

EFFECT OF PARATHYROIDECTOMY ON CARDIAC FUNCTIONS IN PATIENTS WITH PRIMARY HYPERPARATHYROIDISM

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ABSTRACT

Background- Primary Hyperparathyroidism (PHPT) has been associated with increased cardiovascular morbidity and early death. Data on the extent and clinical significance of cardiovascular abnormalities in primary hyperparathyroidism (PHPT) are conflicting. The main objective of this study was to evaluate the cardiac function in patients with PHPT without other known risk factors and to analyze the effect of parathyroidectomy.

Methodology- In a Prospective Observational Cohort design, sixteen patients with Primary Hyperparathyroidism underwent Two-dimensional echocardiography, Electrocardiography, serum N-terminal pro-brain natriuretic peptide (NT-proBNP, a myocardial damage marker), before and 3 months after successful parathyroidectomy.

Result- We observed significant improvement in Left ventricular ejection fraction ($p = 0.010$) in patients undergoing parathyroid surgery after 3 months postoperatively. There is significant reduction in LVMI ($p=0.044$) & posterior wall thickness ($p=0.007$), which are indicators of left ventricular hypertrophy after 3 months of surgery.

Conclusion- Patients with PHPT who are symptomatic exhibit significant cardiovascular dysfunction, which improves three months following successful parathyroidectomy. As a part of screening, we should consider routine cardiovascular evaluation in all symptomatic

patients of PHPT. Symptomatic PHPT patients should undergo early curative surgery for the reversal of the cardiovascular dysfunction and in asymptomatic PHPT patients also early surgery is recommended for the prevention of end organ damage.

Keywords: Primary Hyperparathyroidism, Parathyroid adenoma, Parathyroid surgery, Cardiac functions, PHPT, NT-proBNP, ECHO

1. INTRODUCTION

Primary hyperparathyroidism (PHPT), the third most prevalent disorder, is characterized by an excessive release of parathyroid hormone from single or many parathyroid glands in conjunction with hypercalcemia, elevated or high normal parathyroid hormone (PTH), but a normocalcemic variant also exists^{1,2}. PHPT is most frequently benign, sporadic (>90%), with a single adenoma (85–90%) or numerous glands, typically hyperplastic (5–10%), and very rarely (1%) by parathyroid cancer². The prevalence of the condition has dramatically increased since the 1970s, and its clinical manifestation has shifted from a symptomatic condition to an asymptomatic condition, as a result of the development of automated procedures for the detection of serum calcium. PHPT is substantially less common and manifests as an overt clinical condition in nations like India where biochemical screening is not standard practise^{2,3}. PHPT affects roughly 1% of adults, with a 3to4:1 female preponderance; it rises in both sexes with age, but is most prevalent in postmenopausal women, where it is 3-4%^{1,3}.

PHPT has been linked to early death, increased cardiovascular morbidity, reduced glucose tolerance, lipid metabolic abnormalities, metabolic syndrome, and hypertension⁴⁻⁶. It also found to cause structural changes in the heart and cardiac conduction abnormalities due to hypercalcemia and increased PTH hormone.^{4,5} It is possible to hypothesize that PHPT may cause structural abnormalities throughout the duration of the disease; as a result, parathyroidectomy may only be helpful if done at the beginning of the course of the disease. In contrast to patients with mild PHPT and NC-PHPT, those with symptomatic PHPT have better descriptions of the degree and type of cardiovascular involvement; The information that is currently available for the earlier situations is insufficient to give a full picture. However, if Normocalcemic-PHPT is thought of as an early stage of hypercalcemic PHPT, this population should be the main focus of research. If a cardiac examination were to become a standard component of PHPT patient evaluation, it could be possible to discover a lesser degree of damage, as it has done with renal and bone involvement.⁴

The degree and nature of cardiac involvement in people with mild disease are yet unknown, and it has been reported that more severe disease is linked to a higher risk of cardiovascular disease.⁷ Despite the fact that certain studies have revealed that individuals with PHPT had arterial hypertension, left ventricular hypertrophy, stiffened arteries, and poor diastolic filling, these results lack a clear pathophysiologic explanation and don't seem to have improved with the successful Parathyroidectomy.⁸ While some research claimed that following a successful parathyroidectomy, systolic and diastolic function improved.^{9,10} According to the “American Society for Bone and Mineral Research's (ASBMR) Fifth International Workshop on the Evaluation and Management of Primary Hyperparathyroidism”, the presence of cardiovascular abnormalities should not be utilized as a criterion for deciding whether to have surgery due to insufficient data. They also highlighted that there is room for investigation into

the repercussions of indexes over time, with or without surgery, and if they are reversible by surgical intervention.¹¹ Therefore, it is intended for this prospective study to examine the nature and incidence of cardiovascular alterations in PHPT patients using objective diagnostic instruments and to record their reversal, if any, following successful parathyroid surgery.

2. MATERIALS AND METHODS

Study Design

The study was Prospective Observational Cohort study on patients undergoing Parathyroidectomy in the Department of Otorhinolaryngology in Conjunction with Department of Cardiology and Department of Endocrinology in a tertiary care hospital in Western Rajasthan from July 2021 to August 2022.

Subjects

The patient population was consecutively recruited from the referrals for parathyroid surgery due to PHPT were included in this study. Patients with secondary and tertiary hyperparathyroidism & those who refused for consent were excluded from the study. Patient were recruited into the study after getting an informed consent for the same which was approved by Institutional ethical committee. Patients with PHPT underwent biochemical evaluation, radiologic evaluation and parathyroid imaging, and were treated as per standard protocols.

Laboratory methods

Serum calcium, Intact PTH levels and serum NT pro BNP were done in all patients preoperatively and 3 months postoperatively. Serum calcium levels were measured using Beckmann coulter AU series by turbidimetric method and Serum PTH and NT pro-BNP levels were measured using Advia siemens by Chemiluminescence Immunoassay technique. Electrocardiography was done in all patients using standard 12 lead ECG.

Echocardiography

All examinations were performed by experienced echocardiographer, using a PHILIPS EPIQ 7C ultrasound system. The patients were placed in the left lateral recumbent position, and the two-dimensional, M-mode, and Doppler echocardiography was performed. Standard echocardiographic measurements for measuring systolic and diastolic functions indices were noted. Left Ventricular mass (g) was calculated using “Devereux formula” and Body surface area (BSA) was calculated using “Du Bois method”. LVMI (g/m²) was calculated by LVM/BSA. LVEF (%) and left ventricular volumes was calculated using “Simpson’s biplane method”. Isovolumetric relaxation time (IVRT) was measured as time interval between the closure of aortic valve and opening of mitral valve using Pulse-wave doppler echocardiography. E/A ratio was measured as ratio between early mitral filling velocity and late mitral filling velocity using Pulse-wave doppler echocardiography.

Surgical procedure

In our study, 13 patients underwent Minimal invasive parathyroidectomy and 3 patients underwent four gland exploration- of which 2 patients had multiple parathyroid adenoma and one had recurrent disease. Successful parathyroidectomy was considered after interoperative PTH monitoring (IPM) using Miami criteria. Patients were followed regularly.

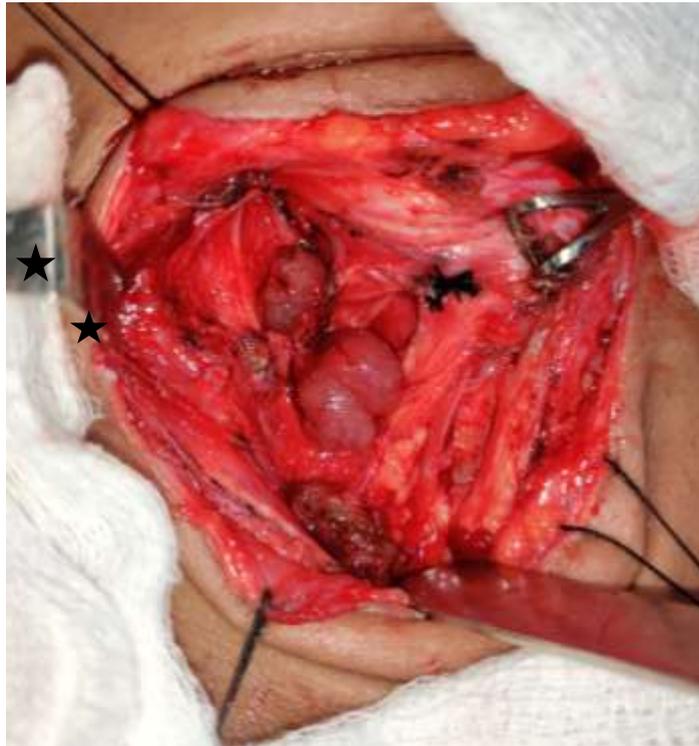


Figure 1 Multiple parathyroid adenoma

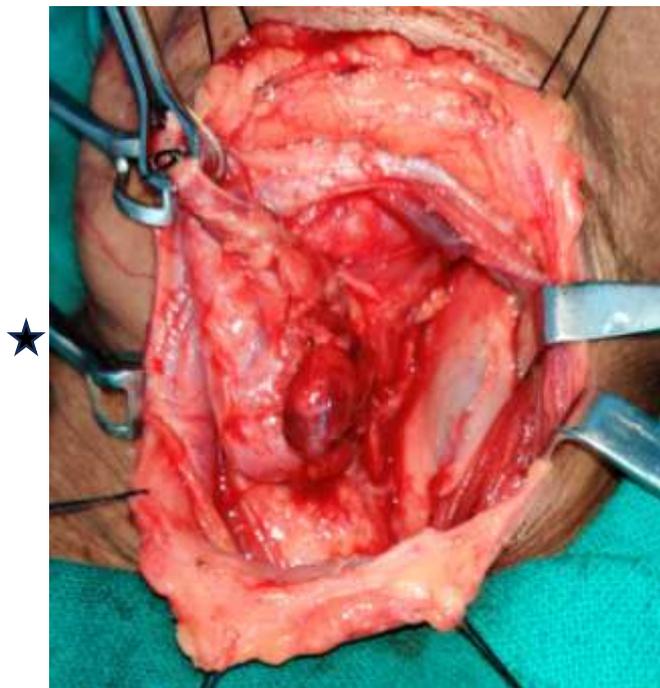


Figure 2.1 Parathyroid adenoma infiltrating thyroid gland



Figure 2.2 specimen showing parathyroid adenoma infiltrating the thyroid gland

Statistical analysis

Data was entered in Microsoft excel and analyzed using SPSSv26 (IBM Corp. released 2021 IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp.). Quantitative variables were described using the chi-square test, t-test and non-parametric data was analyzed using Wilcoxon sign rank test and Friedman's ANOVA test. Nominal Variables were described using proportions and descriptive analysis. A p-value of <0.05 was considered as significant.

3. RESULTS

The mean age of patients with Primary Hyperparathyroidism was 43 (+/- 10) years. Around 81% (n=13) of the patients were females and 19% were males in our study. Around 87% (n=14) had presented with symptoms related to PHPT and 13% (n=2) patients were asymptomatic. The serum PTH levels in patients ranged from 132 to 5670 pg/mL, with a mean of 603.50 (254.50-1842.50). In our study, 13 patients had hypercalcemia and 3 had calcium levels within normal limits preoperatively. All patients had fall in calcium levels within normal limits after 3 months of successful parathyroidectomy. Of which 4 patients had hypocalcemia after 3 months postoperatively.

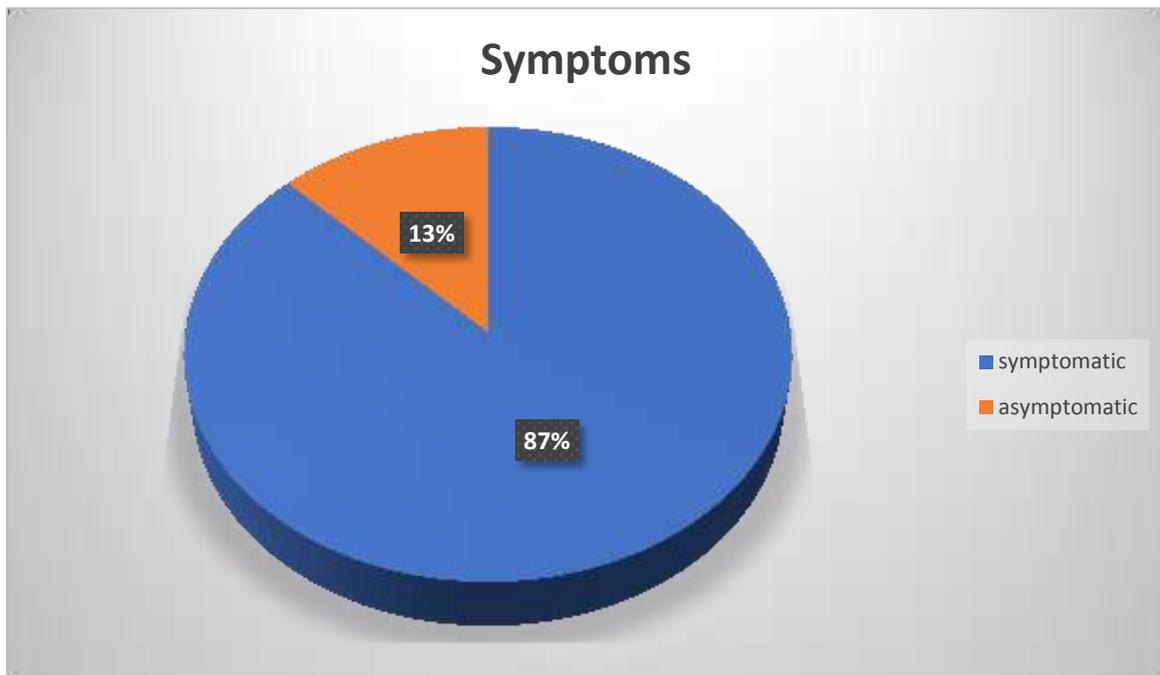
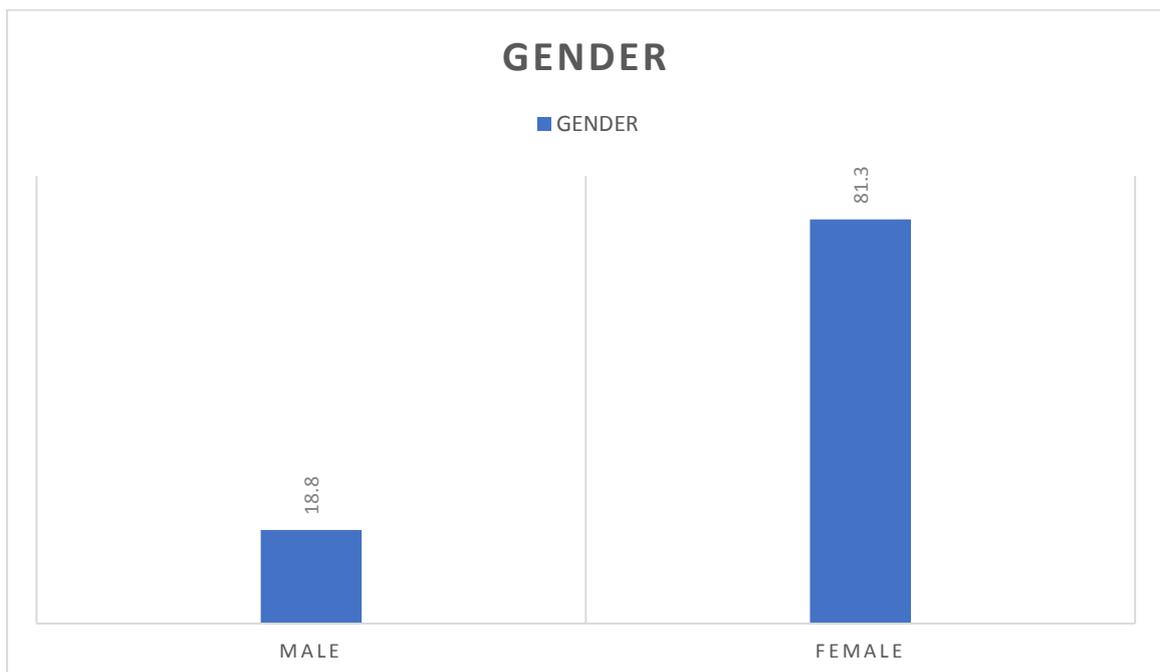


Figure 3.1 Pie chart showing Patient profile



Frequency- Number of patients
Figure 3.2 Bar diagram of Gender distribution

Table:2 provides the summary of biochemical values and 2D ECHO indices.

VARIABLES	PREOPERATIVE (baseline)	POSTOPERATIVE (3 months after Surgery)	p value
S.Calcium	11.67 (+/-1.35)	9.11(+/- 0.68)	0.001
iPTH	603.50 (254.50- 1842.50)	114 (40.5-252)	0.001
Vitamin D	19.93 (+/-9.17)	24.25 (+/-11.31)	0.672
NT-pro BNP	48.50 (35-420.38)	56.47 (35-191.75)	0.124
2 dimensional echocardiographic indices			
LVEDD (mm)	41.794 (+/-4.10)	41.63 (+/- 4.16)	0.879
LVESD (mm)	27.44 (+/-4.91)	26.99 (+/- 4.58)	0.594
LVEDV (ml)	74.806 (+/-25.06)	79.313 (+/-24.73)	0.400
LVESV (ml)	33.63 (+/-11.9)	32.37 (+/- 12.76)	0.610
LVM (g)	135.37 (+/-34.33)	124.69 (+/- 28.55)	0.092
LVMI (g/m ²)	87.87 (+/-26.48)	80.55 (+/- 21.21)	0.044
IVS (mm)	9.65 (+/-1.33)	9.55 (+/- 0.89)	0.109
PW (mm)	10 (+/-0.89)	9.55 (+/-1.10)	0.007
LVEF (%)	60.306(+/-3.97)	63.83 (+/- 5.46)	0.010
E/A ratio	0.99 (+/- 0.36)	1.00 (+/- 0.37)	0.786
IVRT (ms)	96.50 (63.50-96.50)	73.00 (60-94.25)	0.107
ECG	WNL	WNL	NS

Values shown are mean (+/- SD); non parametric data represented as median (IQR). “E/A ratio, early/late mitral inflow filling velocity ratio; IVRT, iso-volumetric relaxation time; IVS, interventricular septal thickness; LV, left ventricular; LVEDD, LV end-diastolic dimension; LVEDV, LV end-diastolic volume; LVEF, LV ejection fraction; LVESD, LV end-systolic dimension; LVESV, LV end-systolic volume; LVM, LV mass; LVMI, LV mass index; PW, posterior wall thickness; s. calcium, serum calcium; s. NT-pro BNP, serum N-terminal pro-brain natriuretic peptide”

In our study, 5 patients had increased levels and 11 had serum NT pro BNP levels within normal limits preoperatively. In all 5 patients with increased levels of serum NT pro-BNP

levels had fall in serum NT pro BNP levels but not within normal limits after 3 months of successful parathyroidectomy. Out of 16 patients, 5 patients had abnormal LVMI preoperatively. All 5 patients with abnormal LVMI had statistically significant decrease in LVMI (p=0.04) after 3 months of surgery. All patients had LVEF % in normal range but there is significant improvement (p=0.010) in LVEF% within normal limits in all patients. The Left ventricular end systolic dimension (LVESD), LV end diastolic dimension (LVEDD), LV end systolic volume (LVESV), LV end diastolic volume (LVEDV) was mostly within normal limits. Interventricular thickness (IVS) was mildly abnormal in 8 patients (50%). But there is no significant decrease (p=0.109) in Interventricular thickness after 3 months postoperatively. Posterior wall thickness (PW) was mildly abnormal in 11 patients (69%). There is significant decrease (p=0.007) in Posterior wall thickness after 3 months postoperatively. Eight patients (50%) had prolonged IVRT and 6 had reduced IVRT (37%). Only 2 patients had Normal IVRT. There is no significant change (p=0.107) in IVRT after 3 months of surgery. Nine patients (56%) had reduced E/A ratio (≤ 0.8). There is no significant change (p=0.786) in E/A ratio after 3 months postoperatively. Seven patients (44%) had Grade 1 diastolic dysfunction (E/A ratio ≤ 0.8 ; IVRT >100 ms) of which 3 patients had normal diastolic function after 3 months of surgery, our study shows that there is significant improvement in Left ventricular ejection fraction (p = 0.010) in patients undergoing parathyroid surgery after 3 months postoperatively. There is significant reduction in LVMI (p=0.044) & posterior wall thickness (p=0.007), which are indicators of left ventricular hypertrophy after 3 months of surgery.

4. DISCUSSION

In India, Primary hyperparathyroidism still diagnosed as a symptomatic disease with long duration of illness before diagnosis due to less prevalent calcium and PTH screening. Since symptomatic long duration PHPT patients has elevated levels of calcium and PTH, they are at more risk of end organ damage including cardiovascular dysfunction. This is validated by our study where ~87 % patients were symptomatic in nature. Majority of symptomatic patients had renal stones (60%) followed by bone disease (36%). One patient in our study was presented with bony deformity and short stature. Patients with severe PHPT exhibit higher degree of cardiac dysfunction while those with asymptomatic PHPT have only subtle changes.^{12,13} The level of hypercalcemia alone is an independent indicator of cardiovascular changes¹². In our study, around 81% patients had hypercalcemia which was normalized 3 months after parathyroid surgery. All patients underwent ultrasonography neck as an initial investigation out of which parathyroid adenoma could be localized in 56% patients. For confirmation of localization, all patients underwent SPECT scan accordingly. 2 of these patients had inconclusive reports for which Fluoro-choline PET-CT was done and parathyroid adenoma was localized. parathyroidectomy was successfully done in all PHPT patients with a predictable and significant drop in serum calcium and PTH (p<0.001) levels at 3 months following Parathyroidectomy.

Our study included both symptomatic and asymptomatic PHPT and cardiac functions were evaluated in all these patients. **Farahnak et al.**¹⁴, in his prospective study concluded that patients with mild PHPT who had no previous cardiac risk factors had normal global systolic and diastolic functions as well as cardiac morphology. In our study, as evaluated by 2D echo and NT pro-BNP, one asymptomatic PHPT and one patient with normocalcemic PHPT had normal systolic and diastolic functions

Almqvist et al.¹⁵, in his prospective study highlighted that even mild PHPT affects the heart and causes myocardial abnormalities that worsen over time. They indicated that the group randomized to later surgery experienced an increase in LVMI, whereas the group randomized to early surgery experienced an increase in the E/A ratio. In contrast our study showed significant decrease in LVMI after parathyroidectomy ($p=0.044$) in symptomatic PHPT but no significant increase in E/A ratio after parathyroidectomy ($p=0.501$). In our study, 3 patients with diastolic dysfunction at presentation had normal diastolic function 3 months postoperatively.

In our study, 31% patients had abnormal LVMI without evident systolic dysfunctions. LVM is an independent risk factor for cardiac morbidity and mortality¹⁶. **Georgios Tzikos et al.**¹⁷, in his prospective, single-center study of 18 participants of mild PHPT concluded that curative parathyroidectomy reduced the mean LVMI at six months of surgery and LVEF remained in normal range. In our trial with 16 participants, significant decrease in LVMI ($p=0.044$) is shown at 3 months of surgery and most of the symptomatic PHPT patients (56%) shows decrease in LVMI even within normal limits. Our study also shows that significant improvement in LVEF ($p=0.010$) within normal limits after 3 months of parathyroidectomy.

Stefenelli et al.¹⁸ in his prospective cohort study with 54 patients concluded that patients with PHPT frequently develop left ventricular hypertrophy, myocardial calcium deposits, and/or aortic and mitral calcification. They also observed significant decrease in Posterior wall thickness and interventricular septal thickness. They also mentioned that there was no evidence of complete heart block or severe arrhythmias on the electrocardiograms of PHPT patients. Similarly, we also observed significant decrease in posterior wall thickness ($p=0.007$) of PHPT patients and no significant electrocardiographic changes like complete heart block, arrhythmias in our study (same as previous study¹⁸).

“Serum NT-pro BNP level” is a sensitive indicator of myocardial dysfunction, both in the presence and absence of systolic dysfunction. Regardless of the underlying disease, it has become a helpful tool for the detection and treatment of cardiac dysfunction¹⁹. **Erik G. Almqvist et al.**²⁰ in his study with 42 patients stated that normal increase in circulating NT-pro BNP levels in mild PHPT with adequate renal function was further increased after parathyroidectomy, indicating subclinical changes in heart function. In our study, 30% of patients with symptomatic PHPT had very high levels of circulating NT-pro BNP which was decreased after 3 months of parathyroid surgery but not to the normal levels indicating residual persistent cardiovascular damage ($p=0.124$).

Kishore Abuji et al.²¹ in his prospective study with 30 patients, assessed the left ventricular functions with 2D ECHO and MUGA study preoperatively and six months after surgery. They mentioned that left ventricular ejection fraction remained within normal range and no significant change following surgery. In our study also patient had left ventricular ejection fraction within normal range but it changed statistically significant ($p=0.010$) after the surgery although within normal limits. They also mentioned that there was significant improvement in diastolic dysfunction in PHPT patients 6 months after curative surgery. In our study there is no statistically significant improvement in diastolic dysfunction 3 months after the successful parathyroidectomy. This indicates that longer time may be needed for diastolic dysfunction to become normalized. Hence Long term follow up is needed.

Gaurav Agarwal et al.⁹ in his prospective case control study with 56 patients mentioned that symptomatic PHPT patients had Left ventricular hypertrophy (68%), diastolic dysfunction (53.5%) and increased level of NT-pro BNP (48%) which improved after

successful parathyroidectomy. They also mentioned that there was progressive improvements in the diastolic function between 3 to 6 months after the surgery. Improved diastolic relaxation of the myocardium brought on by the reduction in LVM itself results in optimal systolic contraction (Starling law), which in turn causes a reduction in LVEDD and an increase in LVESV. In our study, 31% of patients had abnormal LVMI and 30% patients had increased level of NT-pro BNP which improved statistically significant 3 months after parathyroid surgery. Similar to the above study, around 45% of our patients who had diastolic dysfunctions preoperatively showed no statistically significant improvement in diastolic function parameters at 3 months of successful parathyroidectomy.

Birgander et al.²² in his prospective study with 49 patients concluded that cardiac abnormalities present in the asymptomatic PHPT patients at baseline did not improve after surgery even after 1 year of follow-up. Three months following parathyroid surgery, we found in our study that symptomatic PHPT patients had statistically significant improvements in their cardiac functioning. This implicates that cardiac dysfunction in asymptomatic patients might be due to some other conditions unrelated to PHPT. They also mentioned that LV systolic function in asymptomatic PHPT patients which was normal at baseline had deteriorated after the parathyroid surgery.

In this single center study, we found the improvement in cardiac functions in symptomatic PHPT patients 3 months after parathyroidectomy. To further understand better and evaluate cardiovascular risk factors in PHPT, we propose that, multicenter randomized studies with bigger sample sizes and longer follow up are necessary.

5. CONCLUSION

As a part of screening, we should consider routine cardiovascular evaluation in all symptomatic patients of PHPT. Symptomatic PHPT patients should undergo early curative surgery for the reversal of the cardiovascular dysfunction and in asymptomatic PHPT patients also early surgery is recommended for the prevention of end organ damage. As per this study, we concluded that there is improvement in cardiac functions in patients with symptomatic PHPT 3 months after successful parathyroidectomy.

6. DECLARATION

Funding: Nil

Conflict of interest: Nil

Ethics Approval: Study was approved by the Institutional Ethical Committee.

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