Original Article

To assess vascular calcification in the patients of hypoparathyroidism using multidetector computed tomography scan

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ABSTRACT

Background: Our pilot data showed an increased intima media thickness in the patients with sporadic idiopathic hypoparathyroidism (SIH). Alteration in homeostasis of calcium, phosphate, and parathyroid hormone (PTH) may predispose to increase the risk of cardiovascular morbidity and mortality. The data on objective assessment of this increased risk is however lacking. **Objective:** To assess the effect of altered calcium, phosphate, and PTH homeostasis in the patients with SIH on coronary calcium score (a marker of increase vascular risk) by multidetector computed tomography scan (MDCT). **Methods:** In this case-control study, we measured coronary CT calcium score in 30 patients of SIH and compared with 40 age and sex matched healthy subjects. Correlation of coronary calcium score with biochemical parameters was evaluated. **Results:** Three of the 30 cases (10%) with SIH were found to have coronary artery calcification (CAC) of varying degree, whereas none of the control showed CAC (P = 0.07). The patients with CAC had significantly lower serum calcium levels (albumin corrected), as compared to the patients without CAC. Inverse correlation of CAC was found with serum calcium levels. No correlation was found with other biochemical parameters. **Conclusion:** The vascular risk is increased in the patients with SIH as assessed by coronary calcium score measured by MDCT. Low serum calcium levels might be a predisposing factor for this increased risk.

Key words: Cardiovascular risk, coronary calcium scores, coronary computed tomography, hypoparathyroidism, multidetector computed tomography scan

Introduction

Hypoparathyroidism is a rare metabolic bone disease that commonly presents with neurological manifestations and is biochemically characterized by hypocalcemia, hyperphosphatemia, and low or low normal parathyroid hormone (PTH) level.[1] This situation is almost similar to chronic kidney disease (CKD) (low calcium and high phosphate) however; the major difference is low serum PTH in hypoparathyroidism. Changes in calcium, phosphate, and PTH homeostasis is a predisposing factor for vascular calcification and increases the risk of cardiovascular disease (CVD).[2,3] Plethora of literature is available for abnormal calcium homeostasis, relative hypoparathyroidism, increased vascular calcification and its correlation with increased cardiovascular events but are mainly in relation to end-stage renal disease patients.[2-8] The increase in calcium and phosphate product in the patients with CK promotes the vascular calcification via multiple mechanisms. This may explain the alarmingly

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high cardiovascular mortality in the patients with CKD. Strategies to control calcium and phosphate levels in the patients with CKD have met with early success in preventing progression of vascular calcification.[9,10] Available literature also suggests that the relative hypoparathyroidism is associated with the increased mortality in the patients with CKD.[11,12] CVD is the leading cause of death worldwide and early disease detection continues to be the bedrock of most preventative strategies.[13]

In our pilot studies, we found an increase in intima media thickness (IMT) at carotid, renal as well as abdominal aorta in the patients with sporadic idiopathic hypoparathyroidism (SIH).[14,15] Carotid plaque and increased carotid IMT (CIMT) are associated with the presence and severity of coronary calcification.[16] However, the assessment of IMT by ultrasonography is still operator dependent and a component of subjectivity can bias the results. We undertook the present study, in which the effect of altered calcium, phosphate and PTH homeostasis in the patients with SIH on coronary calcium score (marker of increase vascular risk) was studied by multidetector computed tomography scan (MDCT).

Coronary artery calcification (CAC) measurement improves CVD risk classification over traditional risk factors substantially more than does inclusion of ankle-brachial index or high-sensitivity C-reactive protein in risk classification schemes.[17] The CAC score is strongly correlated with the overall atherosclerotic burden and has highly reproducible results.[18]

Methods

Patient selection

The study comprised of 30 consecutive patients with SIH attending the endocrine clinic of a tertiary care hospital, from January 2012 to May 2013. Forty age and sex matched healthy individuals were taken as control. The study was approved by the Institutional Ethics Committee. Written informed consent was taken from each subject.

The diagnosis of SIH was based on hypocalcemia and hyperphosphatemia associated with low or low normal PTH level. The exclusion criteria was: Patients with history of postoperative hypoparathyroidism or autoimmune polyendocrinopathy syndromes; subjects with history of smoking or any other chronic illness including hypertension, diabetes, dyslipidemia, obesity, deranged renal function, patient on antiepileptic drugs; patients with coronary metallic stents and presence of arrhythmia such as frequent extrasystole or uncontrolled atrial fibrillation.

Office blood pressure was measured in the sitting posture after 15–20 min of rest in the right arm twice and mean of two was taken for the calculation. Blood samples were collected in fasting status prior to any medications between 0800 and 0900 h by venepuncture from antecubital fossa (without tourniquet application) by a technician. Blood samples for the estimation of PTH were centrifuged immediately and processed and stored at −20°C in cases of anticipated delay in processing, till the time of analysis.

Laboratory methods

Serum PTH (reference range [RR], 15–65 pg/mL) was measured by chemiluminescence assay using commercially available kits (DiaSorin Inc., Stillwater, MN, USA) and rest of biochemical parameters (corrected serum calcium [RR, 2.2–2.6 mmol/L], inorganic phosphate [RR, 0.9–1.5 mmol/L], serum albumin [RR, 34–48 g/L], and total cholesterol [RR, 3.9–5.2 mmol/L], high density lipoprotein cholesterol [0.9–1.4 mmol/L], and low density lipoprotein cholesterol [0.8–2.6 mmol/L]) were measured by auto analyzer (Roche diagnostics, Modular P 800).

Coronary artery calcification measurement

CAC scores were evaluated by using Toshiba Aquillion computed tomographic scanner (Nasu, Japan; 64 sets of detectors) and Aquarius iNtuition edition, version 4.4.5.49.2104 software package (Vital Images Inc., Minnetonka, MN, USA). The data acquisition parameters were 120 KVp voltage, 300 mAs currents, and slice width 3.0 mm, DFOV 320.0 and gantry rotation time 0.25. The scan was taken from carina till the apex of the heart. The calcium score was calculated by algorithm suggested by Agatston *et al*. by determining the density of the highest density pixel in each plaque and applying a weighting factor to each plaque, dependent upon the peak density in the plaque: (Area × cofactor; 1: 130–199H; 2: 200–299H; 3: 300–399H; 4: >400H).[19] All pixels with density >130H are automatically highlighted in color on the images. An electronic region of interest was placed around each highlighted CAC and assigned one of four locations to each calcified plaque: Left main left anterior descending, circumflex or right coronary.

For interpretation of the Agatston scores, certain guidelines have been proposed for the asymptomatic persons with correlations between plaque burdens, the probability of significant CAD, implications for cardiovascular risk, and recommendations for treatment [Table 1].[20] Calcium scores have the greatest negative predictive value. When they are either absent or low (<10 for Agatston scoring), it almost certainly indicates the low risk for the development of coronary heart disease.[21]

Table 1: Recommended calcium score guidelines[20]

Calcium score	Plaque burden	Probability of significant CAD#	Implications for CV risk	Recommendations
0	No identifiable atherosclerotic plaque	Very low generally <5%	Very low	Reassure patient while discussing general public health guidelines for primary prevention of CVD
1-10	Minimal identifiable plaque burden	Very unlikely, <10%	Low	Discuss general public health guidelines for primary prevention of CVD
11-100	Definite, at least mild atherosclerotic plaque burden	Mild or minimal, coronary stenoses likely	Moderate	Counsel about risk-factor modification, strict adherence to NCEP primary prevention cholesterol guidelines
101-400	Definite, at least moderate atherosclerotic plaque burden	Nonobstructive CAD highly likely, although atherosclerotic obstructive disease possible	Moderately high	Institute risk-factor modification and secondary prevention NCEP cholesterol guidelines. Consider exercise testing for further risk stratification
>400	Extensive atherosclerotic plaque burden	High likelihood of at least one significant stenosis (≥90%)	High	Institute very aggressive risk-factor modification. Consider exercise or stress pharmacologic stress imaging to evaluate coronary stenosis for inducible ischemia

#Reproduced with permission. CAD: Coronary artery disease, CV: Cardiovascular, CVD: Cardiovascular disease, NCEP: National Cholesterol Education Program

Statistical analysis

The statistical analysis was carried out using SPSS dear (version 17, SPSS, Chicago, IL, USA). Normality of data was checked by Kolmogorov–Smirnov test. For normally distributed data means were compared using independent *t*-test for two groups. For skewed data, Mann–Whitney test was applied. Categorical variables were described as frequencies and proportions. Proportions were compared using Chi-square. Pearson's correlation was used to correlate the clinical and biochemical variables with CAC in SIH and control group. All statistical tests were two-sided and performed at a significance level of $P < 0.05$. The data are presented as mean ± standard deviation unless otherwise specified.

Results

Baseline characteristic of study population

Thirty subjects (13 men) with SIH and 40 age and sex matched healthy subjects (14 men) were included in this study. The mean age of the patients included in our study was 30.5 ± 6.5 years (range 15–39 years) whereas the age of healthy controls was 32.9 ± 4.1 years (range 21–40 years). Baseline characteristic of two groups are shown in Table 2. The mean total serum calcium, intact PTH levels were significantly lower and the value of serum phosphate levels significantly higher in the patients with SIH than in controls [Table 2].

Coronary artery calcification

Three of the 30 cases (10%) with SIH were found to have showed CAC of varying degree, whereas none of the control showed CAC ($P = 0.07$). The CAC score in these three patients (cases) were 120.13 (moderately high plaque burden) [Figure 1], 209.16 (moderately high plaque burden) [Figure 2], and 4.90 (low plaque burden) based on Agatston *et al*. criteria. The mean CAC score in cases was 11.14 ± 43.34. As none of the control had CAC and the score of all the subjects was zero.

Table 2: Baseline characteristic of the study participants

Variables	Mean±SD		*P*
	Cases	Controls	
Age (years)	30.5±6.5	32.9±4.1	0.06
Sex distribution (men) (%)	13 (43.3)	14 (35)	0.62
BMI (kg/m^2)	22.8±2.2	23.4±3.0	0.37
iPTH (ng/L)	7.5±4.0	19.6±6.8	<0.001
Serum calcium (mmol/L)	1.8±0.2	2.3±0.1	<0.001
Corrected serum calcium (mmol/L)	1.7±0.2	2.2±0.1	<0.001
Serum phosphorus (mmol/L)	2.0±1.5	1±0.3	<0.001
TC (mmol/L)	4.4±0.6	4.4±0.5	0.90

TC: Total cholesterol, HDL-C: High density lipoprotein cholesterol, BMI: Body mass index, iPTH: Intact parathyroid hormone, SD: Standard deviation

Characteristics of patients with coronary artery calcification

The patients with CAC had significantly lower serum calcium levels (albumin corrected), as compared to the patients without CAC. No other parameter was significantly different in the two groups [Table 3]. The presence of CAC had a significant negative correlation with serum calcium levels (albumin corrected). No other parameter had a significant correlation with CAC [Table 4].

Discussion

We found coronary plaques in 10% of the individuals with SIH, whereas none of the individuals in age and sex matched control group had coronary plaques. Our pilot data showed an increase in IMT at carotid, renal as well as abdominal aorta in patients with SIH.[14,15] In our previous study we found no significant association with any of the biochemical parameter,[15] whereas in the present study inverse correlation was found between corrected serum calcium and coronary calcium score. The concept of relative hypoparathyroidism and increased cardiovascular risk has been previously explored in the patients with renal failure.[22] In patients on dialysis, hyperphosphatemia is an independent risk factor for CVD.[6] Contrarily, both high as well as low calcium and PTH levels have been associated

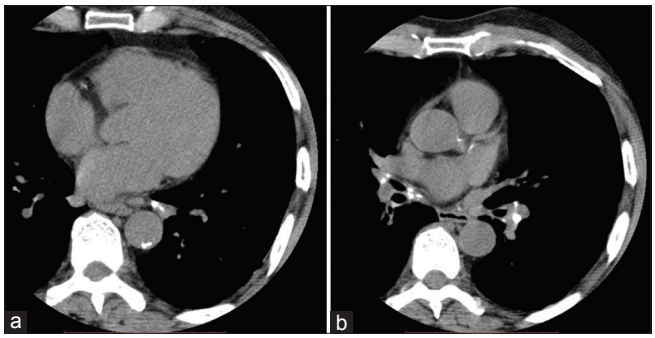

Figure 1: (a and b) Axial computed tomography images show eccentric calcified plaques in proximal right coronary and left anterior descending artery which that a score of 120.13

Table 3: Characteristics of the patients with and without CAC

Parameters	Cases with negative CAC score	Cases with positive CAC score	*P*
Intact parathyroid hormone (ng/L)	7.6±4.2	6.1±1.1	0.49
Serum calcium (mmol/L)	1.8±0.2	1.6±0.2	0.08
Corrected serum calcium (mmol/L)	1.8±0.2	1.4±0.2	0.02
Serum phosphorus (mmol/L)	2.0±0.5	2.1±0.3	0.21
Glucose (mmol/L)	5.4±0.9	5.5±0.6	0.73
Serum albumin (g/L)	43±5.0	48±1.0	0.13
25(OH) D (nmol/L)	68.3±22.8	56.8±25.0	0.60
TC (mmol/L)	4.3±0.6	4.9±0.3	0.10
HDL (mmol/L)	1.2±0.2	1.4±0.3	0.19

CAC: Coronary artery calcification, TC: Total cholesterol, HDL: High density lipoprotein, 25(OH) D: 25-hydroxy Vitamin D

Table 4: The correlation of each parameter with CAC score

Variables	Correlation with CAC score	*P*
Product of serum calcium and serum phosphorus	−0.82	0.67
Intact parathyroid hormone	−0.46	0.810
Serum calcium	−0.27	0.14
Corrected serum calcium	−0.36	0.05
Serum phosphorus	0.08	0.67
Fasting plasma glucose	0.17	0.38
Serum albumin	0.28	0.14
25(OH) D	0.04	0.85
TC	0.19	0.32
HDL	0.03	0.89
Age	0.32	0.08
BMI	0.001	0.997
Systolic blood pressure	0.313	0.09
Diastolic blood pressure	0.06	0.77
Low density lipoprotein-cholesterol	0.25	0.19
Triglycerides	0.03	0.86

CAC: Coronary artery calcification, TC: Total cholesterol, HDL: High density lipoprotein, BMI: Body mass index, 25(OH) D: 25-hydroxy Vitamin D

with increased cardiovascular mortality.[2,22,23] While planning study we hypothesized that hyperphosphatemia in the patiens with SIH may result in higher CIMT as it can induce the production of bone-forming proteins in the vascular smooth muscle and later deposition of calcium in the vascular smooth muscle cells leads to vascular

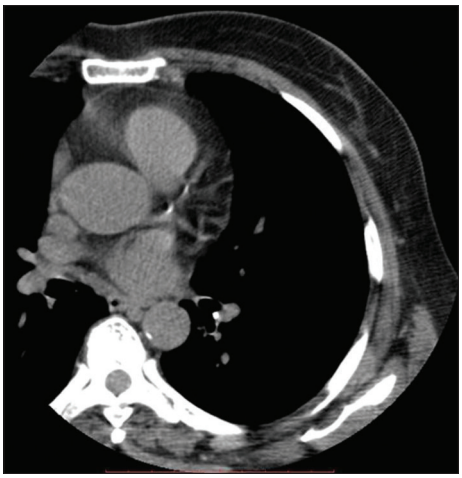

Figure 2: Axial computed tomography image shows eccentric calcified plaques in a proximal left anterior descending artery which that a score of 209.16. Rest of the coronary arteries did not show any calcified plaques

calcification.[9,10] Furthermore, transient hypercalcemia occur during the course of treatment of hypoparathyroidism may also elevate the calcium phosphate product and promote vascular calcification.[9] In our study, low calcium level was associated with atherosclerotic plaques. However, high phosphate and low PTH levels did not account for increased cardiovascular risk in our study.

The apparent relationship remains unexplained. The possible explanation for the increased cardiovascular risk and low calcium could be related to the severity of disease itself. The other reason might be that the patients with low serum calcium were receiving higher calcium supplementation dose though this was not documented. The nonskeletal risks of calcium supplements appear to outweigh any skeletal benefits of calcium supplementation.[24] In meta-analyses of three placebo-controlled trials, calcium and Vitamin D increased the risk of myocardial infarction (relative risk 1.21 [95% confidence interval [CI] 1.01–1.44], $P = 0.04$), stroke (1.20 [1.00–1.43], $P = 0.05$), and the composite of myocardial infarction or stroke (1.16 [1.02–1.32], $P = 0.02$).[25] On the other hand, another recent collaborative meta-analysis of randomized controlled trials found that, the current evidence does not support the hypothesis that the calcium supplementation with or without Vitamin D increases the coronary heart disease or all-cause mortality risk in elderly women.[26] Therefore, the hypothesis of calcium supplementation and increased cardiovascular risk is still a debated one with little evidence existing for plausible biological mechanisms to link calcium supplement use with adverse cardiovascular outcomes.[27] 1, 25 dihydroxy vitamin D is deficient in the patients with hypoparathyroid, but the data on its deficiency and its supplementation in association with the cardiovascular mortality is not available. The relative risk of CVD death

is 1·41 (95% CI 1·18, 1·68) greater in the lowest quintile of plasma 25-hydroxy Vitamin D (25(OH) D) according to meta-analysis of prospective cohort studies. Although several trials with cardiovascular endpoints are in progress, these are using pharmacological doses. In view of the potential toxicity of pharmacological doses, there remains a need for long-term trials of physiological doses of D2 and D3 with CVD incidence as the primary outcome.[28] In our study, we found no difference in Vitamin D levels (25(OH) D) in the patients with or without CAC.

However, the cardiovascular risk as assessed by CAC was clearly higher in the patients with SIH. The pathophysiological basis for this increased risk need to be delineated. Maybe larger studies may throw more light on this relationship.

A small number of subjects is one of the limitations of this study, but the objective assessment by CAC is one of the greatest strengths of this study.

Conclusion

The vascular risk score is increased in the patients with SIH as assessed by coronary calcium score measured by MDCT. Low serum calcium levels might be a predisposing factor for this increased risk. More data is needed to substantiate these findings.

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Nil.

Conflicts of interest
There are no conflicts of interest.

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