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Thyroid and Heart

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INTRODUCTION

The common signs and symptoms of thyroid disease are due to the effects of thyroid hormone on the heart and cardiovascular system.[1] Both hyperthyroidism and hypothyroidism produce changes in cardiac contractility, myocardial oxygen consumption, cardiac output, blood pressure, and systemic vascular resistance (SVR)[2] ,which are reversible when the underlying thyroid disorder is treated.

The thyroid gland primarily secretes T4 (85%), which is converted to T3 by 5 -monodeiodination in the liver, kidney, and skeletal muscle.[3] The heart relies mainly on serum T3 because no significant myocyte intracellular deiodinase activity takes place, and it appears that T3, and not T4, is transported into the myocyte.

Effects of Thyroid Hormone on Cardiovascular Hemodynamics

Thyroid hormone mediates the expression of both structural and regulatory genes in the cardiac myocyte,[4] includes sarcoplasmic reticulum Ca2-ATPase and its inhibitor phospholamban (which regulate the uptake of calcium into the sarcoplasmic reticulum during diastole).[4] In the VSM cell, thyroid hormone mediated effects are due to both genomic (T3 is binding to TRs, which regulate transcription of specific cardiac genes) and nongenomic actions (direct modulation of membrane ion channels).

Hyperthyroidism

In hyperthyroidism, cardiac contractility is enhanced, and resting heart rate and 50% to 300% higher cardiac output than normal individuals[5] because of increasing blood volume and preload stimulated by T3 via synthesis of renin substrate in the liver.[6] The exercise intolerance occurs because inability to increase heart rate and ejection fraction or lower SVR and skeletal muscle weakness may be the predominant cause in long standing disease or elderly.

Sinus tachycardia is the most common rhythm disturbance which predisposes to atrial fibrillation because T3 increases systolic depolarization and diastolic repolarization, and decreases the action potential duration, the refractory period of the atrial myocardium, and the atrial/ventricular nodal refractory period. It appears that subclinical (mild) hyperthyroidism carries the same relative risk for atrial fibrillation as does overt disease. Rarely patients with hyperthyroidism develop chest pain and EKG changes suggestive of cardiac ischemia.[7] Severe hyperthyroidism leads to high-output HF in preexistent ischemic or hypertensive heart disease and even in patients without underlying heart disease.4Overt and SHyper have been associated with increased markers of thrombogenesis (fibrinogen and factor X levels).

Treatment of atrial fibrillation in the setting of hyperthyroidism can be obtained by oral beltablockers and role of anticoagulation of patients is controversial.[1]

Hypothyroidism

In hypothyroidism, endothelial dysfunction and impaired VSM relaxation lead to increased SVR[8] leading to diastolic hypertension in 30% of patients, and thyroid hormone replacement therapy restores endothelial-derived vasorelaxation and blood pressure to normal in most. It also causes a prolongation of the QT interval that predisposes the patient to ventricular irritability and torsade

which is reversible by treatment. The genomic changes explain the physiological changes such as the slowing of the isovolumic relaxation phase of diastolic function characteristic of hypothyroidism and are responsive to T4 replacement.

Hyperlipidemia in hypothyroidism is due to a decrease in LDL receptors, resulting in reduced cholesterol clearance from the liver and decreased activity of cholesterol[7] a-hydroxylase, which is activated by TH, in breaking down cholesterol. LT4 repalcement is more effective in dyslipidemia in SCH when total cholesterol>240 than <240 mg/dl.

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Metformin versus Insulin for Gestational Diabetes: A Randomized Clinical Trial

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Abstract

Background: Insulin therapy is often started if medical nutritional therapy (MNT) fails to manage Gestational diabetes mellitus (GDM) which is associated with multiple injections and demands more patient compliance. So use of safe and effective oral agents may offer advantages over insulin. **Objectives:** To evaluate glycaemic control in women receiving metformin versus insulin for GDM, and to identify factors predicting the need for supplemental insulin in women initially treated with metformin. **Methods:** Women, 18 – 45 years at 20 –33 weeks of gestation with singleton pregnancy with GDM without satisfactory glycemic control on MNT for a minimum period of 1 week were randomised to receive either insulin or metformin. **Results:** There was no significant difference in mean pre-treatment glucose levels between two groups (P = 0.890). After randomizing, women received their respective intervention. Mean glucose level measured after glycaemic control showed, lower levels in the metformin group (P= .034). Also women under metformin presented less weight gain (P=.02) and a lower frequency of neonatal hypoglycaemia (P= .032). Thirteen women in the metformin group (31.7%) required supplemental insulin. Early gestational age at diagnosis and high BMI were identified as predictors of the need for supplemental insulin. **Conclusions:** Metformin appears to constitute safe and effective treatment option for GDM who do not have satisfactory glycemic control. It was found to provide adequate glycemic control with lower mean glucose level, less weight gain and a lower frequency of neonatal hypoglycaemia. Early gestational age at diagnosis and high BMI were predictors of the need for supplemental insulin therapy in women initially treated with metformin.

Key Words: Gestational Diabetes, Insulin, Metformin

INTRODUCTION

Gestational diabetes mellitus (GDM), affecting 5% of population, has classically been defined as any glucose intolerance first identified during pregnancy[1]. American Diabetes Association (ADA) defined it as "Diabetes diagnosed in the second or third trimester of pregnancy that is not clearly overt diabetes"[2]. As per IADPSG criteria, women can be diagnosed to have GDM even in the first trimester, if fasting plasma glucose (FPG) is ≥ 5.1 mmol/L (92 mg/dL), but ≤ 7 mmol/L (126 mg/dL)[3].

Studies indicate that the severity of maternal and fetal complications is proportional to the level of maternal hyperglycemia[4-6]. The benefits of treating GDM with diet and insulin, if necessary, are well established[7,8]. However women who begin insulin require education to ensure the safe administration of insulin. So use of safe and effective oral agents may offer advantages over insulin because of their ease of use and lower cost.

Investigations on the use of metformin for the treatment of GDM have concluded that metformin seems to be an effective alternative for the treatment of GDM[9-12]. However, response to treatment in patients with gestational diabetes is highly dependent on patient characteristics.[13] Since Nepal is inhabited by mixture of different cast and

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ethnicity which is different from population in other part of the world, we need to test the response of metformin in GDM in our population. Thus this present study is conducted with primary aim to compare glycemic control in women who received metformin versus standard use of insulin for the treatment of GDM in our population. Our secondary objective was to compare neonatal outcome among women in two groups and identify factors that lead to need for insulin in women under metformin.

METHODS

This was a randomised controlled study done over two years from May 2016 to January 2018, involving women with diagnosed GDM not controlled with MNT for a minimum period of 1 week at BP Koirala Institute of Health sciences (BPKIHS), Dharan, Nepal. Women, 18-45 years, who were at 20-33 weeks of gestation having singleton pregnancy, were included. Women with contraindication to taking metformin, pre-pregnancy diagnosis of diabetes, any obstetrical indication for immediate vaginal or surgical delivery and having fetal congenital malformation were excluded. Total of 82 Women who met selection criteria were included in this study. Consent was taken from women before enrolling them to this study. This study was approved by Institutional Review Committee, BPKIHS (IRC/480/015).

After selection women were randomised using computer generated random number table into 2 groups, 41 in each. Women in Group 1, taken as cases, were started with Tab Metformin, 1500mg in 3 divided doses taken with food and increased to maximum of 2500mg depending upon glycemic control till the target blood sugar was met. Metformin was stopped if significant maternal conditions, such as severe preeclampsia, sepsis, or pregnancy cholestasis and also if fetal growth restriction developed. Women in Group 2, as control, received standard Insulin therapy as per our hospital protocol. They were typically started with combination of regular and intermediate acting insulin according to their weight and were adjusted to meet the target blood sugar. The target glucose reference values recommended by the ADA were used: fasting (95 mg/dL) and 2 hours after a meal (120 mg/dL) [14]. Women in group 1 who didn't tolerate metformin or who didn't achieve target glucose level were supplemented with insulin.

At study entry, background maternal demographic data, medical history, family history, obstetric history, medication intake through pregnancy, early pregnancy data, and any pregnancy complications were recorded. Paternal demographic data and height and weight were also recorded. Fetal ultrasound growth within 2 weeks before or 1 week after study entry was documented. During the study, women were asked to continue measuring capillary glucose levels fasting and 2 hour after the start of each meal regularly weekly, self by glucometer as per instructions and report to the investigator. At delivery, pregnancy complications, indication for induction (if performed), mode of delivery, and complications are recorded from the hospital notes. Detailed neonatal morbidity is also recorded. Trained personnel performed anthropometric and blood sugar measurements on the baby within 48 h of birth.

Numerical variables were compared by the Student t test or Mann-Whitney test. The $\chi 2$ test, Fisher exact test or likelihood ratio tests were used to compare categorical variables. In addition, logistic regression analysis was performed to predict the need for supplemental insulin in women initially treated with metformin.

RESULTS

In this study 82 women were enrolled and they were randomised into two groups with 41 in each group. The demographic and clinical characters in two groups were recorded at enrolment. This shows similar pattern as shown in Table-1. It includes age, body mass index (BMI) at enrolment, gestational week and parity. We also recorded fasting blood sugar after overnight fasting and post prandial as well as mean pre-treatment blood glucose level and glycated haemoglobin at enrolment. Also blood test was done for liver function as well as renal function at enrolment to make sure this result does

not preclude the use of metformin. There was no significant difference in mean pre-treatment glucose levels between two groups (P = 0.890). Also the glycated haemoglobin was similar in both the group. After enrolment in the study, patients were randomised into two groups as described in methods. After randomizing, women received their respective intervention.

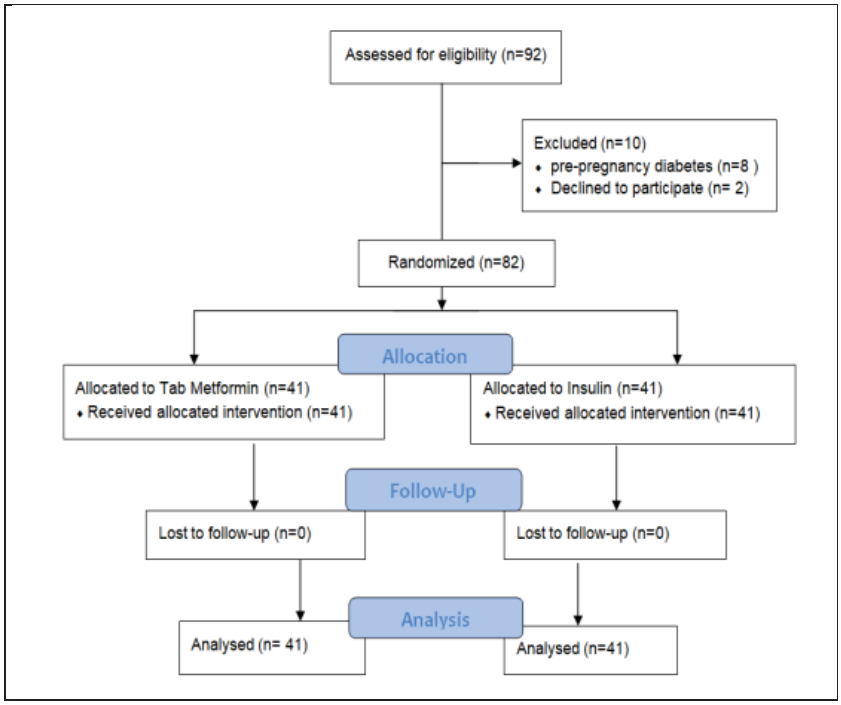

Figure1. Enrollment of Subjects.

Table.1 Baseline maternal Characterstics

Character	Metformin (41)	Insulin (41)
Age (yrs)	33.4±5.4	33.0±5.3
BMI at enrolment	35.1±7.2	34.6±8.3
Period of gestation (weeks)	30.3±3.2	31.2±3.1
Nulliparous(%)	31.7	31.9
Glycated haemoglobin	5.7±0.2	5.8±0.8

Less weight gain was observed in women in group 1 compared to group 2 between the start of medication treatment and delivery (group 1: 0.53 ±2.52 kg vsgroup 2: 2.3 ± 2.77 kg; P = .002). There was no difference in the two groups in terms of frequency of preeclampsia, prematurity and operative delivery.
None of the women discontinued the study protocol (figure 1). Only 10 women in metformin group reported some side effects, most frequent being gastrointestinal effects like nausea and occasional increase frequency of bowel movements. But all of them continued with the treatment protocol. Out of 41 women in group 1, 13 (31.7%) required supplemental insulin to achieve target glycemic control. Regarding glucose control, the mean glucose level measured after glycemic control showed, lower levels in the metformin group (P= .034) compared to insulin group. (Table 3)

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Table 3 Mean blood glucose level after treatment.

Pretreatment blood glucose	Fasting	2 Hr- post prandial	P value
Metformin	102.15 ±21.96	120.61 ± 22.63	0.890
Insulin	100.87 ±15.05	123.72 ± 19.4	
Post-treatment blood glucose			
Metformin	90.09 ± 16.29	106.87 ±11.16	0.034
Insulin	88.35 ± 7.45	111.43 ± 8.84	

Neonatal outcome

No significant differences between the 2 groups were observed regarding thefollowingimmediate neonatal outcomes: gestational age at birth (group 1: 38.33 ± 1.45weeks vs group 2: 38.24 ±1.53 weeks; P = 0.776), 1-minute Apgar score (group1: 9 [0-10] vs group 2: 9 [4-10]; P =.980), 5-minute Apgar score (group 1: 10[0-10] vs group 2: 10 [0-10]; P =.188) and newborn weight (group 1: 3143.7 ± 446.6 g vs group 2: 3237.6 ± 586.8 g; P =.390) (Table 2). There were no fetuses with macrosomia in the group metformin vs 3 (7.3%) cases in the insulin group (P =.342). A lower frequency of neonatal hypoglycaemia was observed in cases treated with metformin (3/41, 7.3%) compared with newborns from the insulin group (10/41, 24.3%) (P = .042).

Table 2 – Neonatal outcome

Variables	Metformin	Insulin	P value
Gestational age at birth (weeks)	38.33 ± 1.45	38.24 ±1.53	0.776
1-minute Apgar score	9 [0-10]	9 [4-10]	0.980
5-minute Apgar score	10(0-10)	10(0-10)	0.188
Newborn weight	3143.7 ± 446.6 g	3237.6 ± 586.8 g	0.390

Early gestational age at diagnosis (odds ratio.0.78; 95%confidence interval, 0.52-0.97;P = .02) and high BMI were identified as predictors of the need for insulin by logistic regression analysis.

DISCUSSSION

As per the primary objective of this study we were able to evaluate glycemic control in both the groups of women. The mean glucose level measuredafterglycemic control showed, lower levels in the metformin group (P= .034) compared to insulin group (Table 3). Similarresults were shown in the study by Spaulonci CP et al. They also demonstrated that lower level of blood sugar was observed especiallyafter dinner[12]. Less weight gain observed in women of group 1 compared to group 2 between the start of medication treatment and delivery (group 1: 0.53 ±2.52 kg vsgroup 2: 2.3 ± 2.77 kg; P = .002) in our study was again comparable to other similar study [10,12]. Also as comparable to Spaulonci CP et al[12] and Rowan et al 10, there was no difference in the two groups in terms of frequency of preeclampsia, prematurity and operative delivery.

In the present study, only [10] (24.3%) women in metformin group reported some side effects, but all of them continued with the treatment protocol. Twenty-one (45.65%) of the 46 womenwho received metformin reported someside effect in the study by Spaulonci CP et al [12]which is similar to our study. Out of 41 women in group [1, 13] (31.7%) required supplemental insulin to achieve target glycemic control. This is more that that reported by Spaulonci CP et al [12] who reported [12] (26.08%) women in metformin group requiring supplemental insulin. In the study by Rowan et al [10] 46.3% of women taking metforminrequired supplemental insulin. These

differencesmay be because of difference in ethnicity and characteristic of population as diabetes widely varies among different population.

Regarding immediate neonatal outcomes like gestational age at birth, 1,5-minute Apgar score and newborn weight, our study showed no significant differences between the 2 groups. There were no fetus with macrosomia in the group metformin vs 3 (7.3%) cases in the insulin group (P = .342). In the study by Rowan et al [10]the primary outcome, a composite of neonatal hypoglycemia, respiratory dis¬tress, need for phototherapy, birth trauma, 5-minute Apgar score lower than [7], or pre¬maturity, occurred with similar frequency in the 2 groups (32% in each group) where 733 women were randomised to metformin versus insulin. Our study also demonstrated lower frequency of neonatal hypoglycaemia in cases treated with metformin (3/41, 7.3%) compared with newborns from the metformin group (10/41, 24.3%) (P = .042) which was comparable to other studies [10,12]. As per the literature review our women with early gestational age at diagnosis and high BMI were identified as predictors of the need for insulin.

The strength of this study is that all women were followed up till delivery. Our group of women included all different caste of Nepal so the results can be implemented to all. Major limitations are we don't have any records of level of glycemic control at home because of poor patient compliance and Cord blood has not been stored for assessment of insulin and c peptide.

CONCLUSION

The primary objective of this study was to evaluate glycemic control in women with GDM treated with metformin or insulin.Metformin appears to constitute safe and effective treatment option for GDM who do not have satisfactory glycemic control with MNT. It was found to provide adequate glycemic control with lower mean glucose level, less weight gain and a lower frequency of neonatal hypoglycemia. Early gestational age at diagnosis and high BMI were predictors of the need for supplemental insulin therapy in women initially treated with metformin

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A study of Anti Thyroid Peroxidase (TPO) Antibody Titres in patients seeking treatment at a tertiary health care centre

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Abstract:

Background: One of the main cause of thyroid disease is autoimmune thyroid disease and anti thyroid peroxidase (TPO) antibodies is a major marker of the condition. There are very few studies in the country regarding the etiology of thyroid disorders and hence this study is being conducted for it. **Methods:** This is retrospective cross sectional study from 28 January 2019 to 29 July 2019 done at National Academy of Medical Sciences , Bir Hospital , Kathmandu . The laboratory serum sample data of all Anti TPO antibody results from patients seeking treatment at the instituition were analyzed for age and gender variation. Anti TPO antibody titre of equal or more than 34 IU/ml was considered as positive. **Results:** Out of 768 samples analysed for study, 79.9% were of women and 20.1 % were of men. A total of 205 (26.7%) were positive for anti TPO antibodies of which 83.4% were women and 16.6% were men . Women had more patients with anti TPO antibodies positive as compared men (27.9 vs 21.1%). Mean Anti TPO titre were also more in women as compared to men (61.01 vs 48.20 IU/ml). **Conclusions:** About one fourth of the patients had siginificant titers of anti TPO antibodies suggestive of thyroid autoimmunity. Both prevalence of positive anti TPO antibody titres and the mean anti TPO antibody titre values were more in women as compared to men. Further well designed larger community studies are required.

Key Words: anti TPO antibodies, autoimmunity , Nepal , thyroid

INTRODUCTION:

Thyroid disorders are very common in the community. Causes of thyroid dysfunction include Graves Disease, multinodular goitre, solitory thyroid nodule, iodine related disorders, autoimmune thyroiditis, infilrative diseases etc.[1] The most common cause of thyroid disorders worldwide is iodine deficiency, leading to goitre formation and hypothyroidism whereas in iodine-replete areas, most persons with thyroid disorders have autoimmune disease. [2]

In a large study done in Colorado US , the prevalence of increased TSH was 9.5% where as that of decreased TSH was 2.2%. [3] A large multicentre Indian study showed that hypothyroidism was seen in approximately one in 10 adults in the study population. [4]

Patients with autoimmune thyroid disease as seen in Hashimoto's thyroiditis, Graves Disease and painless thyroiditis often have autoimmune activity against thyroid peroxidase (TPO) resulting in positive test in Anti TPO antibody titres. The test has its usefulness in determining the cause of primary hypothyroidism or euthyroid goitre is due to Hashimoto's thyroiditis. [5]

Anti TPO antibodies is especially helpful in the case of subclinical hypothyroidism in deciding initiation of treatment and the duration of treatment. In patients with subclinical hypothyroidism, presence of anti TPO antibodies is associated with an increased risk of developing overt hypothyroidism.[1,6]

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It also has importance in management decisions in cases of hypothyroidism with pregnancy. In a study done by Singh A et al , thyroid antibodies proved to be a useful marker for identifying women at risk for clinical miscarriage .[7] Similarly a study from Harayana , India showed that TPO antibody positivity even in women with euythroid status are associated with adverse pregnancy outcomes such as miscarriage and preterm delivery. [8]

Immune cells , anti Thyroid antibodies and cytokines all may have a role in the pathogenesis of autoimmune thyroid disease. The demonstration of immune cells and anti-thyroid antibodies within the thyroid gland, and the determination of the levels of cytokines in peripheral blood, sheds information of their involvement in the development of autoimmune thyroid disorders.[9] A Study done by Chivato et al suggest that TPO maybe a target for cytotoxic attacks.[10] The ongoing progressive destruction of thyroid follicular tissue results in hypothyroidism. [11] There are very few studies of finding the cause of thyroid disorders in the country and this study provides valuable insight into the prevalence of Hashimoto's Disease as one of the cause. Further research has also been recommended by some authors to assess the possibility of changing disease patterns of autoimmune thyroid disease as opposed to simple changes in diagnostic thresholds. [12]

MATERIAL AND METHODS

This is retrospective cross sectional study done at National Academy of Medical Sciences, Bir Hospital, Kathmandu. The laboratory serum sample data of all Anti TPO antibody results from the period of 28 January 2019 to 29 July 2019 duration were analysed. Laboratory testing of blood serum samples that had been done for Anti TPO antibodies in patients visiting for treatment were analysed for age, gender variation. Almost all of the patients in the test are known to have thyroid dysfunction of some magnitude and are sent from the Diabetes and Endocrinology unit at Bir Hospital for testing. Regarding investigations, generally anti TPO antibodies are done those with raised thyroid stimulating hormone (TSH) whereas nuclear imaging , TSH receptor antibodies are done in cases with low TSH values depending upon clinical scenario and necessity . The Anti TPO antibody test was done with high sensitive Anti TPO ELISA Kit from Epitope Diagnostics , Inc which measures high sensitivity of human anti TPO antibody IgG . A cut off point of equal or more than 35 IU/ml were considered as being positive for anti TPO antibodies. Patients who had thyroid disorders and had done anti TPO antibodies test before the study period or those who had done antibody test from some other hospital or health care centres were excluded from the study. Data analysis was done using SPSS software program.

RESULTS

There were a total of 768 patient samples analysed for the study out of which 614 (79.9%) were female patients and 154 (20.1%) were male patients.

Table 1. Age variation among patients

Group	Mean	Age (in years)	Standard Deviations
Total N= 768	39.16	14.55	
Male patients N = 154	45.35	16.49	
Female patients N= 614	37. 61	13.60	
Anti TPO ab positive Male pateints N= 34	41.29	16.23	
Anti TPO ab positive Female pateints N= 171	37.50	11.89	

Anti TPO antibodies were positive in 205 (26.7%) out of 768 patients implying that approximately one fourth of the patients had thyroid autoimmunity markers. Out of 205 total patients 171 (83.4%) were women and 34(16.6%) were men as shown in Table 1.

Table 2. Anti TPO Titre variation among patients

Group	IU/ml	Standard Deviations
Total N= 768	58.44	102.44
Male patients N = 154	48.20	93.75
Female patients N= 614	61.01	103.93
Anti TPO ab positive Male pateints N= 34	182.70	129.38
Anti TPO ab positive Female pateints N= 171	189.94	125.26

From a total of 614 females patients , 171 patients (27.9%) were Anti TPO antibodies positive as compared to 34 (22.1%) males from a total male sample of 154 . This shows that females had slightly more possible thyroid autoimmunity as compared to males. In general, Anti TPO antibodies titre were higher in females (61.01IU/ml) as compared to males (48.20 IU/ml) as shown in Table 2.

Table 3. Anti TPO antibodies in different age groups

Age Group (years)	Total number of cases	Anti TPO Antibody negative	Anti TPO Antibody Positive	Mean Anti TPO antibody titre (IU/ml)
Less than 25	107	74 (69.2 %)	33 (30.8%)	65.7907
25-34	235	182 (77.4%)	53 (22.6%)	49.6736
35-44	157	109(69.4%)	48 (30.6%)	38.83
45-54	143	96 (67.1%)	47 (32.9%)	64.7189
55-64	80	60 (75.0%)	20 (25.0%)	50.8738
65 or more	46	42 (91.3%)	4 (8.7%)	26.4652

From Table 3 it is seen that prevalence of antibodies in positive titres are mostly in similar proportions ranging around 20-30% in each group except for the age group more than 65 years where it is about 4% only. Anti TPO antibody titres are highest in the less than 25 years age group where as it is lowest in the age 35-44 years group . The highest number of the patients being tested belonged to the reproductive age group ie. 25-34 years , probably as a concern for menstrual irregulaity , excess weight gain concerns and fertility issues etc. Anti TPO antibodies positivity were most prevalent in the age group 45 -54 years.

DISCUSSIONS

Autoimmune thyroid disease is one of the common organ-specific autoimmune disorders. 3 It occurs because of complex interactions between genetics and environment .[13]

In our study about one fourth of the patients that underwent the test had positive antibody titres which is a marker for autoimmune thyroid disorders. Similar to our study , in a study done by Unikrisnan et al study , Anti - TPO antibodies suggesting autoimmunity were detected in 21.85% patients. [4] However a study from Kerala , India had a higher prevalence on anti TPO antibodies with about 46% among patients having thyroid dysfunction.[14] In a study done in Delhi , the detection of significant titres of anti TPO antibodies were lower than that seen in our study being about 13 %. [15]

In studies in which no cytological testing done,

among those who were negative for anti-TPO antibodies, there is a possibility of some of them would still have a cytological evidence of autoimmune destruction. [16]

In our study also females were more affected than males and the possible involvement of autoimmunity is also seen more in females. This is consistent with the findings from other studies. The mean anti TPO titre was also higher in women as compared to men in our study. Similarly Unnikrishnan et al. have reported higher prevalence of anti-TPO antibodies in females than in males in eight cities of India. [4] Hollowell et al. while conducting United States national health and nutrition examination survey determined that prevalence of both anti-TPO is higher in females . [17] This was also seen in a study done in subclinical hypothyroid patients by Atluri S et al. [18]

In a study done in Kerala by Sindhu P et al with a study population comprising of women of reproductive age group , maximum number of anti TPO antibodies positive women were in the age group 45-49 years of age however the mean value was highest in the 35-44 years age group. [19] In a study done by Atluri S and team , anti TPO antibodies were more prevalent in the 20-40 years group . [18] In our study, highest number of antibody positivity was seen in the 45-54 years age group however the highest anti TPO antibody titre mean value was in the age group less than 25 years group. There is referral bias in the our study as the patients have to come to a tertiary care centre seeking treatment and hence the results cannot be extrapolated as community data.

As this is a retrospective analysis of the lab reports only, due to unknown history of medication and their possible impact on the thyroid function reports, the Anti TPO reports have not been correlated with the thyroid function status. Although this is a major limitation of the study, because of very little data available in the country in this field , the research does provide useful information regarding the prevalence of autoimmune thyroid conditions and may help to provide a basis for future studies.

Future well designed studies should involve normal population for controls, thyroid function status, testing of treatment naïve thyroid disorders patients, testing of anti TSH receptor antibodies, testing for iodine deficeincy, thyroid ultrasonography, nuclear scan tests and for possible fine needle aspiration cytology (FNAC) in selected patients.

CONCLUSIONS

About one fourth of the patients had siginificant titers of anti TPO antibodies suggestive of thyroid autoimmunity. Positive anti TPO antibodies titre cases and the mean anti TPO titres were are also more in women as compared to men. Further well designed larger community studies are required to have a more clear picture of the current situation.

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Prevalence of Obstructive Sleep Apnea in Type 2 Diabetes

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Abstract:
Introduction: Diabetes are common disorder that often coexist as they have similar risk factors including obesity. As 10% increase in weight accelerates the risk of OSA by 10%it is not surprising to see both disorder in the patient. **Methods:** All the patients who attended to our sleep clinic in OM Hospital and Research Centre were asked about diabeteic history.Those who are already diagnosed as diabetics and on medications or diet control were enrolled into the study. STOP BANG questionnaire was used to categorize the patients for probable obstructive sleep apnea. **Results:** Among 67 patients who underwent diagnostic polysomnography 22 patients had normal AHI, 19 had intermittent snoring and rest had normal diagnostic polysomnography. Among 45 patients 5 had predominantly central sleep apnea and 40 had obstructive sleep apnea. **Conclusion:** In our study that OSA is very common in patients with Type 2 diabetes and worse glycaemic control is a high index of suspicion and sleep history especially for OSA should be included in all the patients of type 2 diabetes. Any patients with uncontrolled diabetes despite medications independent of obesity should be screened for OSA.

Key Words: Diabetes, obstructive sleep apnea, polysomnography

INTRODUCTION:

Obstructive sleep apnea (OSA) is a common sleep disorder characterized by episodic cessation of breathing during sleep with intermittent hypoxaemia and sleep fragmentation. The recurrent obstruction of the upper airway obstruction result in recurrent oxygenation desaturation/resaturation, cyclic changes in the intrathoracic pressure and recurrent micr-oarousals that cause sleep fragmentation and reduction in slow wave and rapid eye movement. The prevalence of OSA is approximately 3-7% for adult males and 2-5% for adult females in the general population.[1-3] Diabetes is another disease with a global prevalence of 382 million (8.3%)and expected to rise to 592 million (10.1%)by 2035.4OSA and Diabetes are common disorder that often coexist as they have similar risk factors including obesity. As 10% increase in weight accelerates the risk of OSA by 10%it is not surprising to see both disorder in the patient. Weight gain results in an increased risk of incident OSA and worsening preexisting OSA in those with and without OSA respectively.[5,6] As OSA often go undiagnosed though physician understand the algorithms for the diagnosis of sleep apnea ,the majority are unable to identify the patients for whom diagnostics are needed.[7] As OSA is independently associated with glucose intolerance and insulin resistance, it is very important to include history of snoring, witnessed apnea and sleep pattern in all patients with diabetes.[8,9] OSA is associated with poorer glycaemic control despite adjustment for a wide range of confounders including age, sex, race, body mass index number of diabetes medications, level of exercise, diabetes duration and total sleep time in some studies.[10-12].All studies show high prevalence of OSA in patients with diabetes. In a study done by Einhorn et al the prevalence of OSA in patients with was reported to be 48%.6 In a study by Shim et al 50.8% of the patiuents were at high risk of OSA according to Berlin Questionnaire.[13] Study from Jordan revealed 48.5% of the patients with diabetes were at high risk of OSA.[14] All

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studies show high prevalence of OSA in diabetic patients.It has also been demonstrated that the association between OSA and diabetes is bidirectional as neuropathy associated with diabetes can affect the central control respiration and upper airway neural reflexes resulting in OSA.[15] In a couple of studies nighttime hypoxia has found to be responsible for glucose intolerance and insulin resistance.[16]

As there seems to be high prevalence of OSA in patients with type 2 diabetes and the fact that OSA could worsen the complications of diabetes and complicate the disease management we carried out this study to recognize the prevalence of OSA in patients with type 2 diabetes.

METHODOLOGY:

All the patients who attended to our sleep clinic in OM Hospital and Research Centre were asked about diabeteic history.Those who are already diagnosed as diabetics and on medications or diet control were enrolled into the study. STOP BANG questionnaire was used to categorize the patients for probable obstructive sleep apnea. STOP BANG questionnaire include eight components which were snoring, daytime tiredness, observed apnea, high blood pressure, body mass index (>35 kg/m2), age (>50 yrs), neck circumference (male>42cm, female>40cm) ,gender(Male).According to the scoring system of the STOPBANG score, if it was 3vs.0-2,the risk of obstructive sleep apnea 2.5 fold. If the score was 4 vs. 0-2, the risk of obstructive sleep apnea is 4 fold, 5 vs. 0-2, the risk was 5 fold. If the score was 6vs 0-2, the risk of obstructive sleep apnea was 6 fold and if 7 vs. 0-2, the risk of obstructive sleep apnea was 7 fold.[18] All the patients with score more than 3 underwent diagnostic polysomgraphy with or without titration.[18] They undergo level A diagnostic polysomnography in the presence of sleep technician. For scoring events, an "event" can be either an apnea, characterized by complete cessation of airflow for at least 10 seconds, or a Hyp-opnea in which airflow decreases by 50 percent for 10 seconds or decreases by 30 percent if there is an associated 4% decrease in the oxygen saturation or an arousal from sleep. To grade the severity of sleep apnea, the number of events per hour is reported as the apnea-hypopnea index (AHI). An AHI of less than 5 is considered normal. An AHI of 5-15 is mild; 15-30 is moderate and more than 30 events per hour characterize severe sleep apnea.[20]

RESULTS:

Among 197 patients referred for polysomnography 67 were already diagnosed as diabetics and were on medication or diet control.

Table 1. Baseline characteristics of diabetic patients undergoing polysomnography

Age (years)	**Number (n)**
Less than 40	17
40- 60	30
More than 60	20
Gender	Number
Male	40
Female	27
BODY MASS INDEX (kg/m2)	NUMBER
Less than 23.9	18
23.9-30	32
More than 30	17

Age (years)	Number (n)
COMPONENTS OF STOP BANG QUESTIOONAIRE	
Snoring	65
Witnessed Apnea	50
Morning Headache	43
Daytime tiredness or somnolence	57
Hypertension	43

TABLE 2: SCORING OF PATIENTS USING STOP BANG QUESTIONNAIRE

Less than 3	1
More than 3 or equal to 5	40
More than 5	26

Among 67 patients who underwent diagnostic polysomnography 22 patients had normal AHI. Among them 19 had intermittent snoring and rest had normal diagnostic polysomnography. Among 45 patients 5 had predominantly central sleep apnea and 40 had obstructive sleep apnea.

TABLE 3: Patients having Obstructive sleep apnea and AHI Score:

Number of Patients	AHI Score
AHI < 5	22
AHI 5-15	12
AHI 15-30	
AHI >30	16
17	

Among 45 patients who had significant obstructive sleep apnea only 7 had HBA1C level less than 7.

DISCUSSION:

In our study more number of male patients attended our sleep clinic than females, this supports the notion that frequency of OSA is more in men (2-4%) than females (1-2%).This might also be due to cultural reason in our part of the world where male patients seek medical attention more than females. Most number of presenting patients were in the middle age group which is consistent with the finding that it is more prevalent in the middle age group.[21] Among the STOP BANG questionnaire snoring was the most common symptoms followed by witnessed apnea and daytime somnolence which are more common in OSA. 66 patients STOP BANG questionnaire was more than 3 which needs diagnostic polysomnography. Among the patients who went under diagnostic polysomnography 17 had severe obstructive sleep apnea and 16 had moderate sleep apnea which are both indications for CPAP treatment. It has also been seen that significant patients with moderate to obstructive sleep apnea had poor glucose control as it has been that insufficient sleep was associated with short and long term hyperglycaemia. Thus alteration in sleep pattern were proposed as a risk factor for developing type 2 DM.

CONCLUSION:

As it has been seen in our study that OSA is very

common in patients with Type 2 diabetes and worse glycaemic control a high index of suspicion and sleep history especially for OSA should be included in all the patients of type 2 diabetes. Any patients with uncontrolled diabetes despite medications independent of obesity should be screened for OSA.

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CLINICAL ANALYSIS OF PERIPHERAL VASCULAR DISEASE IN PATIENTS WITH DIABETES MELLITUS

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Abstract

Introduction: Diabetes Mellitus (DM) is clinical syndrome characterized by hyperglycemia due to absolute or relative deficiency of insulin. The metabolic dysregulation associated with DM causes multitude of secondary pathophysiological changes in multiple organ system causing macro vascular (coronary artery disease, peripheral vascular disease, cerebrovascular disease) and micro vascular (retinopathy, neuropathy, and nephropathy) complications. This study aimed to study the prevalence of peripheral vascular disease in patients with diabetic mellitus presenting to this tertiary care centre. **Methods:** This clinical study was conducted in first affiliated hospital of Yangtze university, Jingzhou. All patients with a diagnosis of diabetic mellitus who came to Out patient department of Endocrinology & diabetic clinic and admitted in the hospital during a period between October 2013 to October 2014, who fulfill, were enrolled for the study. This was a single centered retrospective observational analylitcal study conducted in Department of Endocrinology of First affiliated Hospital of Yangtze, China. **Results**: Peripheral vascular disease was found in 35% of patients studied . There was significant correlation. **Conclusion**: A significant number of diabetics presenting with diabetes mellitus have underlying peripheral vascular disease .The patients might not all be symptomatic or show obvious signs of PVD but need to be investigated for the same. The older the individual the more the chances of having peripheral vascular compromise. Also a tobacco user and patient presenting with worse clinical findings is more likely to have PVD. Thus the detection of peripheral vascular disease in patients using Arterial Doppler studies along with routine clinical and laboratory assessment can be of great value in long term care of these individualsith age, and history of tobacco use.

Key Words: arterial Doppler: diabetic foot: peripheral vascular disease

INTRODUCTION

Diabetes is a common affliction in all parts of the world. Its incidence is rising in developing countries like china with high incidence in the developed world . Diabetic foot infections are one of the most common manifestations of the disease necessitating hospital admissions and special care. Diabetes is also commonly associated with PVD. At least 20-30% of patients with PVD have diabetes and it is the most common cause of non-traumatic lower extremity amputation. More than 60% of these amputations occur in people with hyperglycemia. Diabetes duration and poor control increase the risk for peripheral vascular disease. It has been estimated that with every 1% increase in hemoglobin A1C, peripheral vascular disease risk increases by 28%., In addition to neuropathy and trophic ulcers, peripheral vascular disease plays a major role in the evolution and outcome of diabetic foot infection.

The early detection of peripheral vascular disease in seemingly asymptomatic and early cases is useful in correction and improving the blood flow and hence healing and reduction of risk of major limb amputations.

Arterial Doppler studies are useful in determining the presence of peripheral arterial occlusive disease,

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the level of occlusion or stenosis, the extent as also the presence of collaterals. Doppler studies however need to be coupled with angiography for further vascular interventions.

There is a need for systematic evaluation of peripheral vascular disease in all diabetic patients especially patients presenting with diabetic foot infections. The information can help in formulating protocols for affective management of diabetic patients with the aim of limiting the morbidity and social costs associated with the disease.

The Objectives were to estimate the prevalence of peripheral vascular disease among diabetic patients receiving inpatient and outpatient service at People's First Hospital, to find out the association of the duration of symptoms suggesting of diabetes mellitus with peripheral vascular disease and to study the correlation of clinical manifestation and arterial doppler test in peripheral vascular disease in diabetic patients receiving outpatient and inpatient service in People's First Hospital.

MATERIALS AND METHODS

This clinical study was conducted in first affiliated hospital of Yangtze university, Jingzhou. All patients with a diagnosis of diabetic mellitus who came to Out patient department of Endocrinology diabetic clinic and admitted in the hospital during a period between October 2013 to October 2014, who fulfill, were enrolled for the study. After recording the pertinent information ,patients were subjected to a lower limb arterial Doppler as a routine examination and findings were tabulated. The Inclusion Criteria was patients with diagnosed Diabetes mellitus and comes to our opd with clinical features of Peripheral vascular disease like Intermittent claudication ,pain and Numbness on foot aged above 18 yrs, Patients admitted to inpatient department of Endocrinology department with diabetic related disease who underwent Doppler study as routine examination as per protocol of the department, Patients willing for arterial Doppler study as a routine examination. The Exclusion Criteria was patients with previous amputation of lower limbs digits or any degree of amputation due Diabetic foot and now presenting with necrotizing fasciitis and severe sepsis.

This was a single centered retrospective observational study conducted in Department of Endocrinology of First affiliated Hospital of Yangtze University, jingzhou, Hubei,China.
The statistical analysis of the data collected was done using XLSTAT's statistical analysis software version 2015.The results of the depended and independent variables were analyzed using Chi-square test. The p Values ($p<0.05$) were considered statistically significant.

RESULTS

During the period of study from October 2013 to October 2014, a total of 234 patients with diabetes mellitus and peripheral vascular disease were observed in OPD and inpatient department of Endocrinology . Of them however 162 patients did not follow up to us with results of Doppler study so were excluded from our study. Thus 72 patients were included in the study.

Peripheral vascular disease was found in 35% of patients studied . There was significant correlation with age, and history of tobacco use. There were 50 males and 22 females in the study group.

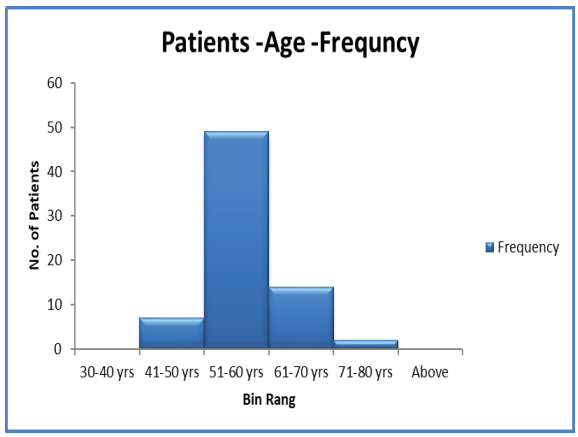

Fig 1 : Descriptive statistics on Patient age frequency

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In my study the mean value of age was 57.73 with standard deviation of 6.22.Among the male patients the mean age was 57.62. The mean value for female was 58.Our study shows that 25 of the patients had already Intermittent claudication presenting in duration of 24 months time.76% of patients were suffering from Diabetes mellitus for 5 years. Presence of peripheral Vascular disease as diagnosed by arterial Doppler where we can see of the 72 patients in the studied population 26 patients or 34.7% were found to have some form of reduced arterial flow the lower limb vessels ,46 patients or 64.3% patients were found to have a normal lower limb arterial doppler study.80% of the patients show a popliteal artery mild to moderate occlusion on Doppler study.

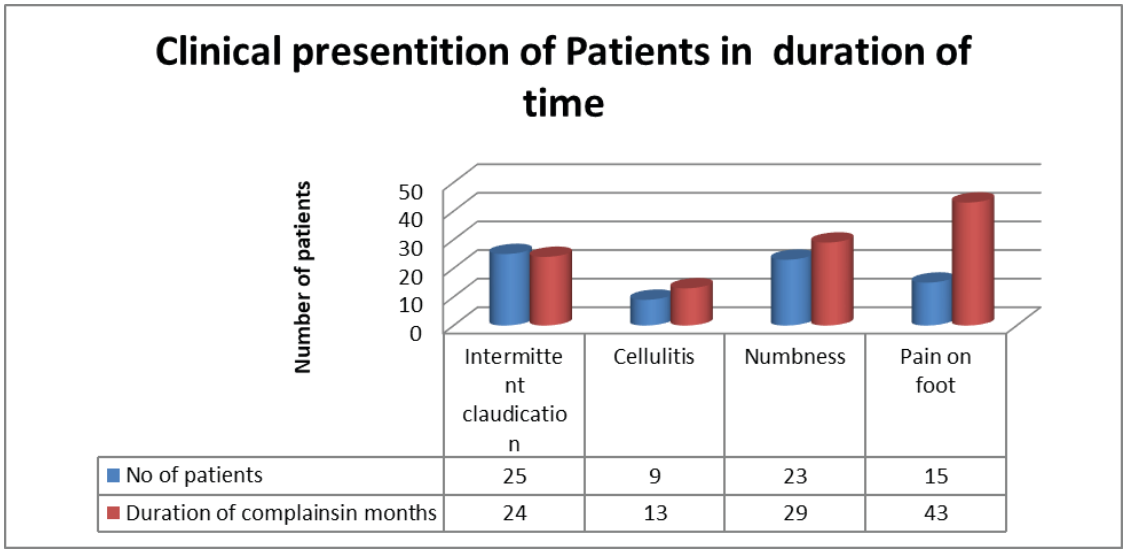

Fig 2: Relation between different clinical presentations in patients who were observed in our study, where we can see 25 of them had already Intermittent claudication presenting in duration of 24 months time

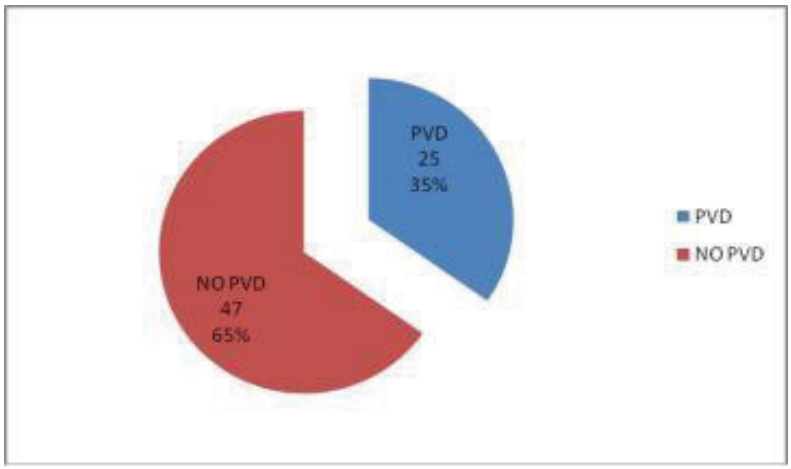

Fig 3: Presence of peripheral Vascular disease as diagnosed by arterial Doppler where we can see of the 72 patients in the studied population 26 patients or 34.7% were found to have some form of reduced arterial flow the lower limb vessels ,46 patients or 64.3% patients were found to have a normal lower limb arterial doppler study

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The male have more incidence of Peripheral Vascular disease than female,where pValue is 0.035.
The mean age for peripheral vascular disease was 56.8.The duration of Peripheral vascular disease <5 years was 8 and >5 years was 18 with pValue of 0.28.10 male and 8 female gave us past history of smoking with pValue of 0.139.18 patients with history of smoking developed peripheral vascular disease with pvalue of 0.035

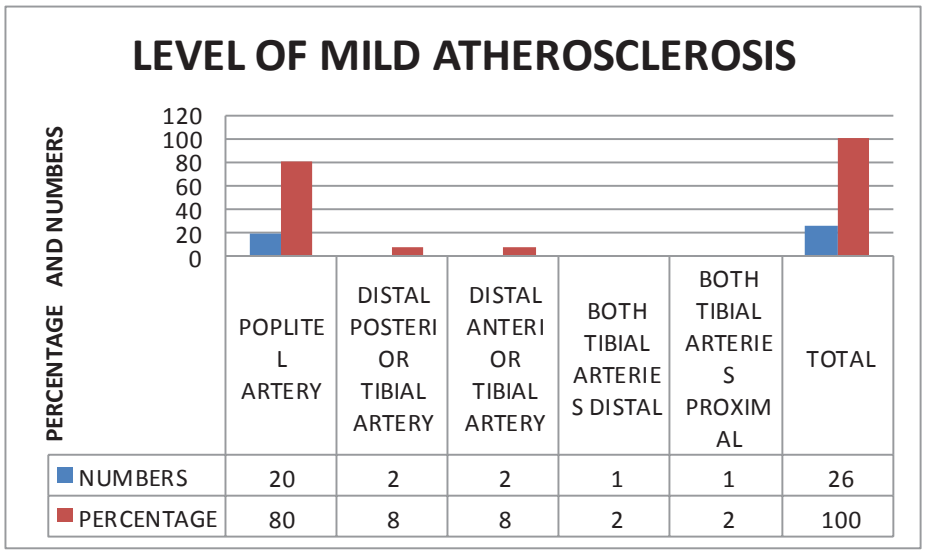

Fig 4: The location of Mild atherosclerosis found in some patients

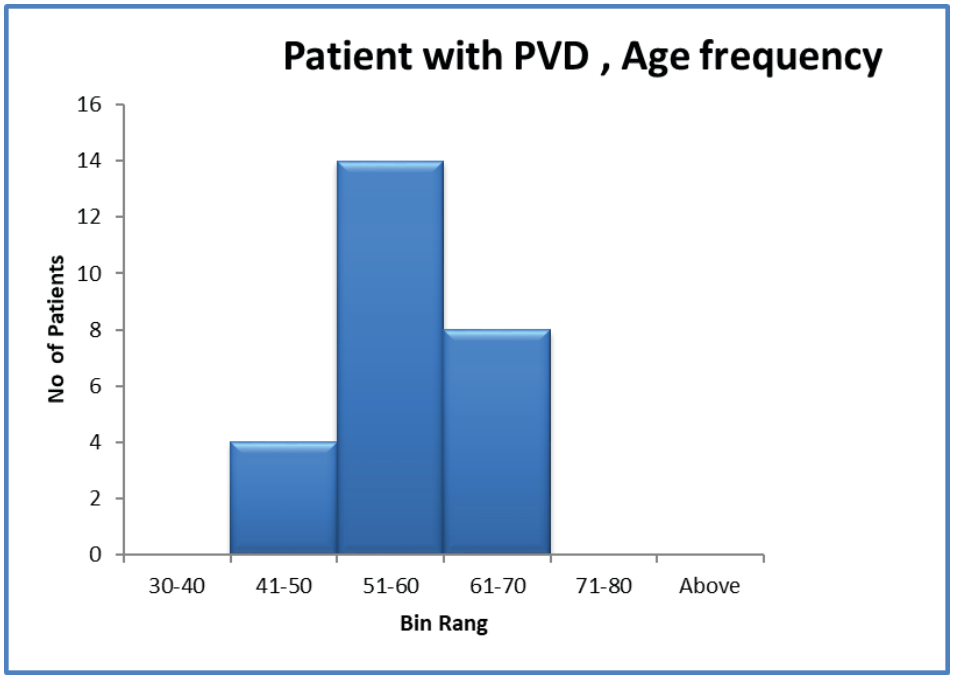

Fig 5: Shows a comparison study with age and PVD

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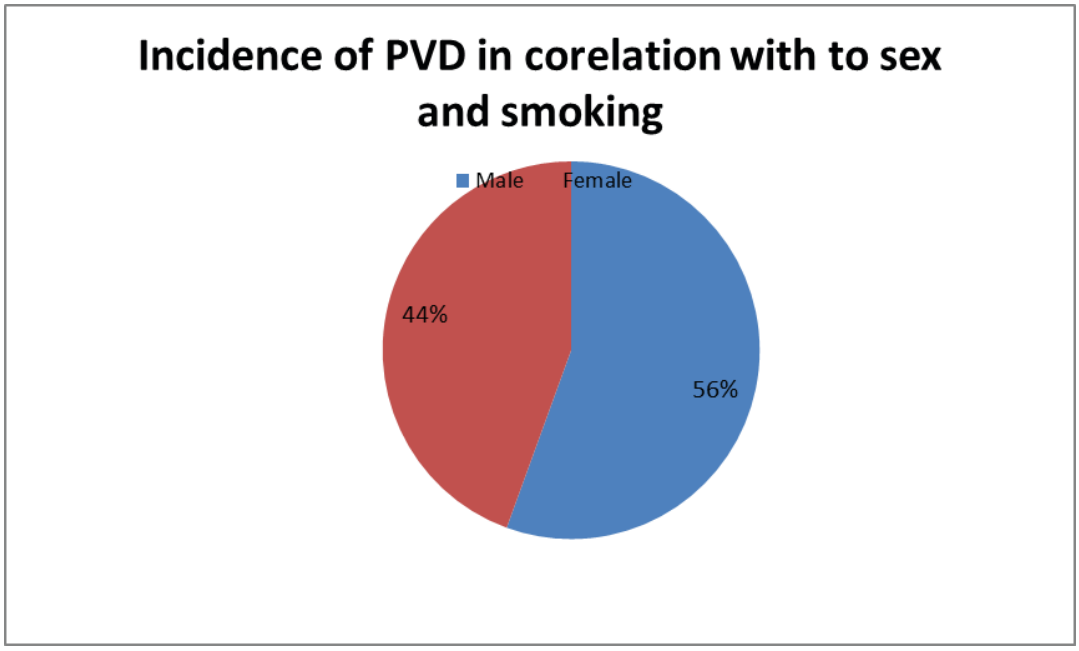

Fig 6: Pie chart with incidence PVD in correlation with sex(Male and Female) with smoking

DISCUSSION

Diabetes mellitus results when the pancreas is unable to meet insulin requirements to maintain euglycemia. In patients with type 2 diabetes mellitus (T2DM), insulin resistance typically precedes beta cell dysfunction and hyperglycemia. Type 1 diabetes (T1DM) is an autoimmune process whereby insulin-producing beta cells are destroyed leading to insulin deficiency. Diabetes is a common disease approximately 11.3% of the US population over the age of 20 years has overt hyperglycemia (CDC diabetes fact sheet, 2011). In people over the age of 65 years, almost 27% have diabetes. Even more staggering, approximately 79 million people over the age of 20 years have prediabetes; this makes up 35% of the US population (50% of those over the age of 65 years).

Diabetes is also commonly associated with PVD. At least 20-30% of patients with PVD have diabetes [1-3] and it is the most common cause of non-traumatic lower extremity amputation. More than 60% of these amputations occur in people with hyperglycemia. Diabetes duration [4] and poor control [5] increase the risk for peripheral vascular disease. It has been estimated that with every 1% increase in hemoglobin A1C, peripheral vascular disease risk increases by 28%.

Ultrasound technology has revolutionised vascular imaging. The availability of high resolution portable scanners, with heads accommodating a range of tissue depths, allows for non-invasive longitudinal assessment of virtually the entire circulatory tree outside of the thoracic aorta. Duplex ultrasound combines the traditional b mode two dimensional images with Doppler measurements of blood flow parameters

After reviewing the results of the study certain pertinent inferences could be made.

The prevalence of PVD was found to be 35% with 25out of 72 patients showing vascular compromise as diagnosed by arterial Doppler study. The prevalence in males was found to be 38% while in females was 27 %. This however was not found to be statistically significant owing to lesser number of female subjects in the study. Also the patients in the study were asymptomatic and the rate

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represents more of subclinical peripheral vascular compromise.

Most of the individuals in this study were in the age group of 51 - 60 years accounting for 51% of subjects .The prevalence of PVD was found to increase with age with patients above 60 yrs showing a prevalence of 75%. Although this seems a higher compared to existing studies it correlates with accepted data that progression with age is significant and indeed faster in diabetes patients. [6,7,8]

This can also be explained by the fact that age related atherosclerotic changes independent of diabetic status worsen with advancing age. [9] As also seen from this data most patients were diagnosed less than 5 years prior to admission to be diabetics, some with age more than 60yrs.The problem of late diagnosis of diabetic status seen in our region could explain the very high prevalence of PVD in older age groups , as by the time the patients presents to a tertiary care centre with complications of diabetes the pathophysiological changes in the foot including vascular compromise is at an advanced level. This also can explain why this study could not demonstrate a statistical correlation between the duration of diabetes and the prevalence of peripheral vascular compromise.

A significant association however was found with regard to tobacco usage either in smoked or chewed form .There were a total of 18 tobacco users in the study population 10 were males and 8 females .The females all-consuming the chewed variety of these 16 individuals (80%) showed presence of PVD,2 of these were females and remaining 14 males .This when compared to only 9 out of 52 non smokers showing presence of PVD was significant. This correlates with existing data wherein tobacco as an independent factor is implicated in the aetiology of PVD and also seen to accelerate changes in diabetic individuals. [10,11,12]

On the basis of this study the relevance of investigating the presence of peripheral vascular disease and the need to do it on a routine basis even in apparently asymptomatic individuals can be advocated.

CONCLUSIONS

A significant number of diabetics presenting with diabetes mellitus have underlying peripheral vascular disease .The patients might not all be symptomatic or show obvious signs of PVD but need to be investigated for the same. The rate of prevalence in the present study was 35%.

The older the individual the more the chances of having peripheral vascular compromise. Also a tobacco user and patient presenting with worse clinical findings is more likely to have PVD. Thus the detection of peripheral vascular disease in patients using Arterial Doppler studies along with routine clinical and laboratory assessment can be of great value in long term care of these individuals.
This study and the others before it have consistently proven the need and benefit of investigating diabetics for peripheral ischemia and the value of the same in giving better care to these patients.

Also the need for smoking cessation especially in individuals with other risk factors for diabetes is clearly shown by this and many other studies before.

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Thyroid Function Test Abnormalities in Patients with Liver Cirrhosis

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Abstract

Introduction: Liver plays a central role in thyroid hormone metabolism. A normal function of both the thyroid gland and the liver is therefore necessary to maintain normal thyroid hormone levels and action. This study was done to find the thyroid function test (TFT) abnormalities in patients presenting with liver cirrhosis. **Methods:** This was a single centre hospital based, cross-sectional observational study carried out from 21 April 2019 to 20 October 2019 in the Department of Internal Medicine, Universal College of Medical Sciences-Teaching Hospital (UCMS-TH), Bhairahawa, Nepal. All the patients presented with liver cirrhosis during the study period after using inclusion and exclusion criteria were included in the study. Data was collected as per predesigned proforma and TFT level (free T3, free T4 and TSH) was done. **Results:** Total 110 patients with liver cirrhosis and 110 healthy controls were enrolled in this study with mean age of 51.1±12.13 years and Male : Female ratio of 4:1. According to Child Pugh score (CPS) 62 (56.36%) patients were in Class C, 35 (31.82 %) patients were in Class B. Low level of FT3 was seen in 27 (24.6%) patients, low level of FT4 was in 11 (10 %) patients and high TSH level was seen in 25 (22.7 %) patients. Overall abnormal TFT levels were seen in 43 (39.1 %) patients. Among these overt hyperthyroidisms was seen in 3 (2.7%) patients, subclinical hypothyroidism was seen in 14 (12.7%) patients, overt hypothyroidism was seen in 11 (10%) patients. Isolated low FT3 level was seen in 15 (13.6%) patients. Correlation between AST ALT and ALP were found to be statistically significant with both FT3 and FT4. Correlation between different CPS categories was found to be statistically significant with mean score of FT3 (p=0.0048), and mean score of FT4 (p=0.045). **Conclusions:** Overall abnormal thyroid hormone levels were seen in 39.1 % patients with liver cirrhosis. Correlation between AST ALT and ALP were found to be statistically significant with both FT3 and FT4. So all the cirrhotic should be evaluated for thyroid dysfunction for early diagnosis and timely treatment.

Key Words: Hypothyroidism; liver Cirrhosis; thyroid dysfunction.

INTRODUCTION

Liver cirrhosis is an end result of a variety of liver diseases characterized by fibrosis and architectural distortion of the liver with the formation of regenerative nodules. It is a leading cause of morbidity and mortality worldwide. The Global Burden of Disease (GBD) reported that over one million people died due to cirrhosis in 2010 worldwide, compared with 676,000 deaths in 1980.[1] Thyroid hormone is very important in the growth and development in adults, and plays a critical role in the regulation of the function and metabolism of almost every organ system.[2,3] The liver plays a central role in thyroid hormone metabolism, transport, and clearance by producing thyroid binding globulin, albumin and transthyretin.[4] Liver is also the most important for the peripheral conversion of thyroxine (T4) to triiodothyronine (T3) by Type 1 deiodinase.[5] A normal function of both the thyroid gland and the liver is therefore necessary to maintain normal thyroid hormone levels and action.

T4 is secreted from the thyroid gland in about twenty-fold excess over T3 and both hormones are mostly bound to plasma proteins.[6] Thyroid diseases

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may perturb liver function; liver disease modulates thyroid hormone metabolism; and a variety of systemic diseases affect both the organs. Patients with chronic liver disease may have thyroiditis, hyperthyroidism, or hypothyroidism. Patients with subacute thyroiditis or hyperthyroidism may have abnormalities in liver function tests.[7]

Data regarding thyroid function abnormalities in patients with liver cirrhosis are variable and scarce from this part of world. So, this study was done to find the TFT abnormalities in patients presenting with liver cirrhosis and to look for any correlation between TFT abnormalities and severity of liver disease.

METHODS

This was a single centre hospital based, cross-sectional observational study. Study was carried out from 21 April 2019 to 20 October 2019 in the Department of Internal Medicine, Universal College of Medical Sciences, Bhairahawa, Nepal. The study protocol was approved by the Institutional Review Committee and written informed consent was taken from all the participants. All the patients aged more than 16 years presented with liver cirrhosis in the internal medicine department of UCMS-TH during the study period were included in the study. Patients who refused to give consent or age up to 16 years were excluded.

Similarly Patients with pregnancy, previously known thyroid disease, diabetes, nephrotic syndrome renal failure or any other acute or chronic illnesses were excluded. Patient receiving drugs that may interfere with thyroid hormone metabolism and function like amiodarone, phenytoin, β- blocker, steroids, estrogen and iodine containing drugs/contrast were also excluded.

Equal number of healthy age and sex matched controls were also taken. A detailed history including history suggestive of hypothyroidism, hyperthyroidism and liver cirrhosis was taken in all the patients as per predesigned proforma. Each patient was also subjected to a detailed clinical examination. Special attention was given to pallor, icterus, edema, hydration status, asterixis, stigmata of chronic liver disease like alopecia, spider naevi, parotid enlargement, palmar erythema, gynaecomastia and testicular atrophy. Detailed thyroid, abdominal and neurological examination was done in all cases. After cleaning the site with rectified spirit swab, a tourniquet and a 5 ml syringe were used to draw 5 ml of blood and the following investigations were done in all the cases: complete blood count, glucose, liver function test (LFT), renal function test (RFT), hepatitis B surface antigen, hepatitis C virus antibodies and thyroid function tests. LFT includes total bilirubin, direct bilirubin, alanine transaminase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP) total protein and albumin level. LFT and RFT, was measured by using Humastar 600 fully automated biochemistry analyser, (Human diagnostics, Germany). TFT included measurement of free T3 (FT3), free T4 (FT4) and thyroid stimulating hormone (TSH). For TFT the samples of blood were allowed to stand to clot. Serum was separated by centrifugation. Serum FT3, FT4 and TSH were measured by chemiluminescence immunoassay technique (CLIA) with Maglumi 2000 analyser (Snibe diagnostic, Shenzhen, China). Thyroid hormone abnormalities were made if patients thyroid hormones were outside the normal values; FT3 (2.0-4.2 pg/ml), FT4 (8.9-17.2 pg/ml) and TSH (0.3-4.5 mIU/ml). After keeping the patient nil per oral for 4 hours, patients underwent ultrasonography of abdomen and pelvis. The focus was mainly in the liver size, echotexture, portal vein diameter, presence of collaterals, gall bladder, common bile duct, spleen size, abdominal collection, renal size, echotexture and corticomedullary differentiation. Severity of liver cirrhosis was categorised by Child Pugh score (CPS).

All the statistical analysis was performed using SPSS Version 20 (IBM Corp.) and Microsoft Excel 2016. Categorical data were presented as frequencies and corresponding percentages. Quantitative data were presented in mean ± SD.

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Correlation between TFT with various biochemical parameters were calculated by using Pearson correlation. ANOVA test was used to compare the TFT level with CPS categories. The level of significance for all analytical test were set at 0.05 and 'p-value < 0.05 was considered significant

RESULTS

Total 110 participants with liver cirrhosis were enrolled in this study and analysed statistically. Baseline characteristics and the demographic profile of the study subjects in the Group 1 are depicted in table 1. Mean age of patients was 51.1±12.13 years (Range: 32 yrs to 94 years). Most of our patients were adults in their fifth and sixth decade of life and together they constituted 63% (n=69) of total study population. Males were 4 times more commonly affected with liver cirrhosis then females in the present study (M:F ratio 4:1) (Table 1).

Table 1: Demographic characteristics of patients with liver cirrhosis

Characteristics	N (%)
Age (yrs)	
31-40	22 (20)
41-50	38 (34.55)
51-60	31 (28.18)
61-70	12 (10.91)
>70	7 (6.36)
Sex	
Male	88 (80%)
Female	**22 (20%)**
Demographic data	
Rupandehi	50 (45.45%)
Kapilvastu	18 (16.36%)
Nawalparasi west	9 (8.18%)
Dang	9 (8.18%)
Gulmi	7 (6.36%)
Pyuthan	5 (4.55%)
Palpa	5 (4.55%)
Arghakhachi	4 (3.64%)
Rolpa	2 (1.82%)
Parbat	1 (0.91%)

Patients included in the present study were from 10 nearby districts from the study site. Rupandehi, Kapilvastu, Dang and Nawalparasi west were the four most common districts respectively which constituted 78,18% of the total study population (table 1). Ethnically, majority of the patients 51.82% (n=57) were janjatis, followed by dalits 17.27% (n=19), chettris 10.21% (n=12), madhesis 10.21% (n=12), brahmins 7.27% (n=8) and muslims 1.82% (n=2) respectively. Majority of patients 29.09% (n=32) were farmers by occupation, followed by shopkeepers 20.91% (n=23), businessmen 12.73% (n=14), housewives 9.09% (n=10), driver 9.09% (n=10), servicemen 8.18% (n=9), retired army men 8.18% (n=9) and labourers 2.73% (n=3).

The most common cause of cirrhosis was ethanol ingestion which was found in 97 (88.18%) patients. Chronic hepatitis B infection was the second most common cause which was seen in 8 (7.27%) patients followed by chronic hepatitis C infection in 3 (2.73%) patients. The cause of cirrhosis was unknown in 2 (1.81%) patients. Clinical and laboratory characteristics are given in table 2.

Table 2: Clinical and lab characteristics of the patients

Parameters	Mean±SD
Pulse (Beats/min)	91.49±14.09
SBP (mmHg)	113.67±18.98
DBP (mmHg)	72.30±13.45
BMI (Kg/M2)	21.98±2.61
Haemoglobin (g/dl)	9.37±2.72
TLC (/cu.mm)	10380±801.76
Platelets (/Cu.mm)	98227.27±36206
Na (meq/dl)	137.15±3.97
K (meq/dl)	3.95±0.69
INR	1.59±0.59
Serum Urea (mg/dl)	32.96±7.63
Serum Creatinine(mg/dl)	0.88±0.43
Total Protein (mg/dl)	6.45±0.68
Albumin(mg/dl)	3.31±0.39
Total Bilirubin (mg/dl)	4.20±4.07
AST (IU/L)	158.77±89.42
ALT (IU/L)	85.73±78.23
Alkaline phosphatise (IU/L)	250.75 ±106
Duration of hospital Stay (days)	5.56 ±2.59

The patients were grouped according to CPS for the severity of liver cirrhosis, in which 62 patients (56.36%) were in Class C, 35 patients (31.82 %) were in Class B and remaining 13 patients (11.82%) were in Class A (Figure 1). Majority of our patients were in class C which shows that they were in advance stage of liver disease.

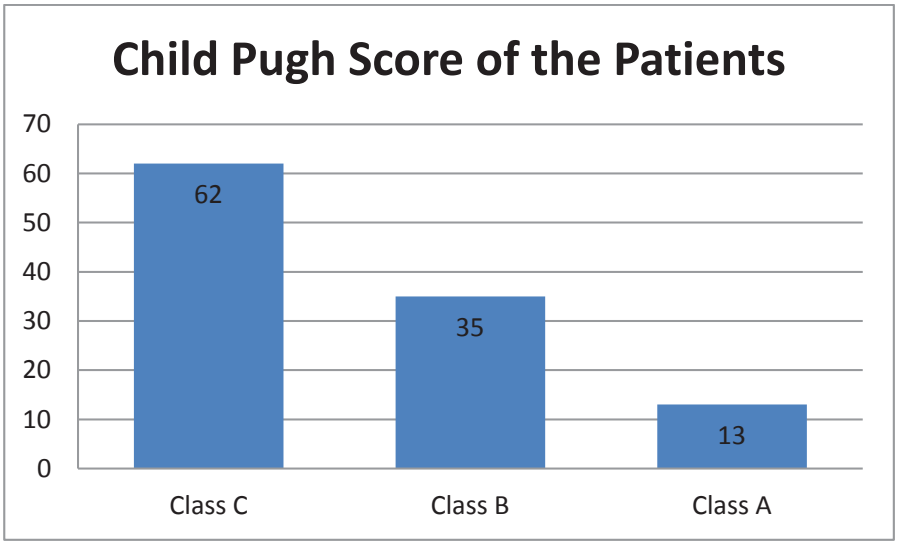

Figure 1: Distribution of patients according to Child Pugh Score

Table 3: Mean value of thyroid function test in liver cirrhotics

Thyroid Function Test	Mean±SD	Reference range
Free T3 (pg/ml)	2.53±0.78	(2.0-4.2)
Free T4 (pg/ml)	12.19±2.60	(8.9-17.2)
TSH (µIU/ml)	4.18±3.98	(0.3-4.5)

The mean value of FT3 was 2.53±0.78 pg/ml with minimum of 1.16 pg/ml and maximum 5.97 pg/ml. The low level of FT3 was seen in 27 (24.6%) patients out of which 23 patients were male and 4 female and high level of FT3 was seen in 3 (2.7 %) patients. The mean value of FT4 was 12.19±2.60 pg/ml with range of 5.59 to 21.41 pg/ml. In our study, 11 (10 %) patients had low FT4 level and 3 (2.7 %) patients had high FT4 level. Out of 11 patients with low FT4, 9 were male and 2 were female. The low level of both fT3 and fT4 was seen in 9 (8.18%) patients. The mean value of TSH was 4.18±3.98 µIU/ml with range of 0.024 to 25.61 µIU/ml. Serum TSH level was abnormal in 28 (25.5%) patients. Among these 28 patients, 25 (22.7 %) had high level of TSH and 3 (2.7 %) had low level of TSH (table 3 and 4).

Table 4: Abnormal thyroid hormone level

		Creatinine	Total bilirubin	AST	ALT	ALP	Total Protein	Serm Albumin	PT	INR
FT3	Pearson Correlation	.178	.015	.241*	.218*	.227*	-.064	.022	-.077	-.072
	P-value	.063	.878	.011	.022	.017	.510	.818	.425	.456
FT4	Pearson Correlation	.078	.037	.286**	.240*	.194*	-.186	-.036	-.152	-.094
	P-value	.420	.699	.002	.011	.042	.052	.706	.115	.331
TSH	Pearson Correlation	.024	-.008	-.063	-.017	.003	-.026	-.027	.006	-.072
	P-value	.803	.935	.510	.863	.971	.789	.781	.947	.453

We also compared mean score of FT3, FT4 and TSH with CPS score by using ANOVA test. It was seen that mean score of FT3 with different CPS categories was found to be statistically significant (p=0.0048). Similarly Mean score of FT4 with different CPS categories was found to be statistically significant (p=0.045). Mean score of TSH with different CPS category was found to be statistically insignificant (p=0.308) (table 6).

Table 6: Correlation between FT3 FT4 and TSH with different CPS categories

Thyroid function		N	Mean	Sandard Deviation	F-value	P-value
Free T3	CPS A	13	2.85	.801	5.59	0.0048
	CPS B	35	2.80	.994		
	CPS C	62	2.31	.642		
	Total	110	2.53	.821		
Free T4	CPS A	13	13.77	2.774	3.1882	0.045
	CPS B	35	12.31	2.908		
	CPS C	62	11.82	2.265		
	Total	110	12.21	2.595		
TSH	CPS A	13	2.69	2.10	1.1903	0.308
	CPS B	35	4.06	4.21		
	CPS C	62	4.59	4.28		
	Total	110	4.19	4.08		

DISCUSSION

The thyroid gland produces three hormones T3, T4 and calcitonin. These hormones play an important role in cell differentiation and also help to maintain thermogenic and metabolic homeostasis in the body. Thyroid hormone secretion is controlled by TSH secreted from the anterior pituitary gland, which itself is regulated by thyrotropin-releasing hormone (TRH) produced by the hypothalamus. T4 is secreted twenty

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times in excess over T3 from the thyroid gland. Both hormones are bound to plasma proteins, including thyroxine-binding globulin, transthyretin and albumin.8 The liver has an important role in thyroid hormone metabolism because it manufactures the proteins that bind thyroid hormone. It is also one of the major sites of peripheral metabolism of thyroid hormone and is involved in its conjugation, biliary excretion, oxidative deamination and the extrathyroidal deiodination of T4 to T3 and to reverse T3 (rT3).6 This peripheral conversion is accomplished by two enzymes, the type 1 (D1) and type 2 (D2) deiodinases. A third deiodinase, type 3 deiodinase (D3) participates in the clearance of both serum T4 and T3.9 D1 is expressed predominantly in liver and kidney and contribute approximately 24% of circulating T3 in healthy individuals. In some chronic systemic disease like hepatic cirrhosis rT3 increases simultaneously with the decrease of T3 level. Therefore, one can describe particular alteration of thyroid pattern of chronic liver disease; low T3 syndrome, low T3 and T4 syndrome or high T4 syndrome mixed form.[10]

Mean age of our patients was 51.1 years with males 4 times more commonly affected with liver cirrhosis then females. This is similar to study done by Patira NK et al. where majority of patients 72% belonged to age group 41-60 years with male predominance (78%).[10] Similar results were seen in other study done by Punekar et al. in Jabalpur where males (71%) were involve more than female.[11] The most common cause of cirrhosis in our study was ethanol ingestion which was found in 88.18% patients followed by hepatitis B and C infection. Findings are similar to another study from Rajasthan, India where also the most common etiology of liver cirrhosis was alcoholism which was seen in 70% patients followed by hepatitis B related cirrhosis.[10] This can be explained by the fact that ethanol consumption is predominantly seen in young males then females which leads to alcohol related problem occurring more in males then females. In our study, patients presented to us in the late stages of cirrhosis. According to CPS, most of our patients (56.36%) were in Child-Pugh class C followed by 31.82 % in Child-Pugh class B and remaining 11.82% were in Child-Pugh class A. This shows that most of our patients presented to us in advanced stage of decompensated cirrhosis of liver. Similar result was seen in the study carried out in Lucknow where 56.86% patients were classified as Child-Pugh class C, 39.22% were classified as Child-Pugh class B and rest of 3.92% were classified as Child-Pugh class A.[12] This can be explained by the fact that patient comes late to health facilities in developing country may be because of poor socio-economic condition and poor health insurance coverage. Overall abnormal TFT levels were seen in 39.1 % patients with hypothyroidism in 25% patients. Similar results were seen in another study where hypothyroidism was seen in 21.6% patients.[13] The low T3 syndrome has frequently been reported in patients with chronic liver disease. The low level of FT3 was seen in 24.6% patients in our study. Whereas in another study low free T3 levels were found in 67.8% (n=19/28) of patients with hepatitis B related cirrhosis, 54.5% (n=6/11) of patients with hepatitis C related cirrhosis, 67.6% (n=23/34) of patients with alcoholic cirrhosis and 83.8% (n=26/29) patients with cryptogenic cirrhosis.13 This is in contrast to the prevalence of hypothyroidism in the general population has been estimated 4.6% by the National Health and Nutrition Examination Survey (NHANES III).[14] In our study mean score of FT3 with different CPS categories was found to be statistically significant (p=0.0048). Similarly Mean score of FT4 with different CPS categories was found to be statistically significant (p=0.045). Similarly in the study done by Patira et al. has found association between serum T3 and CPS categories (p value 0.00).[10]

Certain potential limitations of this study should be noted. The present study was a single-centred hospital based study with small sample size so results obtained in this study can not be generalised. There is a potential for referral bias as the study was performed at a tertiary care center. In future, we need multi centric study with larger sample size. Another limitation of the present study is that liver cirrhosis was diagnosed based

on clinical, biochemical and radiological ground and liver biopsy was not done to confirm liver cirrhosis due to logistic constrains and as it is an invasive procedure. Detailed work up for thyroid profile like reverse T3 and thyroid antibodies lie thyroperoxidase antibody, thyroglobulin were also not carried out. Despite these limitations, there are several strengths in our study. This study has shown a significantly high prevalence of thyroid dysfunction in patients with liver cirrhosis. Which further indicate the association between thyroid dysfunction and liver cirrhosis.

CONCLUSIONS

Overall abnormal thyroid hormone level was seen in 39.1 % patients with liver cirrhosis. Most of these patients have various degree of hypothyroidism. Isolated low Free T3 was seen in significant number of patients. Correlation between AST ALT and ALP were found to be statistically significant with both FT3 and FT4. Correlation between different CPS categories was found to be statistically significant with the mean score of FT3, and the mean score of FT4. So all the liver cirrhotic patients should be evaluated for thyroid dysfunction for early diagnosis and it's management.

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Does the Central Corneal Thickness (CCT) retain its predictive value as a risk factor in Primary Open Angle Glaucoma patients with Diabetes Mellitus?

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Abstract

Background: Central Corneal thickness (CCT) is thicker in diabetic patients. This may cause the CCT to lose predictive power as a risk factor for primary open angle glaucoma (POAG) in patients with diabetes. **Objective:** To evaluate if CCT of POAG patients with diabetes retains its predictive value as a risk factor. **Methods:** A cross sectional analysis of sequential group of patients with POAG with and without diabetes were evaluated HbA1C in diabetic patients and CCT in both groups was measured and the severity of POAG was evaluated using visual field changes and optic disc changes. The correlation was evaluated using confidence interval and liner regression estimator analysis. **Results:** Five hundred and eighty-seven patients with POAG were evaluated. The mean CCT for the group combined was 540.4±34.9 µm. Three hundred and thirty-seven patients had no history of diabetes and had mean CCT of 531.1±19.6µmTwo hundred and fifty of them had diabetes with mean corneal thickness of 549±20.2µm. CCT retained its predictive value as a risk factor for severity in POAG patient without diabetes ($p<0.05$). CCT however was a less sensitive for evaluating risk/severity in POAG patients with diabetes ($p>0.05$). **Conclusions:** CCT values may not retain its predictive value of severityof POAG in patients with diabetes. Hence, CCT alone may not be a reliable marker and mislead treating physicians

Key Words: POAG, CCT, Diabetes, Severity of POAG, CCT and Diabetes

INTRODUCTION

Central corneal thickness(CCT) is one of the strongest independent markers of primary open-angle glaucoma(POAG) development.Ocular Hypertension Treatment Study (OHTS)[1] and the European Glaucoma Prevention Study (EGPS)[2] both have evaluated and established this association. Both the studies have concluded that irrespective of the age or other associated risk factors, people with thinner corneas are more likely to develop POAG. The risk of developing POAG doubled for every 40 µm decrease in CCT from the overall mean of 573.3 µm in the OHTS and EGPS pooled sample.[3]

One of the most important risk factors for primary open angle glaucoma is an elevated intraocular pressure measured by Goldmann Applanation tonometry (GAT) and is influenced by the individual's CCT. GAT assumes a standard CCT of 520 µm for all corneas.[4] Hence, if the cornea is any thicker or thinner ,the IOP needed to be adjusted to avoid over or underestimation.[5]

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The normal range in most studies was between 427–620 µm. Though most studies have quoted comparable central corneal thickness in primary open angle glaucoma and normal individuals.[6–8], some studies have found that central corneal thickness in primary open angle glaucoma patients is significantly lesser than in the normal population. This has made CCT an individual risk factor for development of POAG,hence denoting that patients with thinner corneas h as of greater chances of developing POAG and in some instrances having greater severity[9–12]

Diabetes is now being studied as a risk factor for development and progression in of POAG.[13–16] From various studies, the CCT in the diabetic patient has also been reported to be thicker than non-diabetic patient.[17,18] This had been thought to be mainly due to deposition of glycosaminoglycan or endothelial pump dysfunction.[18, 19] This could mean that the CCT in patients who have POAG and diabetes could be misleading and CCT may not retain its value as a risk factor and a prognostic predictor.

The aim of this study was to evaluate if CCT still remains a reliable indicator of severity or risk factor in POAG patients in diabetes when compared with those without diabetes.

In this study, we compare the CCT among the patients of POAG with and without diabetes mellitus to evaluate if it retains its predictability on severity of POAG.

MATERIALS AND METHODS

Study Population

This study is a cross-sectional review of patients evaluated and treated at tertiary eye center. Five hundred and eighty-seven patients diagnosed with primary open angle glaucoma were evaluated . Since this was an exploratory analysis, no sample size calculation was needed.

Patients with PACG or any history of intraocular surgery (e.g. vitreoretinal procedures, glaucoma filtration surgeries), with secondary open-angle-closure glaucoma, inflammatory glaucoma, acute congestive glaucoma, high myopia, and optic disc abnormalities were excluded from the study. The research was approved by the ethics committee and the institutional review board of Birat eye hospital,Biratnagar, Nepal and has adhered to the tenets of the declaration of Helsinki.

Study Measurement

For every eligible patient, clinical evaluation was conducted were recorded in a database. Information collected includes the subject's age, sex, refraction, intraocular pressure (IOP) (Haag-Streit, Koeniz, Switzerland) and central corneal thickness (Ocuscan Pachymeter, Alcon, USA). Furthermore, the medical, ocular, surgical, and medication histories of the subjects were obtained from patient files and recorded. Patients with POAG were divided into two groups – nondiabetic and diabetic. Criteria for including a patient as a diabetic was defined as having nonfasting glucose levels 200 mg/dl (11.1 mmol/l) or confirmed cases usually via correspondence from general practitioners, optometrist, or previous treating ophthalmologists and using diabetic medications.Random blood sugar and HbA1C were evaluated at the time of eye examination in diabetic patients.Severity on the basis of cup-disc ratio (CDR) – meaning optic nerve head with larger cups denoting more severe form of POAG, neuro-retinal rim changes and Humphrey Visual FieldAnalysis Score (ZEISS Humphrey 750 Field Analyzer) using Parrish-Anderson andSpeath FieldDamage likelihood score staging system[21].

Statistical Analysis

Statistical analysis was performed using SPSS (version 20, SPSS Inc., Chicago.Mean, standard deviation, Linear regression models, confidence interval and estimation analyzers were used to assess the severity of POAG and correlate with CCT measurements in non-diabetic and diabetic patients.

RESULTS

Five hundred and eighty-seven patients with POAG were evaluated.

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Three hundred and thirty-seven patients had no history of diabetes and two hundred and fifty of them had diabetes.

We analyzed these groups differently to evaluate the thickness of CCT and severity of glaucoma based on visual field findings and optic nerve head- Cup to disc ratios.

The mean CCT for the group combined was 540.4±34.9 µm.

CCT AS A RISK FACTOR FOR SEVERITY OF POAG IN NON-DIABETIC PATIENTS.

The mean CCT among the patients without diabetes was 531.1±19.6µm. Our study showed that the patients with thinner corneas had more severe form of visual field defects. Patient with mild severity had mean CCT of 539.16µm (95% CI: 532.09, 546.24, P<0.05), moderate visual field changes had mean CCT of 537.16µm (95% CI: 528.57,545.75, P<0.05),) ,severe visual field changes had mean CCT of 529.18µm (95% CI 506.55, 551.81,P<0.05),) end-stage visual field changes had mean CCT of 519.30µm (95% CI 506.08, 532.53, P<0.05),) (Table1).

Table 1: Severity of VFD in patients with POAG without Diabetes mellitus and analysis with the CCT.

HUMPHREY VISUAL FIELD ANALYSIS			STATISTICS	STD.ERROR
MILD	Mean		539.16	3.562
	95% Confidence Interval for Mean	Lower Bound	532.09	
		Upper Bound	546.24	
MODERATE	Mean		537.16	4.285
	95% Confidence Interval for Mean	Lower Bound	528.57	
		Upper Bound	545.75	
SEVERE	Mean		529.18	10.674
	95% Confidence Interval for Mean	Lower Bound	506.55	
		Upper Bound	551.81	
END-STAGE	Mean		519.30	6.378
	95% Confidence Interval for Mean	Lower Bound	506.08	
		Upper Bound	532.53	

Linear regression estimator in these patients predicted that thinner CCT were likely to have more severe form of visual field changes compared to thicker CCT (p = 0.013). (Figure 1)

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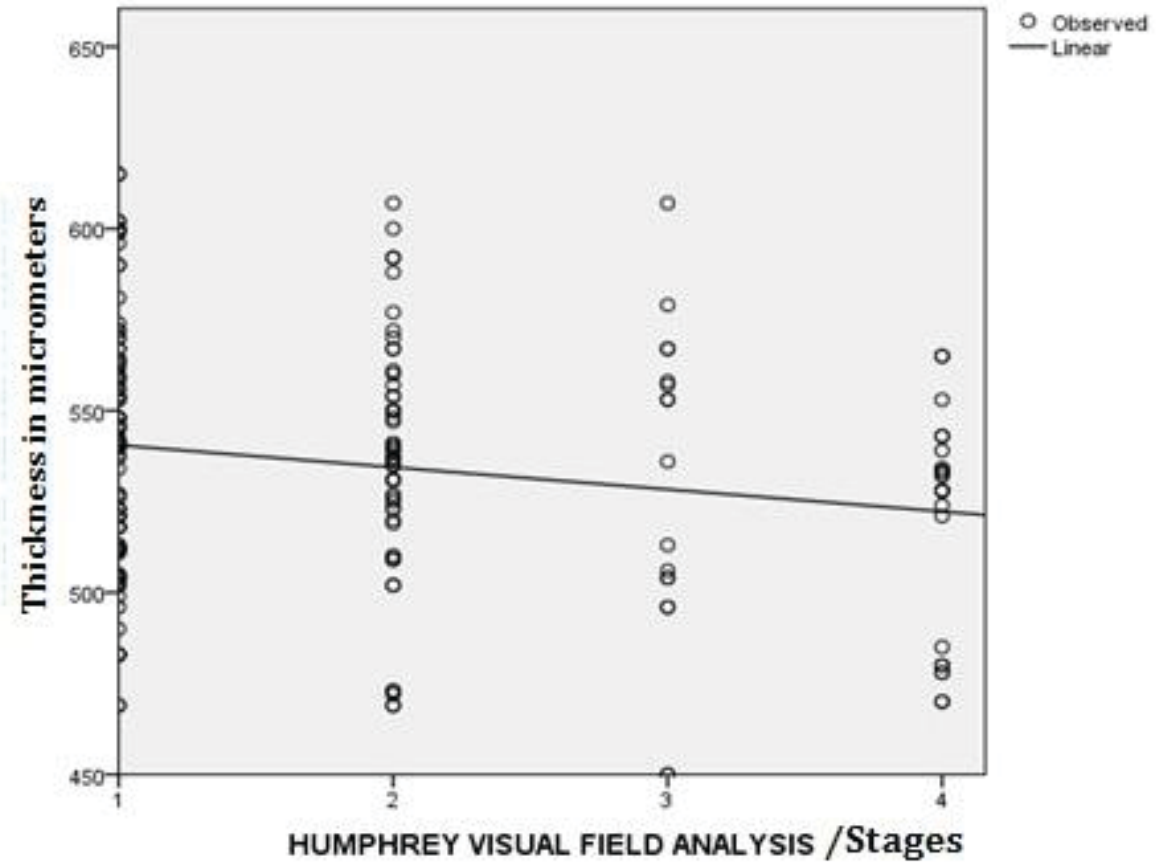

Model Summary				
R Square	F	df1	df2	Sig.
.033	6.305	1	336	0.013

Fig. 1: Severity of visual field defect and its relation with central corneal thickness in glaucoma patients without diabetes (Legend X-axis 1. Mild, 2. Moderate, 3. Severe, 4. very Severe/end stage)

We also analyzed if thinner corneas had a more severe form of glaucomatous optic disc changes in term of cup disc ratios. Linear regression estimator showed that thinner CCT also had a more severe form of optic disc changes compared to thicker CCT ($p = 0.037$). (Figure 2)

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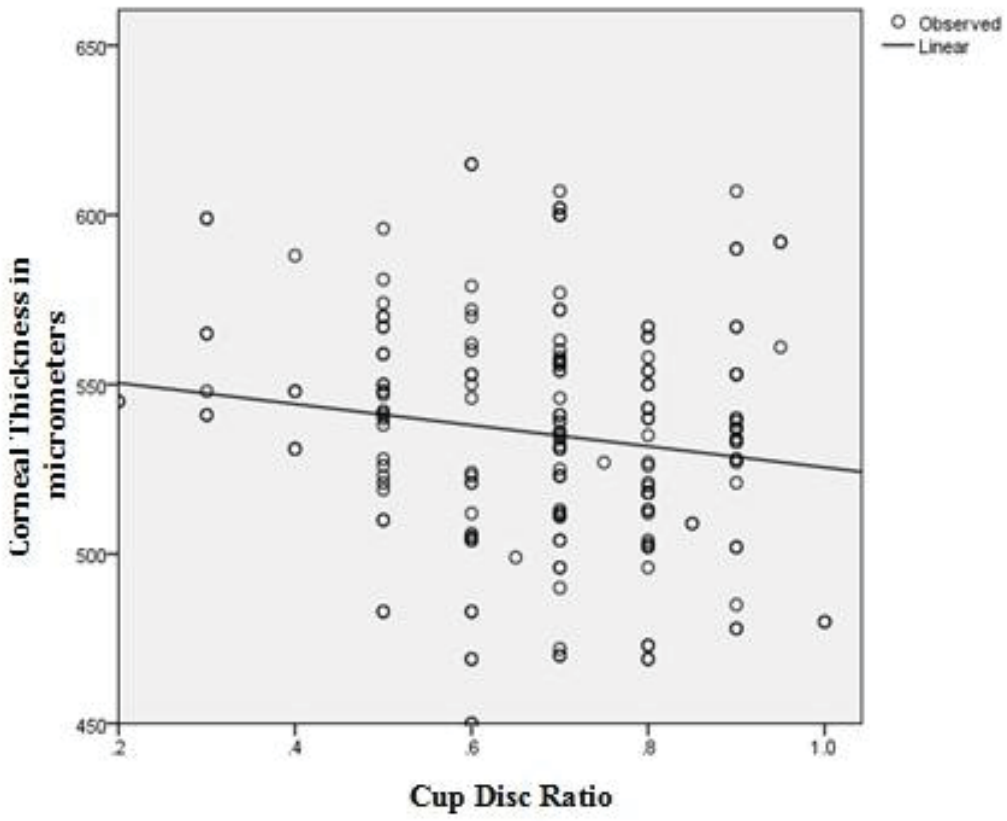

Model Summary				
R Square	F	df1	df2	Sig.
.023	4.417	1	336	0.037

Fig. 2: Severity of optic disc changes and its relation with central corneal thickness in glaucoma patients without diabetes.

CCT IN POAG PATIENTS WITH DIABETES AND ITS PREDICTIVE VALUE

Two hundred and fifty patients with POAG and diabetes were evaluated for their CCT and its correlation with severity. This group of patients had a mean corneal thickness of 549±20.2µm.

The details of the findings are illustrated in Table 2. CCT and visual field changes did not seem to agree with the general consensus.

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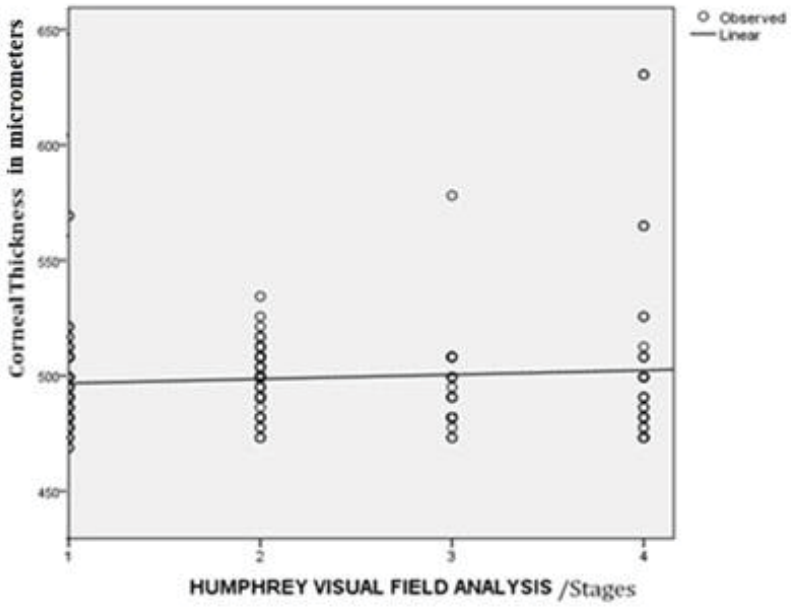
Table 2: Severity of VFD in patients with POAG with Diabetes mellitus and analysis with the CCT

HUMPHREY VISUAL FIELD ANALYSIS			STATISTICS	STD.ERROR
MILD	Mean		535.50	4.26
	95% Confidence Interval for Mean	Lower Bound	519.68	
		Upper Bound	551.32	
MODERATE	Mean		555.93	5.85
	95% Confidence Interval for Mean	Lower Bound	542.38	
		Upper Bound	569.48	
SEVERE	Mean		561.00	11.9
	95% Confidence Interval for Mean	Lower Bound	491.95	
		Upper Bound	574.85	
END-STAGE	Mean		545.00	7.83
	95% Confidence Interval for Mean	Lower Bound	518.84	
		Upper Bound	551.91	

We also analyzed if CCT in diabetic patients followed the general agreement that thinner corneas have a more severe form of glaucomatous visual field and optic disc changes. Linear regression estimator of both the parameters failed to agree with the expected relationship.(Figure 3 and Figure 4) Both demonstatedthat CCT had poor predictive value for severity of POAG in diabetic patients - p = 0.640 and p = 0.826 respectively.



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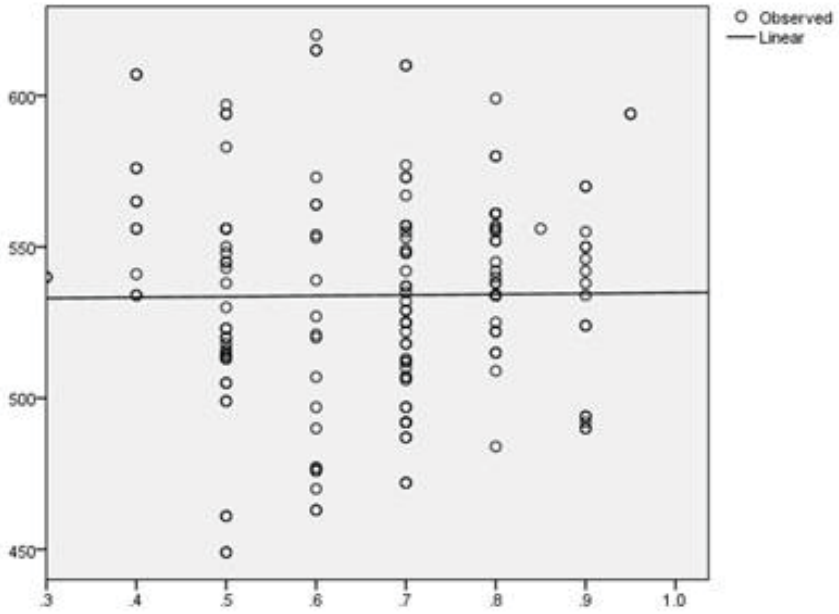
Model Summary				
R Square	F	df1	df2	Sig.
.008	.224	1	249	0.640

Fig. 3: Severity of visual field changes and its relation with central corneal thickness in glaucoma patients with diabetes (Legend X-axis 1. Mild, 2. Moderate, 3. Severe, 4. very Severe/end stage)



Model Summary				
R Square	F	df1	df2	Sig.
.002	.051	1	249	.824

Fig. 4: Severity of optic disc changes and its relation with central corneal thickness in glaucoma patients with diabetes.

Comparison of severity predictability of CCT in POAG patients with and without diabetes.

Using the linear regression values, we categorized the patients with diabetes according to their HbA1c levels and evaluated the mean CCT in each of the group. The mean resultant CCT was used as a comparison parameter among two groups to determine what severity it corresponded to (Table 3).The CCT was found to be thicker in diabetic with higher HbA1c levels and found to be not correlating to expected outcomes. CCT of 528.75 microns in diabetic patient was corresponding to a milder form of POAG while a patient without diabetes with similar value of CCT were found to have more severe form of POAG.

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Table 3: CCT correspondence compared among non diabetic and diabetic patients on severity of POAG.

HbA1c Levels(gram %)(only for Diabetic Group)	6-6.4	6.5-6.9	7-7.4
Average CCT In Diabetic Group (µm) (Corresponding CCT) (95% CI, p<0.05)	528.75±11.8µm	547.1±19.5µm	565.7±27.2µm
Visual Field Defect for Corresponding CCT for Diabetic Group	Mild	Mod- Severe	Mod- Severe
VFD for Corresponding CCT for Non - Diabetic Group	Severe	Mod-Mild	Mild
CDR for Corresponding CCT for Diabetic Group	0.61	0.58	0.64
CDR for Corresponding CCT for Non- Diabetic Group	0.98	0.88	0.82

DISCUSSION

It is a very well established finding that POAG patients with advanced disease have significantly thinner corneas. This has been recorded in many studies.[8,22,23] The inverse correlation between CCT and VF stage underlines the importance of taking into consideration the corneal thickness in the long-term strategy of treatment of POAG.[24,25] Various studies have also evaluated that thinner CCT is associated with more profound optic disc changes [26,27]

However, it is now known from various studies that the patients with diabetes have thicker corneas.[16, 24] Endothelium pump dysfunction or increased deposition of glycosaminoglycan in the cornealstroma or both are some of the many proposed mechanisms.This could mean that CCT measurements can be confounded and hence cause it loses its predictability value in detecting the severity of POAG.

We evaluated if the CCT still retains its predictability as a risk factor and severity in POAG patients with diabetes. To our knowledge, various studies have evaluated and established the fact that patients with diabetes have thicker corneas but none has evaluated if this correlation confounds the predictive value of CCT of POAG patients with diabetes. Our study supports the expected outcome/ finding cased on CCT in POAG patients without diabetes that thinner corneas are at higher risk of having more severe form of POAG>.

However, the CCT measurements did not correlate with severity of POAG patients with diabetes. Our study showed that the CCT was unreliable marker in diabetic patients and tends to lose its predictability value on severity. This is possibly due to the endothelial pump dysfunction, stromal swelling due to higher glucose level and deposition of glycosaminoglycans as mentioned earlier. Patients with diabetes failed to show a correlation of severity of POAG in terms of both visual field changes and optic disc changes with their corresponding CCT. The severity of POAG which would have been normally been expected/ obtained for a particular CCT reading showed significant deviation. This denotes that CCT is greatly influenced by hyperglycemic state and while measuring a CCT as a risk factor or a predictor for severity, history of diabetes, duration and status of glycemic control must be taken into consideration.

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CONCLUSION

CCT values may not retain its predictive value for a risk factor/severityof POAG in patients with diabetes. Hence, CCT alone may not be a reliable marker and mislead treating physicians. Diabetes should always be ruled out and a meticulous examination of both visual field changes and optic nerve head changes should be done irrespective of the CCT measurements in patients with diabetes.

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The profile of thyroid disorders in patients attending a tertiary care hospital in Pokhara, Nepal

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Abstract

Background: The profile of thyroid disorder has been reported with limited evidence in Nepal. The aim of this study was to examine the profile and incidence of different types of thyroid disorder in patients attending a hospital appointment in Western Nepal and identify factors associated with it.

Method: This was a hospital-based study. A total of 1000 patients attending the department of medicine at Gandaki Medical College, Teaching Hospital and Diabetes, Thyroid and Endocrinology Care Centre, Pokhara for thyroid examination were recruited. Thyroid disorders were classified as hypothyroidism, hyperthyroidism, T4-thyrotoxicosis including their sub types where applicable. **Results:** Nearly 33% of the participants were found to have some form of thyroid disorders. Majority of the patients with thyroid disorder were females (87%). Hypothyroidism was found to be the most common type of thyroid disorder (57.5%) followed by hyperthyroidism (37.5%) and secondary hyperthyroidism (5.0%). BMI was found to be independently associated with hyperthyroidism on regression model. **Conclusion:** Hypothyroidism was found to be the most common thyroid disorder followed by hyperthyroidism. The findings highlight that thyroid disorder is a significant clinical burden and a major public health concern in Western Nepal. The findings also emphasize a need to roll out thyroid screening programmes in the general population so that this condition can be identified and treated early.

Key Words: Hypothyroidism, Hyperthyroidism, Thyroid Disorder

INTRODUCTION

It is a widely known fact that thyroid gland produces two hormones, namely triiodothyronine (T3) and thyroxine (T4) [1], which are essential for our health and wellbeing; they play a vital role in growth, neuronal development, reproduction, and regulation of energy metabolism in our body[2]. The activities of our thyroid gland is regulated by Thyroid Stimulating Hormone (TSH) which is produced by the anterior pituitary gland. British Thyroid Foundation[3] has outlined the normal levels of these thyroid hormones as following; TSH 0.4-4.0 milliunits per litre, FT4 9.0-25.0 picomoles per litre, FT3 3.5-7.8 picomoles per litre. However, the units and cut off criteria vary widely between different countries and clinical practices.

Hypothyroidism and hyperthyroidism are the two most common types of thyroid disorders reported in the literature [4,5]. In hypothyroidism, the thyroid gland is underactive, as a consequence of which it cannot produce enough hormones. Usually increased TSH level and decreased T4/T3level indicates that thyroid gland may be under-active. Hypothyroidism is often caused by the Hashimoto's disease [6], which is also called chronic autoimmune lymphocytic thyroiditis. Fatigue, memory problems, constipation, depression, weight gain, weakness, slow heart rate are some of the common symptoms associated with hypothyroidism. In contrary, in hyperthyroidism the thyroid gland is overactive and produces excessive hormones; increased T4/T3 and decreased TSH levels indicate that thyroid gland may be overactive. Graves' disease is the

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most common cause of hyperthyroidism[7], affecting about 70% of people with an overactive thyroid gland. Restlessness, nervousness, racing heart, irritability, increased sweating, shaking, anxiety, trouble sleeping are some of the common symptoms associated with hyperthyroidism.

Other types of thyroid-related disorders include T4 thyrotoxicosis (increased level of T4 hormone, TSH of normal level), sub-clinical hyperthyroidism (decreased TSH level, T4/T3 of normal level), sub-clinical hypothyroidism (increased TSH level, T4/T3 normal level), secondary hypothyroidism (decreased TSH, T4, T3 hormone levels), and secondary hyperthyroidism (decreased TSH, T4, T3 levels).

Prevalence of thyroid disorder is a much debated research topic. Inconsistency across studies in the definition of thyroid disorder, participant selection criteria, environmental and geographical factors, and different techniques and criteria used for assessment of thyroid functions are some of the major factors identified to contribute towards this debate[7].This is further complicated by social stigmas and lack of awareness associated with thyroid disorders due to which people may feel hesitant to visit a doctor specially in countries where health literacy rate is lower[8]. It is possible that prevalence of thyroid disorder in the literature is often underestimated.

A recent study from Australia reported the prevalence of 0.3% for both clinical and subclinical hyperthyroidismin general population[9]. In 2002, United States National Health and Nutrition Examination Survey (NHANES III) found the prevalence of hyperthyroidism and subclinical hyperthyroidism in general population to be 0.5% and 0.7%, respectively[10]. A meta-analysis of studies from European countries showed the mean prevalence rate of 0.75% for males and females combined and an incidence rate of 51 cases of thyroid disorder per 100,000 per year[11]. A UK-based longitudinal study found an incidence of thyroid disorder of 80 cases per 100,000 women per year [12]. Also, a higher prevalence of hyperthyroidism has been found in iodine-deficient countries [13].

In Nepal the profile of thyroid disorder has been reported with limited evidence. A recent study by Gupta et al[14] found the prevalence of thyroid disorder in Achham district hospital to be 17.11% (range, 14%-o 20%), of which hypothyroidism was most common followed by hyperthyroidism. Also females were found to disproportionately have higher prevalence of thyroid disorder compared to men (14.7% vs. 2.4%). Another study from Eastern Nepal showed that chronic iodine deficiency persisted in a small fraction of pregnant women, and that the mild thyroid dysfunction was also common in these women [15]. Khatiwada et al[16] reported that thyroid dysfunction was widely common co-morbid condition (38.6%) in patients with chronic kidney disease. Another study showed that 3.2% of the school age children have thyroid dysfunction in Eastern Nepal [17]. To our knowledge there are no studies from Western Nepal that have examined the profile of thyroid disorders, which this study examined. In addition to examining the profile, we also fitted regression models to identify which factors (age, gender, BMI, pulse, blood pressure) were associated with thyroid disorder independently.

METHODS

Study type: This was a hospital-based retrospective study of case-control design. Most of the data were collected at the outpatient department of Gandaki Medical College and Teaching Hospital, Pokhara The study protocol was approved by the Institutional Review Board of the same institute.

Inclusion criteria: (i). Patients attending the Outpatient Department of Gandaki Medical College and Teaching Hospital and Diabetes, Thyroid and Endocrine Care Centre to be evaluated for the thyroid function tests or thyroid disorders; (ii). Patients able to provide informed consent for taking part in the study

Exclusion criteria: (i). Patients not wanting their

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medical records to be included in the study; (ii). Patients with incomplete data.

In total, 1000 patients examined from May 2016 to April 2018 were recruited retrospectively. Using our previous (unpublished) data, and to attain a power of 80% with a precision error and type 1(α) error of 5% each, the required sample size was calculated to be 965. A slightly greater number (n=1000) has been used in this study.

Patients were briefed during their visit that their data could be used to report in scientific journals but they will remain anonymous. All data were handled with applicable ethical guidelines, and followed the tenants of Helsinki Declaration. The reporting follow the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guidelines [18].

The patient data were collected by reviewing their medical files by the same author (TU), who is also the consultant endocrinologist at, both, the Gandaki Medical College and Teaching Hospital, and the Diabetes, Thyroid, and Endocrinology Care Centre, Pokhara Nepal. The main variables collected were age, T3, T4, TSH, random blood sugar, systolic and diastolic blood pressure, pulse rate and Body Mass Index (BMI) for each participant. Lab tests were done at either one or the other of the two institutes with which the first author (TU) is affiliated to by certified professionals. Data entry was double checked before processing and analyses.FT3 level of 2.27-4.55 picomoles/litre, FT4 level of 0.65-1.74 picomole/litre and TSH level of 0.35-5.29 millinternational units/litre were considered normal levels. The following criteria were used to classify thyroid disorders: t3,t4 normal and high level of TSH-subclinical hypothyroidism; low TSH with normal t3,t4 levels-subclinical hyperthyroidism; high t4 but normal TSH and t3 levels- thyrotoxicosis; high t4,t3 and TSH levels-secondary hyperthyroidism; low t3, t4, and TSH-secondary hypothyroidism; low t3,t4 but high TSH levels-primary hypothyroidism.

Data were analysed using Statistical Package for the Social Sciences (SPSS, version 24). No data were excluded from the analyses. Data of continuous variables were normally distributed (Levene's test, $p>0.05$). Independent t-tests was used to compare between any two variables between the participant groups (i.e., with thyroid disorder vs. normal). Multiple linear regression models were fitted to identify which of the variables (age, BP, BMI, pulse, etc.) were independently associated with different thyroid disorders.

RESULTS

Mean, standard deviation and standard error for participants with some form of thyroid disorder and normal participants is provided in Table 1. Out of the total 1000 participants, 339 (33.9%) had some form of thyroid disorder. As expected participant groups (normal vs. thyroid disorder) differed significantly in age, T3, T4, TSH and pulse levels ($p\leq0.02$). Surprisingly, diastolic blood pressure (but not the systolic blood pressure) was also found to differ significantly between the participant groups. Since the aim of the study was to examine the profile of patients with thyroid disorder, the subsequent analyses do not include data from normal participants.

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Table 1. Mean, standard deviation, and standard error for the variables examined for participants with and without thyroid disorders. Comparisons between participant groups were done using independent samples t-tests. * indicates significant p-values.

Variable	Participant group	Mean value	Standard Deviation	Standard Error Mean	p-values
Age (years)	With thyroid disorder	42.93	11.89	0.68	0.02*
	Normals	44.72	12.26	0.50	
T3 (pg/ml)	With thyroid disorder	3.20	1.94	0.12	<0.001*
	Normals	2.95	0.41	0.02	
T4 (ng/dl)	With thyroid disorder	3.83	5.58	0.34	<0.001*
	Normals	1.19	0.33	0.01	
TSH (mlu/ml)	With thyroid disorder	8.07	9.75	0.46	<0.001*
	Normals	2.67	1.39	0.06	
FBS (mg/DL)	With thyroid disorder	105.51	36.05	2.16	0.97
	Normals	106.05	36.86	1.52	
BP:systole	With thyroid disorder	119.17	15.69	0.89	0.4
	Normals	119.92	16.40	0.68	
BP:Diastole	With thyroid disorder	77.11	10.87	0.61	0.04*
	Normals	78.49	9.69	0.40	
Pulse/minute	With thyroid disorder	79.46	8.05	0.46	0.009*
	Normals	78.35	7.70	0.32	
BMI (Kg/m^2	With thyroid disorder	27.17	4.95	0.28	0.97
	Normals	27.12	4.71	0.19	

Fig.1 provides a pie chart showing the incidence of each type of thyroid disorders.

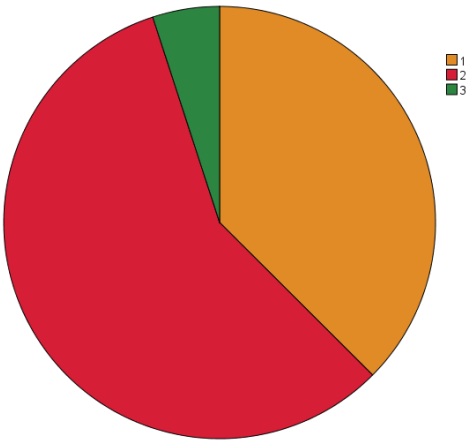

Figure 1. Pie chart showing incidence of different types of thyroid disorder.

1=Hyperthyroidism 2=Hypothyroidism 3=secondary hyperthyroidism.

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Hypothyroidism was found to be most prevalent, wherein primary hypothyroidism and subclinical hypothyroidism (not shown separately in the pie chart) together accounted for 57.5% of the total cases of thyroid disorder. There is a wealth of evidence to suggest that hypothyroidism is the most common type of thyroid disorder. Hyperthyroidism was found in 37.5% of the participants of which 21.8% had presented with clinical findings suggestive of thyrotoxicosis. Secondary hyperthyroidism was the least common type of thyroid disorder identified (5.0%).

Next, we examined which of the variables such as age, BMI, pulse, BP, and FBS for independently predicted hypothyroidism (n=195), hyperthyroidism (n = 127) and secondary hyperthyroidism (n = 17) by using multiple regression models in SPSS. Overall, the regression model did not statistically significantly predict hypothyroidism, $F(6, 188) = 1.31$, $p = 0.25$, $R2 = 0.04$. None of these variables studied added statistically significantly to the prediction of hypothyroidism. Also, the regression model did not statistically significantly predict hyperthyroidism, $F(6, 120) = 0.99$, $p = 0.43$, $R2 = 0.05$. None of the variables except BMI ($p=0.05$) added statistically significantly to the prediction of hyperthyroidism. For secondary hyperthyroidism, although the regression model overall statistically significantly predicted the condition, $F(6,16) = 3.40$, $p = 0.04$, $R2 = 0.67$, none of the variables studied individually added statistically significantly to the prediction of secondary hyperthyroidism except diastolic BP ($p = 0.01$).The results suggest that measurements of BMI and diastolic BP are important parameters in predicting patients at risk of developing thyroid disorders (in particular in those with hyperthyroidism and secondary hyperthyroidism respectively) and may be considered adjunctive entities in screening for thyroid diseases.

[1]As female gender is widely known as an independent risk factors of thyroid disorder we did not use that variable to fit regression models.

DISCUSSION

In this study we examined the profile of different types of thyroid disorders encountered in patients attending a tertiary care practice in Western region of Nepal (Pokhara and surrounding places). Consistent with the literature we also found that hypothyroidism was the most prevalent thyroid disorder. In the general population various studies have shown the prevalence of hypothyroidism to be as high as 10% [19-21]. The worldwide prevalence of hypothyroidism in various studies shows a very significant variation and current prevalence ranges from 1% to 20% for sub-clinical and 1-2% for overt hypothyroidism [24]. Although hypothyroidism is very common endocrine problem, but frequency and severity of the symptoms vary between individuals. Sign and symptoms reflect the numerous organ systems affected by thyroid hormones but not a single clinical manifestation specially indicates thyroid dysfunction [25]. In our study majority of the subjects are females which indicates this is the disease of the females which is also supported by other studies [26] . The prevalence of hypothyroidism in our study was followed by hyperthyroidism and secondary hyperthyroidism. Nearly 87% of those with thyroid disorder were females. Using the regression models we showed that pulse and BMI are significant parameters associated with hyperthyroidism. When compared with normal participants (i.e., those without thyroid disorders) participants with thyroid disorders were found to differ significantly not just in the level of thyroid hormones and TSH, but also in age, diastolic blood pressure and pulse rates. Indeed it has been reported that that patients with thyroid disorders have abnormal pulse rates [22].

Following limitations of our study should be noted; data were collected from patients attending a tertiary care hospital/centre so that our results may not be representative of the general population. Also, patients whose thyroid hormone levels were normal may have been on medication previously as a result of which their blood tests may have revealed normal T3, T4 or TSH levels, and hence were classified as normal. Also we did not examine

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life style factors such as the effect of smoking and co-morbid conditions like diabetes and depression. Smoking has been linked with thyroid disorder [23]. Nonetheless, our findings highlight that thyroid disorder is a significant clinical burden and a major public health concern in Western Nepal, thereby warranting a need to roll out thyroid screening programmes in the general population so that this condition can be identified and treated early. Our findings also suggest BMI which is easily measurable in the community may be useful additional tools for screening patients with thyroid disorders, particularly hyperthyroidism.

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CASE REPORT OPEN ACCESS

TYPE 1 DIABETES MELLITUS PRESENTING AS DISTAL RENAL TUBULAR ACIDOSIS (RTA TYPE 1)

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Abstract

Background: Type 1 Diabetes Mellitus (DM) is an autoimmune process which causes destruction of b-cells and absolute insulin deficiency. This insulin deficiency prone patient to hyperglycemia and resultant early micro-vascular and macro-vascular complications. Macro-vascular complication seen early in diabetes are CAD, CVA and PAD. In micro-vascular complications, we have retinopathy, neuropathy and nephropathy. In diabetic nephropathy, usually glomerular injury is widely described in literature but little is known about the tubular changes. We report a case which has tubular damage in the form of distal tubular damage causing renal tubular acidosis. Patient has classical bilateral nephrocalcinosis, normal anion gap acidosis and persistently low HCO3. This entity in type 1 DM is not reported in literature. **Case :** Patient S, 42 yr Male with Type 1 DM for 15 years on Inj. Insulin mixtard presented to emergency with swelling of bilateral lower limb associated with pain/tingling and numbness for 3 months. **Conclusion:** In a patient with type 1 DM, acidosis can occur due to causes other than DKA and workup should be done if acidosis persists even after treatment.

Abbreviations: DM(diabetes mellitus), HCO3(bicarbonate), RTA(renal tubular acidosis), CAD(coronary artery disease), CVA(cerebrovascular accident), PAD(peripheral artery disease).DKA(diabetic ketoacidosis)

INTRODUCTION

Type 1 Diabetes Mellitus (DM) is usually an auto-immune[1] process in which there is an immunological destruction of beta(β) cell which causes absolute insulin deficiency. In absence of insulin deficiency, there is lactic acidosis which is a high anion gap metabolic acidosis. Patient with type 1DM generally presents with DKA (Diabetic keto-Acidosis) in which acidosis is due to high ketones in body. We present a case which has normal anion gap acidosis in type 1 DM with uncontrolled hyperglycemia. Distal RTA commonly occur in condition like amyloidosis, Sjogren syndrome, SLE (Systemic Lupus Erythematosus) and Sickle cell diseases. Distal RTA presents as nephrocalcinosis, normal anion gap with hyperchloremic acidosis which occurs due to inability of distal convoluted tubule to produce hydrogen(H+) ions[2]. This in turn, leads to loss of H+ ions and subsequently loss of potassium(K) in the body causing hypokalemia and alkaline urine. This alkaline in urine causes precipitation of calcium stones in urine and patient presents as asymptomatic/ symptomatic nephrolithiasis.

CASE REPORT

Patient S, 42yr Male with Type 1 DM for 15 years on Inj. Insulin mixtard presented to emergency with swelling of bilateral lower limb associated with pain/tingling and numbness for 3 months. Swelling in bilateral lower limb was gradual, extending up to ankle. No history of pain abdomen, nausea, vomiting, chest pain, shortness of breath, syncope, palpitation, sweating, burning micturition or decreased urine output. No history of Hypertension, Tuberculosis, Asthma in past. Family history was

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also not significant. Patient left Inj. Insulin for the past 3 days due to unavailability. Patient was admitted and investigations were sent. Investigations at admissions were (Table 1):

TABLE 1

Date	**24/01/2019**	**28/01/2019**
Hemoglobin	7.49g/dl	
Total Leucocyte Count	11340/mm3	
Differential Leucocyte count	N89L5M5	
Platelets	146 lakh/mm3	
Hematocrit	23.7	
Blood Urea	81mg/dl	22mg/dl
Serum creatinine	1.96mg/dl	0.96mg/dl
Serum sodium	124mEq/l	137mEq/L
Serum K	5.5mEq/L	3.2mEq/L
Serum Chloride	98mEq/L	106mEq/L
Serum Calcium	7.6mg/dl	7.7mg/dl
Serum Phosphorus	3.9mg/dl	3.4mg/dl
Total bilirubin	0.46mg/dl	
Direct bilirubin	0.12mg/dl	
SGPT	15U/L	
SGOT	36U/L	
ALP	168U/L	
Total Protein	5.3gm/dl	
Albumin	3.2gm/dl	
Globulin	2.1gm/dl	
pH	7.32	
HCO3	11.1mEq/L	
Anion gap	11mEq/L	
RBS	High	
HbA1C	12.7	
Urine R/M	Glucose ++, protein + and ketones absent	

Patient was managed on the line of DKA with Intravenous fluids and insulin as the patient had very low bicarbonate (HCO3) and high dextrose. During 2-day course, patient ABG showed persistent low HCO3 in spite of blood sugar being controlled, so cause of persistent acidosis other than DKA was sought, urine pH was advised which came out to be 6.0.

Patient was evaluated for causes of low HCO3 with high urinary pH. USG (ultrasound) abdomen was suggestive of multiple hyperechoic calculi seen in upper pole with largest measuring 7.8mm in the right kidney. Left kidney size normal with multiple hyperechoic calculi in lower pole and posterior pole longest 9mm. Ophthalmology evaluation suggested bilateral moderate Non Proliferative Diabetic Retinopathy (NPDR). Patient repeat investigations were (Table 2):

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TABLE 2			
Date	**28/01/2019**	**30/01/2019**	**04/02/2019**
Urine pH	6.0	6.0	6.0
Urine R/M	Glucose-nil, protein-nil, ketone-nil	Protein +,glucose-nil	Proteins +, glucose - nil
pH	7.29	7.41	
HCO3	15.6mEq/L,	18.8	
Anion Gap	9mEq/L	5mEq/L	
iPTH	14.9(11-79)		

Patient had kidney stones despite serum calcium to be low. iPTH was advised due to low calcium which also lies in the lower range, ruling out secondary hyperparathyroidism. We searched literature for the same and most common cause for this presentation was distal RTA.

DISCUSSION

Type 1 DM is a chronic autoimmune disease beginning with genetic susceptibility and progressing to autoimmunity leading to destruction of β-cells. Autoantibodies against the pancreatic islet, islet cell antibodies (ICA) and Glutamic acid decarboxylase (GAD) are detected in childhood in these patient[3]. It is usually a disease of childhood/ young. According to 2009 census, 6666 of 3.4 million youth were diagnosed with type 1 diabetes for a prevalence of 1.93 per 1000. The highest prevalence of T1D was 2.55 per 1000 among white youth and the lowest was 0.35 per 1000 in American Indian youth[4].

Distal RTA is a syndrome of systemic hyperchloremic acidosis with alkaline urine pH, hypocitraturia and hypercalciuria due to reduced secretion of H+ ions by the cells of the collecting tubules[5,6]. Metabolic acidosis in distal RTA contributes as a predisposing factor to recurrent nephrolithiasis and bone loss[6]. Patients with distal RTA are unable to lower urine pH normally in the presence of systemic metabolic acidosis regardless of its severity[7].

15-30% of subjects with type 1 DM have autoimmune thyroid disease, 4–9% have celiac disease, and 0.5% have Addison's disease [3]. Distal RTA is also multifactorial, it can develop as a consequence of autoantibodies, most commonly in Sjögren's syndrome and systemic lupus erythematosus(SLE). There are various case reports which has linked distal RTA with autoimmunity and destruction of collecting ducts[8]. There are only few case reports with patients of type 1 DM developing distal RTA, in which one patient having due to autoimmune and other patient is having Sjogren syndrome[9-10] and no cause could be found in some other[11].

Our patient had all features of distal RTA in the form of nephrocalcinosis, acidic urine, low bicarbonate, metabolic acidosis which persisted even after correction of blood sugar. He had proteinuria and slightly deranged creatinine, also had retinopathy which favours nephropathy. But destruction of glomeruli alone cannot explain the development of distal RTA in our patient. Various studies previously had already shown that diabetic patients have interstitial and tubular injury along with glomerular injury[12-14].

Additional investigations in the form of kidney biopsy would be required for further confirmation of the cause of destruction of collecting ducts Tubular damage.

Distal RTA improved with alkali therapy and it also prevent the formation of renal stones. Our patient already has developed renal stones, still alkali therapy will prevent the progression of stones. We thus present a case which was unusual

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in T1D as every type 1DM doesn't have acidosis due to DKA. Also, patients with hypokalaemia and nephrocalcinosis, we should rule out causes and extensive investigations are required for confirmation of diagnosis. Further research is required in this field.

CONCLUSION

Type 1 DM patients are prone for autoimmune diseases but we should think beyond autoimmunity in type 1 DM as they may develop disease which may be complications of DM per se. Acidosis in type 1 DM is not always due to DKA and we should search for other causes of persistent acidosis.

We have taken a written consent from the patient for the publication of this case report. There is no conflict of interest between the authors. This research has not received any specific grant from any funding agency in public, commercial or not-for-profit sector.

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Non Alcoholic Fatty Liver Disease (NAFLD) and Type 2 Diabetes Mellitus

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Abstract

Background: The pandemic of obesity and type2-diabetes mellitus has led to a increasing prevalence of Non Alcoholic Fatty Liver Disease (NAFLD) globally, including developing countries. The current epidemic of NAFLD is reshaping the field of hepatology because patients with NAFLD are at increased risk for not only liver-related morbidity and mortality but also cardiovascular disease. NAFLD also increases the risk of developing diabetes. Hence patients with diabetes need to be screened for the presence of NAFLD and vice- versa. It is of paramount importance to differentiate between simple steatosis from Non Alcoholic Steatohepatitis (NASH), the later being more associated with hepatic as well as extra hepatic complications.

Key Words: Diabetes Mellitus; Liver Injury; NAFLD

Abbreviations: NAFLD= Non-Alcoholic Fatty Liver Disease; NASH= Non Alcoholic Steatohepatitis; HCC= Hepatocellular carcinoma;EASL = European Association for the Study of the Liver);AASLD = American Association for the Study of Liver Diseases;EASD = The European Association for the Study of Diabetes);EASO=European Association for the Study of Obesity ; CCL2–CCL5 = C-C chemokine receptor types 2 / type5; FXR = Farnesoid X receptor

INTRODUCTION

NAFLD is a broad spectrum of diseases consisting of patients with simple steatosis or Nonalcoholic fatty liver, Non alcoholic steato hepatitis (NASH), NASH-related cirrhosis, and NASH-related HCC. In NAFL there is ≥ 5% hepatic steatosis without significant inflammation. NASH is defined as steatosis and inflammation associated with the presence of one of the three additional features: ballooning of hepatocytes, Mallory hyaline, and fibrosis on liver histology. NASH is usually a histological diagnosis.

It is very important to differentiate between NAFLD and NASH to determine the prognosis, risk of progression, and for assessing the liver-related and cardiovascular morbidity and mortality, which occurs more frequently in patients with NASH as compared to simple steatosis.

Why should NAFLD be of interest to diabetologists?

NAFLD is strongly associated with type 2 diabetes mellitus and abdominal obesity.

NAFLD is the hepatic component of metabolic syndrome. The prevalence of NAFLD in diabetes mellitus has been reported to be 74 %[1], 57% [2] and 70% [3] in different studies. As lifestyles have become increasingly sedentary with obesity and type 2 diabetes mellitus pandemic, NAFLD is rapidly becoming the leading cause of chronic liver disease worldwide [4]. It is projected to be the principal etiology for liver transplantation within the next decade.

NAFLD is a risk factor for Type 2 Diabetes mellitus and cardiovascular disease

NAFLD is associated not only with liver-related morbidity and mortality, but also with an increased risk of developing both cardiovascular disease and type 2 diabetes mellitus [5].

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NAFLD was a significant predictor for future diabetes in a Japanese middle-aged health check population, especially in women. The relative risk of diabetes associated with fatty liver was 4.8 [95% confidence interval (CI) 3.0 -7.8, p<0.0001] in men and 14.5 (95% CI 7.0-30.1, p<0.0001) in women[6]. Current evidence shows that with resolution of fatty liver, there is a potential for decreasing risk of incident type 2 diabetes mellitus [7].

NAFLD is also significantly associated with a moderately increased cardiovascular disease risk among type 2 diabetic patients This risk is independent of other classical risk factors and only party explained by the presence of metabolic syndrome (8). In fact, patients with NAFLD are twice as likely to die of cardiovascular disease than liver disease and liver disease is only the third leading cause of death in patients with NAFLD, following cardiovascular disease and malignancy [9].

Type 2 Diabetes increases the risk of NAFLD progressions to more advanced liver disease

Type 2 diabetes mellitus is one of the strongest clinical predictors of the progression of NAFLD to NASH and cirrhosis (10). The progression of NAFLD to NASH in non-diabetic individuals occurs in about 10-20 % of NAFLD patients[11]. But the presence of Type 2 diabetes increases this risk of the progression by two- to three-fold[12]. The presence of diabetes also increased the risk for cirrhosis or hepatocellular carcinoma (HCC) among patients with NAFLD/NASH. In fact Type 2 diabetes has emerged as a significant predictor of worse outcomes in patients with NAFLD/NASH [13]. There are data to demonstrate that HCC may occur in NAFLD patients without cirrhosis[14,15]. These data emphasize the need to effectively diagnose NAFLD and early HCC in patients with obesity, metabolic syndrome and type 2 diabetes mellitus

Diagnosis of NAFLD

The diagnostic criteria of NAFLD includes hepatic steatosis by either imaging or histology, no other causes of steatosis and no significant alcohol consumption .[16]

All individuals with metabolic risk factors should be screened with ultrasonography of the liver to identify liver fat and assessment of liver enzymes. However, ultrasonography is a relatively insensitive technique for detecting liver fat. The fatty infiltration must be at least 20–30%, before ultrasonography will be able to diagnose hepatic steatosis. As an alternative, a simpler surrogate markers for diagnosing liver fat, such as the fatty liver index (a composite score derived from BMI, waist circumference, fasting triacylglycerol and γ-glutamyltransferase [GGT] concentrations) can be used as a first-line approach that also has an acceptable sensitivity and specificity for identifying liver fat [17].

For diagnosis of NAFLD, other causes of steaosis should be excluded including but not limited to increased alcohol consumption, viral hepatitis, surgical procedures, use of medications and total parenteral nutrition. There is a disagreement among different guidelines in defining the threshold for alcohol intake. According to EASL [17], significant alcohol consumption is defined as > 30 g/d in men and > 20 g/d in women. The AASLD guidance considers [18] > 21 standard drink per week in men and > 14 in women as significant. Asia-Pacific Guidelines[19] defines significant alcohol intake as > 7 standard alcoholic drinks/week (70 g ethanol) in women and > 14 (140 g) in men.

Components of the metabolic syndrome and diabetes should be screened. After making a diagnosis of NAFLD, the next step is assessment of fibrosis as the severity of fibrosis is the strongest predictor of liver-related outcome

Although histological examination of the liver is the 'gold standard' to stage NAFLD severity, it is not a feasible option due to invasiveness of the test, complications, cost involved, and poor acceptability of the patients. Hence the use of non-invasive test for detection of liver fibrosis is recommended which includes NAFLD fibrosis score, Enhanced

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Liver Fibrosis [ELF] or FIB-4 scores.

Depending on the results of these tests either follow-up at 3–5 years or specialist referral for a decision as to whether to undertake a liver biopsy, and/or initiation of therapy. Alternatively, for NAFLD patients with mild abnormalities of non-invasive fibrosis markers, further follow-up at 2 years with repeat testing is advocated [20]. The EASL–EASD–EASO guidelines recommend that all patients with elevated LFTs because of NAFLD and advanced fibrosis should be referred to a hepatologist [20].

Role of liver biopsy

Liver biopsy should be reserved for the following conditions. NAFLD patients who are at increased risk of having steato hepatitis and/or advanced fibrosis and in patients with suspected NAFLD in whom competing etiologies for hepatic steatosis and the presence and/or severity of coexisting CLDs cannot be excluded without a liver biopsy [18].

Treatment

Lifestyle changes: Lifestyle modification including diet, exercise, and weight loss has been recommended for treatment of patients with NAFLD. The recommendation is to give 500-1000 kcal energy deficit diet to induce a weight loss of 500-1000 g/week with a 7%-10% total weight loss. Dietary recommendation also involves exclusion of NAFLD-promoting components (processed food, and food and beverages high in added fructose. Weight loss has been reported to be associated with improvement in histologic features. 150-200 min/week of moderate intensity aerobic physical activities in 3-5 sessions are generally preferred (brisk walking, stationery cycling)[17]. However, lifestyle modification is difficult to achieve and to sustain

Pharmacological treatment
Whom to treat?

Drug therapy is indicated for progressive NASH (bridging fibrosis and cirrhosis) and early-stage NASH with increased risk of fibrosis progression (age >50 years; diabetes, MetS, increased ALT or active NASH with high necroinflammatory activity [17].

The recommendation of drug therapy for the treatment of NAFLD by different society are summarized in table 1.

Table 1.

Drugs	EASL	ASIA-PACIFIC	AASLD
Metformin	Insufficient evidence	Not beneficial	Not beneficial
Vitamin E	Insufficient evidence	Not beneficial	Consider use in
			non-diabetic, biopsy-
			proven NASH
PPAR-gamma agonists	Consider use in selected	Insufficient evidence	Pioglitazone indicated
	diabetic patients	in Asian	in biopsy-proven
			NASH (regardless of
			diabetes)
UDCA	Not beneficial	Not mentioned	Not beneficial
Silymarin	Not mentioned	Insufficient evidence,	Not mentioned
		potentially useful	
Statins	Safe but not beneficial	Safe but not beneficial	Safe but not beneficial

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Future pharmacological options of NASH

Gut microbiome

NAFLD is associated with increased gut permeability and transportation of gut metabolites and bacterial products into the portal circulation.

An increased lipopolysaccharide levels in the circulation occurs, which binds to the monocyte differentiation antigen (CD14)-TLR-4 complex triggering an inflammatory reaction and insulin resistance. The gut microbiota is also involved in choline metabolism by converting it into toxic dimethylamine and trimethylamine, which are transported to liver and converted into trimethylamine oxide (TMAO) that causes liver inflammation and damage [21].

Changing the gut mocrobiota may be a treatment option in NAFLD. Solithromycin, a macrolide antibiotic with anti-inflammatory properties,was found to improve NASH in animal studies and is currently being studied in a phase 2 clinical trial [22].

Antiobesity medications

Orlistat is a gut lipase inhibitor which decreases the absorption of dietary fats. A small pilot study demonstrated reduction in hepatic steatosis associated with Orlistat–induced weight loss[23]. However, it is not currently recommended as a treatment for NAFLD, but can be prescribed as an adjunct medication to help with weight loss in the NAFLD patients [24].

Peroxisome proliferator-activator receptors (PPARs)

PPARs are nuclear receptors that bind fatty acids and fatty acid derivatives to regulate a number of metabolic processes. The three PPAR agonist considered for use in NAFLD are Elafibranor (dual PPAR α/δ agonist) Pioglitazone (PPARγ agonist), and Saroglitazar (dual PPAR α/γ agonist).

Elafibranor has been shown to improve peripheral tissue insulin sensitivity and reduce alanine aminotransferase (ALT) levels in patients with metabolic syndrome [25]. A phase 3 trial using elafibrinor versus placebo for 72 weeks is currently ongoing for the treatment of NASH. (NCT02704403).

PPARγ agonists like thiazolidinediones are used in the treatment of diabetes and demonstrated to be effective in NASH [26]. However, undesirable side effects and the possible need for long-term therapy have limited widespread acceptance.

Saroglitazar is a dual PPARα/γ agonists which combines the beneficial effects of activating both PPAR receptors. It has been shown to improve diabetic dyslipidemia [27] and is currently approved in India for this indication. A retrospective study of NAFLD patients with dyslipidemia treated with saroglitazar for 24 weeks demonstrated a significant decrease in ALT compared with baseline[28]. A phase 3 trial is currently ongoing in India to assess the effect of saroglitazar versus placebo for 52 weeks in biopsy proven noncirrhotic NASH (Clinical Trials Registry-India CTRI/2015/10/006236).

Farnesoid X receptor agonist

Bile acids can negatively regulate bile acid synthesis, decrease hepatic gluconeogenesis, and lipogenesis through interaction with their intracellular receptor, the farnesoid X receptor (FXR).

A synthetic bile acid agonist of FXR, obeticholic acid (OCA) was evaluated in a phase 2b clinical trial (FLINT) which included biopsy-proven noncirrhotic NASH patients who were randomized to OCA 25 mg/day versus placebo for 72 weeks [29]. This important study established the role of FXR in NASH by showing that the FXR bile acid agonist OCA improved histological features of NASH. Histological improvement, with no worsening of fibrosis was demonstrated in a significant study participants on OCA as compared to placebo (45% vs 21%, P = 0.0002). and decrease in fibrosis score was also significant. A phase 3 trial to compare the effectiveness of OCA versus placebo for noncirrhotic biopsy-proven NASH is currently ongoing (NCT02548351).

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Incretins, dipeptidyl peptidase-4 inhibitors and sodium–glucose cotransporter 2 inhibitors.

Glucagon-like peptide GLP-1 receptor agonists or incretin mimetics, liraglutide was investigated in a phase 2 trial for its effectiveness in biopsy proven NASH[30]. This important study (LEAN trial) established the utility of GLP-1 pathway in NASH by demonstrating that the long-acting GLP-1 analogue, liraglutide, led to histological resolution of NASH. The primary end point of histological resolution of NASH without worsening of fibrosis was reached by 39% of study participants on liraglutide versus 9% on placebo (P = 0.02).

Cenicriviroc

Cenicriviroc is an an oral antagonist of the CCL2–CCL5 receptor, A phase 2b trial (CENTAUR) is investigating the effect of 2 years of cenicriviro or placebo on noncirrhotic NASH and liver fibrosis in patients with T2DM or metabolic syndrome (NCT02217475). Interim analysis at year 1 of the CENTAUR study, showed significant improvement in fibrosis and no worsening of stetaohepatitis as compared to placebo[31].

CONCLUSION

NASH is become a leading cause for chronic liver disease worldwide due to the pandemic of diabetes mellitus and obesity. NAFLD and especially NASH also confer an independent risk of adverse cardiovascular events in affected individuals beyond that conferred by the shared risk factors. Hence differentiation of simple steatosis from NASH is of paramount importance along with the staging of fibrosis of liver.

Currently, a number of drugs are undergoing pivotal trails as potential therapy for NASH. The first effective drug to be approved for treatment of NASH is anticipated to be available by 2020.

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The entire manuscript must be typed on one side of standard A4 size paper with a minimum side of 2.5 cm margin all around and double spaced.

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