

RESEARCH COMMUNICATION

Metabolic Changes Enhance the Cardiovascular Risk with Differentiated Thyroid Carcinoma - A Case Control Study from Manipal Teaching Hospital of Nepal

Ankush Mittal^{1*}, Bibek Poudel¹, Dipendra Raj Pandeya¹, Satrudhan Pd Gupta¹, Brijesh Sathian², Shambhu Kumar Yadav¹

Abstract

Objective: To evaluate several metabolic changes in patients with differentiated thyroid carcinoma (DTC) which enhance cardiovascular risk in the western region of Nepal. **Materials and Methods:** This hospital based case control study was carried out using data retrieved from the register maintained in the Department of Biochemistry of the Manipal Teaching Hospital, Pokhara, Nepal between 1st January, 2009 and 31st December, 2011. The variables collected were age, gender, BMI, glucose, insulin, HbA1C, CRP, fibrinogen, total cholesterol, triglycerides, HDL, LDL, VLDL, f-T3, f-T4, TSH. One way ANOVA was used to examine statistical significance of differences between groups, along with the Post Hoc test LSD for comparison of means. **Results:** fT3 values were markedly raised in DTC cases ($5.7 \pm SD1.4$) when compared to controls ($2.2 \pm SD0.9$). Similarly, fT4 values were also moderately raised in cases of DTC ($4.9 \pm SD1.3$ and $1.7 \pm SD0.9$). In contrast, TSH values were lowered in DTC cases ($0.39 \pm SD0.4$) when compared to controls ($4.2 \pm SD 1.4$). Mean blood glucose levels were decreased while insulin was increased and HDL reduced ($39.5 \pm SD4.7$ as compared to the control $43.1 \pm SD2.2$). **Conclusion:** Cardiovascular risk may be aggravated by insulin resistance, a hypercoagulable state, and an atherogenic lipid profile in patients with differentiated thyroid cancer.

Keywords: Cardiovascular risk - differentiated thyroid carcinoma - Nepal

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Introduction

Thyroid carcinoma is a general endocrine malignancy worldwide second just to ovarian cancer. It is the seventh most frequent cancer affecting women, accounting for just about 1% of the entire diagnosed cancers and about 91.5% of the malignancies of head and neck. Increased incidence of thyroid cancer will augment the morbidity and mortality due to its associated metabolic changes and risk factors (Moore et al., 2010). Differentiated thyroid cancer (DTC) accounts for 98% of thyroid cancer, with neoplasm arise from the follicular and parafollicular cells (Kebebew & Clark, 2000). Twenty thousand new cases are diagnosed per year in the United States (Rossing et al., 2000). Prevalence rates of thyroid cancers in women were greater than in men due to hormonal and reproductive factors with a male to female ratio of 1:3 (Akbari et al., 2011).

There is no trustworthy information about the occurrence or prototype of thyroid cancer and associated risk factors in Nepal and consequently an effort was made to appraise the situation based on hospital data which is the single source in the western province of Nepal (Binu

et al., 2007). A crucial factor in the outcome of cancer patients is co-morbidity. The co-morbidity has an effect on the appearance and identification of symptoms, and may have extrapolative significance. The foremost metabolic disparity takes place in lipid metabolism especially in the papillary thyroid carcinoma (Yao et al., 2011). Even modest distorted thyroid status purportedly impinges on serum cholesterol levels, glucose, insulin levels, and ventricular function. In Differentiated thyroid carcinoma (DTC), vague raise in fT4, fT3 levels can persuade an enhancement in insulin secretion and a decline in HDL-cholesterol levels, which are adverse developments. In addition, the momentous converse correlation among fibrinogen and suppressed TSH levels, show the way to increase in cytokines, fibrinogen and the endothelial release of von Willebrand factor, seems to document a greater cardiovascular threat in DTC patients. All the variations in biochemical parameters and hemodynamic system in differentiated thyroid carcinoma enhance the cardiovascular risk (Bauer et al., 2007). Our aim was to evaluate several metabolic changes in patients of DTC which enhances cardiovascular risk in western region of Nepal.

¹Department of Biochemistry, ²Department of Community Medicine, Nepalese Army Institute of Health Sciences, Kathmandu, Manipal College of Medical Sciences, Pokhara, Nepal *For correspondence: drmittala@gmail.com

Materials and Methods

Study subjects and variables

It was a hospital based case control study carried out using data retrieved from the register maintained in the Department of Biochemistry of the Manipal Teaching Hospital, Pokhara, Nepal between 1st January, 2009 and 31st December, 2011. We have enrolled 100 subjects in this study. Out of them, 50 cases were of DTC patients and 50 were normal healthy controls. The variables collected were age, gender, BMI, glucose, insulin, HbA1C, CRP, fibrinogen, total cholesterol, triglycerides, HDL, LDL, VLDL, f-T3, f-T4, TSH. Assessment of blood glucose was done by glucose oxidase and peroxidase method. Evaluation of insulin and glycosylated hemoglobin was done by Insulin C-peptide measurement and colorimeter respectively. Analysis of fT3, fT4, and TSH levels was done by ELISA (HUMAN) (Kirkegaard et al., 1974). Estimation of total cholesterol and triglycerides was done by CHOD-PAP (Trinder et al., 1969) and GPO-PAP method respectively. Estimation of high density lipoproteins was done by kinetic enzymatic method (Moshides, 1987). The values of LDL and VLDL were obtained by the Friedewald formula (Warnick et al., 1990). All these laboratory parameters were analyzed using Human reagent kits and with the help of ELISA and semi autoanalyser (Humalyser 3500, Germany). Preceding the study, approval for the study was obtained from the institutional research ethical committee.

Inclusion Criteria

Patients with abnormal thyroid profile, smokers, history of heart failure, diabetes mellitus, stroke or ischemic heart disease were included in our study.

Exclusion Criteria

Patients having hepatic or renal dysfunction, malignancy, alcohol or drug abuse were excluded from the study. Patients who had used any medications (within the previous six months) that might have contained corticosteroids, antifolates or lipid lowering agents were

Table 1. Demographic and Clinical Data Observed in DTC Cases and Controls.

Clinical factors	DTC subjects (n=50)	Control subjects (n=50)	p Value
Age (years)	58.9 ± 11.0 (55.7, 62.0)	57.6 ± 10.0 (54.7, 60.4)	0.54
Sex (male-to-female ratio)	1:03	1:03	ns
BMI (kg/m ²)	21.6 ± 2.3 (20.9, 22.3)	23.9 ± 2.3 (23.2, 24.5)	0.0001
Systolic blood pressure (mmHg)	124 ± 5	120 ± 3	ns
Diastolic blood pressure (mmHg)	082 ± 2	080 ± 1	ns
Current smokers	09 (18%)	06 (12%)	0.401
Former smokers	13 (26%)	07 (15%)	0.134
Family History of myocardial infarction			
	7 (14%)	5 (10%)	0.538
Family History of stroke	4 (08%)	2 (04%)	0.4

also excluded from the study.

Statistical Analysis

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 control versus case groups. A p-value of <0.05 (two-tailed) was used to establish statistical significance.

Results

Out of 100 subjects, 50 were suffering from DTC and rest 50 were healthy controls.

Table 1 illustrates that body mass index was less in patients of DTC (21.6±SD2.3) in comparison to controls (23.9±SD2.3). Blood pressure both systolic and diastolic did not show much variation in cases and controls. Smoking was more prevalent in DTC cases. The percentage of family history of stroke and myocardial infarction did not show much variation for cases and

Table 2. Thyroid Profile in DTC Cases and Controls

Variables	DTC subjects(50)	Control subjects(50)	p Value
f-T3 (1.4-4.2 pg/mL)	5.71 ± 1.47 (5.29, 6.13)	2.29 ± 0.99 (2.01, 2.57)	0.0001*
f-T4 (0.8-2.0 ng/mL)	4.92 ± 1.31 (4.55, 5.30)	1.76 ± 0.96 (1.48, 2.04)	0.0001*
TSH (0.4-6.2 UIU/mL)	0.39 ± 0.42 (0.27, 0.51)	4.23 ± 1.48 (3.81, 4.66)	0.0001*

Table 3. Variation in Several Metabolic and Inflammatory Parameters in Relation to DTC Cases and Controls

Variables	DTC subjects(50)	Control subjects(50)	Significance
Glucose (mg/dL)	82.22 ± 09.08 (79.64, 84.80)	87.96 ± 09.11 (85.37, 90.55)	0.002*
Insulin (mU/L)	09.40 ± 02.52 (08.68, 10.12)	07.60 ± 01.03 (07.31, 07.89)	0.0001*
HbA1c (%)	04.70 ± 01.26 (04.34, 05.09)	05.08 ± 0.97 (04.80, 05.35)	0.095
CRP (mg/L)	04.29 ± 00.66 (04.10, 04.48)	04.06 ± 00.86 (03.82, 04.31)	0.143
Fibrinogen (g/L)	351.0 ± 08.00 347.0, 355.0	345.0 ± 04.00 343.0, 347.0	0.234
Total Cholesterol (mg/dL)	165.28±25.61 (158.0, 172.6)	183.6 ± 26.34 (176.2, 191.1)	0.001*
Triglycerides (mg/dL)	124.68±40.96 (113.0, 136.3)	118.04±22.64 (111.6, 124.5)	0.318
HDL (mg/dL)	39.50 ± 4.700 (38.16, 40.84)	43.06 ± 02.22 (42.43, 43.69)	0.0001*
LDL (mg/dL)	100.84±27.11 (93.14, 108.5)	116.97±27.75 (109.1, 124.9)	0.004*
VLDL (mg/dL)	24.90 ± 08.19 (22.60, 27.26)	23.60 ± 04.50 (22.32, 24.89)	0.318

controls and was statistically insignificant.

Table 2 depicts that fT3 values were markedly raised in DTC cases ($5.7 \pm \text{SD}1.4$) when compared to controls ($2.2 \pm \text{SD}0.9$). Similarly, fT4 values were also moderately raised in cases of DTC ($4.9 \pm \text{SD}1.3$) in comparison to controls ($1.7 \pm \text{SD}0.9$). In contrast to that TSH values were lowered in DTC cases ($0.39 \pm \text{SD}0.4$) when compared to controls ($4.2 \pm \text{SD}1.4$).

Table 3 illustrates that mean values of blood glucose levels was found to be decreased in DTC cases. The insulin levels were increased in DTC cases when compared to controls. The CRP and fibrinogen levels did not show much significant difference in between cases and controls. The mean values of total cholesterol was found to be decreased in DTC cases ($165.2 \pm \text{SD}25.6$) when compared to controls ($183.6 \pm \text{SD}26.3$). There was insignificant difference in triglycerides levels in cases ($124.7 \pm \text{SD}40.9$) and controls ($118.0 \pm \text{SD}22.6$). The HDL levels were found to be decreased in DTC cases ($39.5 \pm \text{SD}4.7$) when compared to controls ($43.1 \pm \text{SD}2.2$).

Discussion

Thyroid carcinomas are three times more frequent in females than in males: a similar ratio was also seen in our study population with the mean age of (58.94 ± 11.0 years) in DTC patients (Monson et al., 2007). DTC patients have a good prognosis and survival rate but associated metabolic changes tend to increase rate of morbidity and mortality. In our current study, fT3 and fT4 levels were increased in DTC patients and TSH level was suppressed due to negative feedback regulation. Our findings concurred with Yang Y et al. (Yang et al., 2011). The increase in fT3 and fT4 induces circulatory incompetence, atrial fibrillation and arrhythmias due to decrease systemic vascular resistance increase in cardiac contractility, cardiac output, heart rate, left ventricular mass causing diastolic dysfunction (delayed relaxation) (Giovambattista et al., 2008). Besides changes in hemodynamics system in thyroid cancer, other metabolic changes observed in our present study include levels of glucose, HbA1C, insulin, CRP, fibrinogen, total cholesterol, TG and HDL. In our current study, the levels of glucose (82.22 ± 9.08) were found to be significantly decreased in DTC patients when compared to the levels of glucose (87.96 ± 9.11) in controls; p value (0.002*). In contrast to that insulin levels (9.40 ± 2.52) was grossly elevated in DTC patients when compared to levels of insulin (7.60 ± 1.03) in controls; p value (0.0001*). In DTC patients, tissue metabolic rate amplifies considerably. To become accustomed to high energy demand, cellular rates of basal and insulin-stimulated glucose disposal are usually elevated to augment the rates of lactate formation and glucose oxidation. Additionally, it was also shown that increased prevalence of insulin resistance is present in patients with differentiated thyroid carcinoma. Tumor necrosis factor α (TNF α), interleukin 6 (IL-6), Insulin-like growth factor 1 (IGF-1) which specifically regulates and involved in thyrocyte growth, proliferation, and differentiation contribute to insulin resistance in the metabolism of both lipids and glucose in DTC (Vella et

al., 2001). The increment of expression of GLUT3 and GLUT4 glucose transporters at the increased level of insulin reflects the adaptation of the cells to cope with the increased metabolic rates involved in DTC. In our present study, acute phase reactant protein (CRP) was moderately raised in DTC patients (4.29 ± 0.66) when compared to controls (4.06 ± 0.86); p-value (0.143). Since the CRP is an acute phase protein, CRP level is considered to be a widely fluctuating marker of inflammation, and moderate CRP elevation is linked to subsequent changes in hemodynamic system in DTC events. The level of fibrinogen was mildly elevated in cases of DTC (351 ± 8) when compared to controls (345 ± 4); p value (0.234). High fibrinogen level may be associated with an elevation of von Willebrand factor in DTC. This may alter platelet plug formation which can lead to endothelial dysfunction and enhanced cardiovascular risk (Giusti et al., 2008). The mean value of total cholesterol (165.28 ± 25.61) and LDL (100.84 ± 27.11) were found to be decreased in DTC patients when compared to the mean value of total cholesterol (183.64 ± 26.34) and LDL (116.97 ± 27.75) in controls; p-value (0.001*). Excess thyroid hormones in DTC modulate LDL receptor activity, increased clearance of cholesterol from plasma excessive conversion of cholesterol to bile acids in the liver, early removal of low density lipoprotein from the plasma. Hence, it lowers plasma cholesterol concentration in DTC (Abrams et al., 1981). Furthermore, a major change in lipid profile was observed in HDL level. It was significantly lower in DTC patients (39.50 ± 4.70) when compared to controls (43.06 ± 2.22); p-value (0.0001*). Hence, all these metabolic changes related to differentiated thyroid carcinoma enhances the cardiovascular risk. Conclusion: Cardiovascular risk was aggravated by insulin resistance, hypercoagulable state, atherogenic lipid profile in differentiated thyroid cancer.

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