)
Ca x P product (mg ² /dL ²)	36.93 (21.40–53.00)
Parathormone (pg/mL)	12.40 (2.00–29.80)
25-OH vitamin D (ng/mL)	36.34 (21.00–60.00)
24 h urinary calcium (mg/day)	178.10 (24.00–568.00)
Hypoparathyroidism duration (years)	9.76 (0.6–33.8)
Calcitriol use 0.25 mcg (pills)/day	2.5 (1–5)
Calcium carbonate use (mg/day)	1215 (500–4000)

Table 2. Laboratorial and clinical parameters of hypoparathyroidism individuals. Ca x P product: calcium x phosphorus product.

Variable	Control group		Study group		p-value
	Mean ± SD	n	Mean ± SD	n	
PWV (m/s), all patients	7.60 ± 2.10	25	8.74 ± 2.57	30	0.084
Hypertensive patients	9.56 ± 1.71	9	11.31 ± 2.45	9	0.100
Normotensive patients	6.50 ± 1.39	16	7.64 ± 1.73	21	0.039

Table 3. Pulse wave velocity comparative analysis between control and study groups. SD: standard deviation; PWV: pulse wave velocity. *Student’s t test.

Control Groups, respectively. However, obesity did not influence in the PWV values. Thus, no association was observed between BMI and PWV. Around 40% of both groups were menopausal women.

Indication for neck surgery was the presence of thyroid carcinoma in 66.6% of patients with the mean duration of hypoparathyroidism being nine years and six months in this group. Only four patients (13%) demonstrated mild increases in the TSH level. The hypoparathyroidism patients presented adequate Ca x P product (Table 2).

Both groups demonstrated normal PWVs and other hemodynamic variables. The PWV was higher, albeit non-significant, in the hypoparathyroidism group. However, an analysis of just the normotensive subjects showed that the PWV was statistically different between the two groups (7.64 ± 1.73 versus 6.50 ± 1.39 m/s for the Study and Control Groups, respectively; p-value = 0.039) (Table 3).

Table 4 shows data for the subgroups according to presence or not of hypertension (normotensive control, hypertensive control, normotensive hypoparathyroidism and hypertensive hypoparathyroidism). Central and peripheral hemodynamic parameters, including BP, pulse pressure and AIx75%, were higher in the Study Group compared to controls independently of whether hypertension was present. (Table 4).

Linear regression analysis of the Study Group showed a significant association between the biochemical test results (ionized calcium, phosphorus, Ca x P product) and the central and peripheral parameters (p-value < 0.05), including PWV. However, the PTH level was only associated to central systolic and diastolic BPs. (Table 5)

Discussion

Calcium metabolism disorders involving Ca, P and PTH are described as risk factors for vascular calcification, increased risk of CVD,^{18,19} and mortality²⁰. The present study evaluated the AS by PWV in patients with post-surgical hypoparathyroidism. There are conflicting results and few studies that report the effect of hypoparathyroidism on AS. Clinical, BP and laboratorial parameters investigated in this study demonstrated

Variable	Control group			Study group			p-value
	Normotensive (Mean ± SD) n = 21	Hypertensive (Mean ± SD) n = 9	p-value	Normotensive (Mean ± SD) n = 16	Hypertensive (Mean ± SD) n = 9	p-value	
SBP (mmHg)	111.31 ± 9.73	133.00 ± 19.27	0.012	125.14 ± 13.22	143.89 ± 16.36	0.002	0.015
DBP (mmHg)	69.94 ± 6.15	79.22 ± 9.16	0.011	77.52 ± 11.86	75.22 ± 14.69	0.001	0.012
PP (mmHg)	43.13 ± 7.02	53.78 ± 13.27	0.014	48.19 ± 9.42	68.44 ± 15.65	0.003	0.017
cSBP (mmHg)	103.31 ± 10.36	123.56 ± 18.38	0.022	115.95 ± 12.39	133.67 ± 17.38	0.005	0.023
cDBP (mmHg)	69.44 ± 6.57	80.11 ± 9.77	0.016	78.62 ± 11.57	76.78 ± 14.95	0.006	0.021
cPP (mmHg)	34.50 ± 7.02	43.44 ± 11.25	0.017	37.33 ± 7.59	57.33 ± 13.51	0.013	0.031
AIx 75%	26.63 ± 9.44	32.67 ± 8.72	0.010	28.57 ± 7.92	31.44 ± 8.93	0.010	0.010

Table 4. Peripheral and central hemodynamic parameters of control (normotensive and hypertensive) and study (normotensive and hypertensive) groups. SBP: systolic blood pressure; DBP: diastolic blood pressure; PP: pulse pressure; cSBP: central systolic blood pressure; cDBP: central diastolic blood pressure; cPP: central pulse pressure; AIx75%: Augmentation Index (corrected by cardiac rate of 75 beats per/minute); SD: standard deviation.

Variable	Ionized calcium p-value (R2)	Phosphorus p-value (R2)	Ca x P product p-value (R2)	PTH p-value (R2)
SBP (mmHg)	0.023 (69%)	0.003 (64%)	0.013 (84%)	0.100 (12%)
DBP (mmHg)	0.010 (71%)	0.012 (67%)	0.016 (81%)	0.789 (21%)
PP (mmHg)	0.003 (78%)	0.009 (79%)	0.006 (74%)	0.634 (22%)
cSBP (mmHg)	0.005 (81%)	0.05 (67%)	0.009 (65%)	0.002 (77%)
cDBP (mmHg)	0.006 (85%)	0.002 (65%)	0.008 (67%)	0.004 (71%)
cPP (mmHg)	0.001 (67%)	0.004 (83%)	0.013 (65%)	0.323 (16%)
AIx75 (%)	0.008 (77%)	0.013 (78%)	0.010 (79%)	0.379 (13%)
PWV (m/s)	0.005 (87%)	0.005 (84%)	0.018 (88%)	0.445 (19%)

Table 5. Linear regression analysis of hemodynamic and laboratorial parameters of hypoparathyroidism group. Ca x P product: calcium x phosphorus product; SBP: systolic blood pressure; DBP: diastolic blood pressure; PP: pulse pressure; cSBP: central systolic blood pressure; cDBP: central diastolic blood pressure; cPP: central pulse pressure; AIX 75%: Augmentation Index (corrected by cardiac rate of 75 beats per/minute); PWV: pulse wave velocity.

that hypoparathyroidism is associated with higher BP and AS, thereby contributing to increased cardiovascular risk.

Two previous studies investigated PWV in patients with hypoparathyroidism and found higher velocities in hypoparathyroidism patients^{13,14}. In the first study, Pamuk et al. compared hypoparathyroidism patients with volunteers in terms of PWV and BP¹³. The device used to assess PWV was a Mobil-o-graph, different from previous and the present study. Some of the subjects were not surgical hypoparathyroidism cases whereas the present research included only surgical hypoparathyroidism. The authors found a mean PWV of 6.2 m/s (range: 4.5–10.2), lower than that found in the current study which can be explained by the difference in the mean age (40 years), that is, lower than the mean age of the current study (mean 50.43 years) and the fact that hypertensive patients were not included¹³. In the second study, a sample of 56 individuals with non-surgical hypoparathyroidism was compared to 30 patients with pseudohypoparathyroidism in terms of BP and PWV. The method of PWV evaluation, a SphygmoCor-XCEL, which is considered the gold standard, was the same as in the present study¹⁴. Although the PWV was higher in the non-surgical hypoparathyroidism group, neither PWV nor BP were associated to the Ca x P product, or Ca and P levels¹⁴.

The current research demonstrated a higher prevalence of obesity in the Study Group, which could affect the PWV result. However, no correlation was observed between BMI and PWV. This finding agrees with a recent study that did not observe any association between BMI and PWV in women either. The authors concluded that obesity parameters have not influence on PWV in women²¹.

There was no difference in the percentage of menopausal women between groups in the present study. Furthermore, the effect of estrogen deprivation during menopause increases arterial stiffness in an age-dependent manner. As the groups were age-matched, the menopause had no influence on the results²².

According to multivariate linear regression analysis, ionized calcium, phosphorus, and the Ca x P product are independent predictors for PWV. Compared to the work by Pamuk et al., the present study agrees only with the phosphorus level, because phosphorus was found to be an independent predictor of increases in PWV;¹³ it was demonstrated that hyperphosphatemia is related to cardiovascular risk⁷. There is an increase of phosphorus uptake into smooth muscle cells mediated by the sodium-phosphate cotransporter following an increase in extracellular phosphorus. Phosphorus inside the cell stimulates the production of Core-binding factor alpha1 (Cbfa-1), a transcription factor that promotes osteogenic differentiation. The smooth muscle cells become

calcified and gain osteoblast-like phenotypical characteristics, decreasing arterial elasticity which leads to AS. Consequently, the systolic BP and pulse pressure increase, and the diastolic blood pressure decreases^{7,23,24}.

Although the present study demonstrated that calcium, phosphorus and the Ca x P product were adequate in serum, these parameters were correlated to AS. These disorders have previously been described associated to vascular calcification and risk of death in patients with CKD.^{24–27} Recently, cross-sectional studies revealed that the phosphorus concentration has an important influence on calciprotein particles (CPP)^{28,29}, which are mineral-protein products mainly composed of calcium phosphate and serum proteins, in particular fetuin-A³⁰. CPPs are present in the blood and renal tubular fluid with phosphate toxicity being mediated by higher concentrations of CPP in the body. Serum CPP levels have been positively correlated with AS as determined using the PWV³¹. CPP levels have not been studied in hypoparathyroidism individuals. However, as described previously, calcium and phosphorus disorders are similar in CKD patients and so this allows the use of this model to explain the effects of calcification in hypoparathyroidism patients.

Meena et al. studied the intima-media thickness of the carotid artery, aorta, and renal artery of 30 sporadic idiopathic hypoparathyroidism patients compared to healthy controls. They detected a higher intima-media thickness in the hypoparathyroidism group compared to the control group. On the other hand, laboratorial parameters such as calcium, phosphorus, the Ca x P product, 25-OHD and PTH were not correlated to intima-media thickness.³² Another study by Agarwal et al. detected different stages of calcification of the coronary artery in three patients in the hypoparathyroidism group whereas no calcification was found in the 40 volunteers of the control group by multidetector computer tomography (CT). Although the difference was not statistically significant, the hypoparathyroidism group demonstrated a higher calcium score of the coronary artery which was negatively correlated with serum calcium levels¹⁸. Such studies confirm the effect of hypoparathyroidism on arterial stiffness AS. However, the authors did not find a positive correlation between phosphorus concentration and vascular function.

Two previous studies described an association between hypoparathyroidism and mortality^{8,20}, while hyperphosphatemia and Ca x P product were found to be risk factors for fatal outcomes¹⁹. These results support the results in the present study and may confirm the effect of surgical hypoparathyroidism on AS and cardiovascular risk^{13,14}. Additionally, the positive correlation between phosphorus level and the Ca x P product and PWV suggests that AS may be due to an increment in vascular calcification.

A systematic review demonstrated associations between serum calcium, stroke, and arterial calcification in individuals with normal calcium levels.³³ A study with 565 Korean adults showed that serum calcium levels were independently and positively associated with AS and ten-year CVD risk by the Framingham risk score.³⁴ Thus, it was concluded that early detection of higher serum calcium levels may be important for the assessment of AS and the future risk of a cardiovascular event.

Although hypoparathyroidism patients present with undetectable or low levels of PTH, the positive association described in this research between PTH and central BP parameters is compatible with other studies.^{34,35} In the SPRINT trial, higher PTH levels in CKD patients increased the risk of cardiovascular events, especially in the BP intensive control group³⁵. PTH receptors have been found in cardiomyocytes and vascular wall and so, PTH acts direct or indirectly on the heart and arterial system³⁶. Contrasting with these results, PTH and 25-OHD levels were not associated with progression of carotid AS³⁷.

This study has some limitations. As the study has a cross-sectional design, patient outcomes are not reported. Furthermore, laboratory tests of the calcium metabolism were not performed in the Control Group. However, we consider that control subjects had normal levels since they were asymptomatic and did not have any history of radiation or surgical procedures of the neck. In addition, lipid tests were not collected in the Control Group. However, we consider that this did not interfere in the results as Pamuk et al. demonstrated that lipid parameters were similar in both hypoparathyroidism and control individuals¹³.

An important characteristic of the present study was that only women made up both groups, and there was no difference between the groups in terms of cardiovascular risk factors and age. Furthermore, possible causes of AS in hypoparathyroidism patients were discussed. Additionally, the method used to assess AS was the SphygmoCor-XCEL, considered the gold standard to evaluate PWV.

Conclusion

The present study demonstrated an increase of AS in hypoparathyroidism patients, which is a reliable indicator for CVD risk. In addition, a positive correlation between hyperphosphatemia and PWV was detected. Therefore, patients with hypoparathyroidism should be closely monitored for the phosphorus-calcium balance and development of CVD. The relationship can no longer be neglected as a possible cause of CVD. Other studies are needed in patients with this endocrine disease. The current study can guide further comprehensive studies.

Data availability

The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

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Author contributions

The study was conceived by LNC-M and JFV-M. LNC-M and JFV-M provided the research platform. RD, JRRU, VSL, LABE, KAO and AOS performed the literature search, contributed to the methodology and data acquisition. LNC-M and JFV-M wrote the manuscript. JCY-T and MAVS critically revised the study. The final version of the manuscript was reviewed and agreed to be submitted by all authors.

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Declarations

Competing interests

The authors declare no competing interests.

Ethical approval

All data are from publicly available databases that have received ethical approval from their respective institutional review boards and informed consent from all participants. No administrative permissions were required to access the data. This study was approved by the Research Ethics Committee of the Medical School according to national and international guidelines (CAAE: 11934919.5.0000.5415: #3.314.696).

Additional information

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