

## RESEARCH ARTICLE

# Significance of HCG to Distinguish Parathyroid Carcinoma from Benign Disease and in Adding Prognostic Information: A Hospital Based Study from Nepal

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### Abstract

**Objective:** To differentiate between benign and malignant hyperparathyroidism on the basis of excretion of HCG and its malignant isoforms in urine. **Materials and Methods:** This hospital based study was carried out using data retrieved from the register maintained in Manipal Teaching Hospital from 1<sup>st</sup> January, 2008 and 31<sup>st</sup> August, 2012. The variables collected were urinary HCG and HCG malignant isoform, calcium and parathyroid hormone. Preceding the study, approval was obtained from the institutional research ethical committee. Analysis was by descriptive statistics and testing of hypothesis. A p-value of <0.05 (two-tailed) was used to establish statistical significance. **Results:** Out of the 20 cases, 10 were primary hyperparathyroidism and the remainder were parathyroid carcinomas. The urinary HCG  $6.1 \pm 0.6$  fmol/mgCr was within normal range in benign hyperthyroidism but was markedly elevated in three cases of malignant hyperparathyroidism (maximum value of excretion in urine for HCG was 2323 fmol/mgCr). The excretion of malignant isoform of HCG in urine was 0 in benign hyperparathyroidism and in four cases of malignant hyperparathyroidism which fell into the category of persistently low HCG. The maximum excretion of the malignant isoform of HCG in urine was 1.8, in the category of very high HCG. Calcium and parathyroid hormone were mildly raised in benign parathyroidism, while parathyroid hormone was markedly elevated in cases of malignant hyperparathyroidism falling into the category of very high HCG. **Conclusions:** The excretion of urinary HCG in urine has the ability to distinguish between parathyroid adenomas and carcinomas and thus has potential to become a marker of disease progression in malignant parathyroid disease.

**Keywords:** HCG - parathyroid carcinoma - prognostic factor - Nepal

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### Introduction

Primary hyperparathyroidism (PHPT) is one of the most common endocrine disease. This disease typically affects the elderly women. Its clinical appearance is characterized by mild hypercalcemia, traditional classic manifestations of bone and kidney and elevation of parathyroid hormone. Parathyroid carcinoma is a rare endocrine malignant neoplasm resulting from the parenchymal cells of the parathyroid glands and infrequent cause of primary hyperparathyroidism whose diagnosis is very challenging (Rodriguez et al., 2012). The precise aetiology of parathyroid carcinoma is unknown.

However, foremost risk factors which escalates the risk of parathyroid disease are tumor of jaw, chronic renal failure, interaction of multiple environment, genetic and exposure to radiation especially during childhood (Triantafillidou et al., 2006). Human chorionic gonadotropin (HCG) is a glycoprotein composed of two different subunits that is produced by syncytiotrophoblast

(Cole, 2012). The hyperglycosylated HCG is formed by cytotrophoblast cells and elevated in most advanced malignancies (Cole et al., 2008). Both HCG and hyperglycosylated HCG are critical to growth and invasion of the malignancy. It is essential to perceive and treat infrequent cancers at a restricted stage for better prognosis and long-term endurance (Khan et al., 2012). Because of their rarity, the steps to differentiate between benign parathyroid disease and its malignant counterpart are not widely known (Wang et al., 2012).

A perception of the differential diagnosis and knowledge of accessible diagnostic modalities are vital for precise diagnosis and averting of possible harmful treatments (Raj et al., 2012). The factors involved in abnormal parathyroid cell secretory function and growth in patients with primary and secondary hyperparathyroidism are still incompletely understood. This elevated expression of standard or hyperglycosylated HCG is an adverse prognostic indicator and helps to envisage recurrence and are often allied with malignant tumors. Therefore in our

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**Table 1. Excretion of Urinary HCG and its Malignant Isoform in Primary Hyperparathyroidism and Parathyroid Carcinoma Subjects**

Subjects	Urinary HCG fmol/mg Cr (nl:< 50)	Urinary malignant Isoform (nl: <0.5)
Primary hyperparathyroidism (benign) subjects (n=10)		
Mean±SD	6.1±0.6 (5.5, 6.7)	0
Parathyroid carcinoma subjects (n=10)		
Persistently low HCG (n=4)	0 1 2 1	0 0 0 0
Moderately high HCG (n=3)	435 337 215	0.8 0.7 0.6
Markedly high HCG (n=3)	1985 2323 1542	1.6 1.8 1.5

**Table 2. Variation of Serum Calcium and Parathyroid Hormone (PTH) in Primary Hyperparathyroidism and Parathyroid Carcinoma Subjects**

Subjects	Calcium nl: 2.1–2.6 mmol/l	Parathyroid hormone (PTH) nl: 1.0–6.8 pmol/l
Primary hyperparathyroidism (benign) subjects (n=10)		
Mean±SD	2.7±0.1 (2.6, 2.8)	9.7±0.2 (9.5, 9.9)
Parathyroid carcinoma subjects (n=10)		
Persistently low HCG (n=4)	2.7 3 3.1 3.3	27.2 20.5 38.1 32.2
Moderately high HCG (n=3)	2.8 3.2 3.7	55.3 62.7 78.5
Markedly high HCG (n=3)	3.2 2.8 3	135.3 163.2 177.6

present study, the objective was to differentiate between benign and malignant hyperparathyroidism on the basis of excretion of HCG and its malignant isoforms in urine.

**Materials and Methods**

It was a hospital based study carried out using data retrieved from the register maintained in Manipal Teaching Hospital from 1<sup>st</sup> January, 2008 and 31<sup>st</sup> August, 2012. The variables collected were Urinary HCG, Urinary HCG malignant Isoform, calcium, parathyroid hormone. All these biochemical parameters were analyzed in the Central Laboratory of our hospital by standard and validated methods. An immunoradiometric assay was used for estimating urinary HCG and its malignant Isoform (Cole et al., 1998). A new single-reagent colorimetric assay was used for the determination of calcium in serum (Chapoteau et al., 1993). The measurement of parathyroid hormone was done by research quality radioimmunoassay (Endres et al., 1989). All these biochemical laboratory parameters were analyzed using Human reagent kits and with the help of semiautoanalyser (Humalyser 3500, Germany) and

ELISA. Preceding the study, approval for the study was obtained from the institutional research ethical committee. Analysis was done using descriptive statistics and testing of hypothesis. The data was analyzed using Excel 2003, R 2.8.0, Statistical Package for the Social Sciences (SPSS) for Windows Version 16.0 (SPSS Inc; Chicago, IL, USA) and the EPI Info 3.5.1 Windows Version. The One way ANOVA was used to examine the statistical significant difference between groups. Post Hoc test LSD used for the comparison of means of case groups. A p-value of <0.05 (two-tailed) was used to establish statistical significance.

**Results**

Out of the 20 cases, 10 were of primary hyperparathyroidism and rest were of parathyroid carcinoma.

Table 1 illustrates that urinary HCG 6.1±0.6 fmol/mg Cr was within normal range in benign hyperthyroidism. The urinary HCG was markedly high in three cases of malignant hyperparathyroidism. The maximum value of excretion in urine for HCG was 2323 fmol/mg Cr. The excretion of malignant isoform of HCG in urine was 0 in benign hyperparathyroidism and in four cases of malignant hyperparathyroidism which falls in category of persistently low HCG. The maximum excretion of malignant isoform of HCG in urine was 1.8 which falls in category of markedly high HCG.

Table 2 depicts that calcium 2.7±0.1 mmol/l and parathyroid hormone 9.7±0.2 pmol/l was mildly raised in benign parathyroidism. Calcium was mildly raised in cases of malignant hyperparathyroidism which falls in category of persistently low HCG. Parathyroid hormone was markedly raised in cases of malignant hyperparathyroidism which falls in category of markedly high HCG.

**Discussion**

Parathyroid carcinoma is a infrequent endocrine cancer with an insidious clinical course that is time and again misdiagnosed as parathyroid adenoma or hyperplasia. It is allied with noteworthy disease correlated morbidity and mortality. Preoperative diagnosis remains a challenge, which is essential for appropriate and successful patient treatment. In our present study, there was discernible elevation of serum calcium 3.0 mmol/l and parathyroid hormone 177.6 pmol/l in parathyroid carcinoma cases which falls in category of markedly high HCG (Sriussadaporn et al., 2007). In contrast to that, in cases of benign parathyroid disease there was only mild increase in levels of serum calcium 2.7±0.1 mmol/l and parathyroid hormone 9.7±0.2 pmol/l. There was augment of serum calcium and parathyroid hormone in more than half of cases of parathyroid carcinoma in study of Kebebew et al. (2001) and our results concurred with it (Kebebew et al., 2001). HCG is well recognized to be formed in gestational trophoblastic disease and in germ cell tumors. Conversely, it can be expressed by nontrophoblastic cancers when these tumors are poorly differentiated. These comprise of transitional cell carcinoma of the bladder and urinary

tract, renal cancer, prostate cancer, gastrointestinal cancer, carcinoid, lung cancer, gynecologic cancer, oral cancer, and lymphoma. In our present study, the excretion of total HCG  $6.1 \pm 6$  fmol/mg Cr was well within normal range and the malignant isoform of HCG was not seen at all in subjects with PHPT (Stock et al., 1982). In four cases of parathyroid carcinoma which falls in category of persistently low HCG, the excretion of total HCG and its malignant isoform was 1 and 0 fmol/mg Cr respectively. In contrast to that, three cases which fall in category of markedly high HCG, there was incredibly raised excretion of total HCG 1542 fmol/mg Cr and its malignant isoform 1.5 fmol/mg Cr in urine. The findings of our present study was similar to the results of Rubin et al (Rubin et al., 2008). The augment in urinary HCG showed a signal of more aggressive stage of parathyroid carcinoma. The probable elucidation of alliance of HCG with belligerent cancer as it shows the growth of tumor in culture by averting apoptosis. The investigation of subjects who are pathologically benign but clinically and biochemically severe and patients who have malignant pathology, despite mild clinical features further reveals the utility of HCG as a marker for parathyroid carcinoma (Goldfarb et al., 2009). Future studies with larger numbers of subjects would be of assistance to better define the properties of urinary HCG as a diagnostic test in parathyroid carcinoma.

In conclusion, the excretion of urinary HCG in urine had the ability to distinguish between parathyroid adenomas and carcinomas and have the potential to become a marker of disease progression in malignant parathyroid disease.

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