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Principal Contact

Dr. Robin Maskey

Editor- in- Chief

Journal of Diabetes and Endocrinology Association of Nepal

Address: B.P. Koirala Institute of Health Sciences

Tel : 9852045177

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Table of Content

Young Onset Diabetes in South Asia
Jour of Diab and Endo Assoc of Nepal 2020; 4 (2): (1-3)
ISSN Print 2594-3367 ISSN Online 2631-2107

Journal of Diabetes and Endocrinology Association of Nepal

EDITORIAL OPEN ACCESS

Young Onset Diabetes in South Asia-what should we contemplate on?

Thomas N, Jebasingh K Felix
Department of Endocrinology, Diabetes and Metabolism,
Christian Medical College, Vellore, India

Introduction and Epidemiology:

Questions which concern the pathogenesis of diabetes mellitus(DM) in the Indian Subcontinent are many, owing to the high prevalence of the disease, the lower age of onset and low body mass index.[1] The foetal origins of diseases-propounded by Barker and colleagues may in part be responsible; considering that the prevalence of low birth weight(LBW) approaches a figure of 15 to 20%.[2]

A study done by our institution in Rural Tripura (adjacent to the Bangladesh border) and Arunachal Pradesh (border with China) demonstrated an unexpectedly high prevalence of DM of up to 9%.[3]

Adolescent Health and the School Going Age:

The focus on academics rather than physical activities occurs from a very early age, driven by the Indian school curricular system. SPADES, the study done among young males aged 14-17 years had shown that one fifth were having impaired fasting glycaemia and more than half of them had dyslipidemia with HDL cholesterol of <40 mg/dl.

A subsequent follow up study showed a strong correlation between maternal and children waist circumference, indicating an unhealthy phenotype. If both parents had metabolic syndrome (MS), the child is 6 times greater risk in getting MS.In addition, the relationship between the FTO SNP and waist circumference of children, indicate a partial genetic relationship in inducing MS.[4]

Correspondence Author
Prof. Nihal Thomas, Professor and Head, Unit-1, Department of Endocrinology, Diabetes and Metabolism, Christian Medical College, Vellore, India

Thrifty Genotype Hypothesis

Genome–wide association studies (GWAS) from populations in the Vellore birth cohort (VBC), currently 45 years old, had explored genetic variants that modulate birth weight and had identified variants in the ADCY5 (Adenyl Cyclase 5) and CCNL1(Cyclin L1)locus.This differential effect compared to Western population suggest that there could be other genetic variants influencing birth weight in Indians that are responsible for this "negating" effect.[5]

Thrifty Phenotype Hypothesis

Insulin resistance (IR) in itself is more prevalent in South Asian youth.We found that LBW adult males(N-60)were shorter in height and lighter in body weight compared to their NBW counterparts(N-60).Moreover, the LBW individuals had lower lean body mass and total body lean mass and lower bone mineral content.Interestingly, 8% of the LBW individuals had impaired glucose tolerance.However, this was not reflected in the 'm' values(measure of insulin sensitivity)- that were obtained from the hyperinsulinemic euglycemic clamp studies(HEC),who were all associated with a low median BMI(19.5kg/m2) in both LBW and NBW groups.

The parents of LBW subjects were shorter than NBW subjects,suggesting an intergenerational influence on birth weight.The LBW group had greater Fat mass (FM)/fat free mass(FFM) and FM/body weight that reduced following a 45-minute exercise intervention for 6 weeks on a bicycle. However, there was no difference in ectopic fat storage(assessed using NMR spectroscopy) between the groups.Hence, it would be fair to consider a unifying hypothesis linking the thrifty genotype and phenotype hypothesis explain an increase in young onset diabetes. [6]

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Jour of Diab and Endo Assoc of Nepal 2020; 4 (2): (1-3)
ISSN Print 2594-3367 ISSN Online 2631-2107

Journal of Diabetes and Endocrinology Association of Nepal

EDITORIAL

Mendelian Disorders

We examined Mendelian disease as a harbinger of the epidemic of diabetes in India.Genetic testing to identify mutations in a comprehensive panel of ten MODY genes was carried out in 80 subjects with young onset diabetes.A novel multiplex polymerase chain reaction(PCR) based target enrichment was established,followed by Next Generation Sequencing(NGS)on the Ion Torrent Personal Genome Machine(PGM) that was confirmed by Sanger sequencing.We identified mutations in 11(19%) of the 56 clinically diagnosed MODY subjects and seven of these mutations were novel.This was the first report of PDX1, HNF1B, NEUROD1 and PAX4 mutations from India.We identified a higher frequency and novel Digenic mutation patterns involving NEUROD1 and PDX1. Subsequent work has shown that MODY 1, 2 and 3 are the more common forms,MODY 4, 6 and 13are commoner.[7]

Young pregnant insulin requiring women also showed up to eighteen percent positive for MODY. Mutations for PDX1, NeuroD1, HNF1a, BLK, INS, ABCC8 and GCK were detected in this population.

Summarizing, NGS is the modality of choice for profiling young onset diabetes, MODY, mitochondrial, syndromic and neonatal diabetes. At present CMC has a single library preparation handling 62 genes,cost-effectively.

HIV/AIDS Syndrome

Acquired lipodystrophy in the young could be due to HIV/AIDS, wherein highly active antiretroviral therapy (HAART) precipitates this disorder.We studied male subjects with HIV aged between 25-50 years of age,comparing the body composition using DXA scans and metabolic parameters of those who had received HAART versus HAART naive, and with those who were HIV- negative.[8]

Fibrocalcific Pancreatic Diabetes Mellitus

FCPD is a condition wherein individuals present in the first decade of life with abdominal pain, steathorrea in the second decade of life and diabetes mellitus in the third decade and thought to be seen in tropical regions. The pre-diabetic phase characterized by chronic pancreatitis and steathorrea is called tropical chronic pancreatitis (TCP).

Using Indirect Calorinetry, we determined the Resting Energy Expenditure(REE) in subjects with FCPD and demonstrated that these subjects had higher REE.These subjects need dietary requirement exceeding 2500 to 3500 kcal accounting other factors.They had lower carbohydrate and thiamine intake when compared to T1DM subjects,but higher fat intake.In addition,these subjects have lowered bone mineral density(BMD)and was inversely related to stool fat excretion. HEC and intravenous glucose tolerance tests(IVGTT) along with oral glucose tolerance tests (OGTT) in those subjects showed a profound deficiency of insulin secretion.[9]

We discovered a paradoxical elevation in glucagon levels in those with FCPD.Based on this we subsequently proceeded to do OGTT and isoglycemic intravenous glucose infusion (IIGI) to measure other pancreatic endocrine hormones. Despite high GLP-1,the incretin effect is lost, suggesting incretin resistance.(unpublished data).

Ketosis Prone Diabetes (KPD/Flatbush Diabetes)

We noticed a number of patients who had DM of fulminant onset in youth age who were GAD antibody negative(GAD). We followed patients who were GAD+ve versus those who were GAD-ve, who had DKA over a period of a year.It was found that patients who were GAD-ve, a decline in insulin requirements occurred and all subjects were managed entirely on oral antidiabetic agents/ nutritional medical therapy.We concluded, for the first time that KPD occurs in Asian Indians.[10]

'Malnutrition Modulated Diabetes' (MMD)

This condition was characterized in the 1960s and included: diabetes with fasting glucose > 200mg/dl, onset <30 years age, leanness (BMI<18kg/m2), absence of DKA on insulin withdrawal, poor socioeconomic status, rural

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ISSN Print 2594-3367 ISSN Online 2631-2107
Journal of Diabetes and Endocrinology Association of Nepal
EDITORIAL OPEN ACCESS

origin and insulin requirement of >60 units a day with no radiographic features of FCPD or exocrine dysfunction.

We performed advanced pancreatic HEC,IC and D2G measurements to quantify hepatic glucose output. All patients had a normal MRI abdomen, GAD-ve and were MODY genetics negative. Patients were found to be insulinopaenic; there was no exaggerated response of glucagon production. Hepatic IR was comparable to those with Type 1 diabetes.[11]

Summary and Unifying Algorithm

In summary,multiple factors are responsible for young onset and low BMI related diabetes mellitus in India.In South Asia, one should consider LBW, FCPD, lipodystrophy,mitochondrial diabetes, MODY, KPD, MMD and the HIV- AIDS syndrome on HAART in diabetes in the young.

A proper evaluation involves a detailed history,pedigree charting,proper physical examination for syndromic features, C-peptide levels (fasting and postprandial),imaging of the pancreas,HOMA-IR and DXA where relevant and longitudinal Beta cell monitoring(for KPD). Quaternary facilities are required for genetics including NGS,Sanger sequencing and multiple ligation probe dependent amplification for deletions and insertions. This comprehensive algorithm will help in clenching the diagnosis and few patients will labelled as unclassified, that needs further research.

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Journal of Diabetes and Endocrinology Association of Nepal

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A study of levothyroxine substitution therapy on subclinical hypothyroid patients and its effects on lipid profile in the department of medicine at tertiary care hospital

Raut B[1], Paudel N[2], Bhosekar N[3]

[1]Department of Pharmacology, Kathmandu Medical College and Teaching Hospital (KMCTH), Duwakot, Bhaktapur, Nepal. [2]Department of Internal Medicine, Kathmandu Medical College and Teaching Hospital (KMCTH), Sinamangal, Kathmandu, Nepal. [3]Department of Pharmacology, Kathmandu Medical College and Teaching Hospital (KMCTH), Duwakot, Bhaktapur, Nepal.

Abstract

Background: Subclinical hypothyroidism is represented by high serum thyroid stimulating hormone (TSH) and normal serum free T4 and T3, Recent studies on subclinical hypothyroidism and lipid profile indicates that the serum total cholesterol, LDL-C, and total triglycerides were significantly increased. Clinical evidence suggests that thyroid replacement therapy with levothyroxine has beneficial effect. **Methods:** It is a hospital based prospective observational study involving 122 patients based on non probability sampling conducted in the Department of Internal Medicine. The study involved patients who have been diagnosed with subclinical hypothyroidism with normal level of free T4, T3 and elevated levels of TSH with positive Thyroperoxidase (TPO) antibodies. Patients were advised to investigate lipid profile before and afterprescribing levothyroxine. Follow up was done after 6-9 wks. **Results:** In this study 122 patients diagnosed with Subclinical hypothyroidism were prescribed with levothyroxine in which 112 came for follow up.The mean age of the patient was 46.81.There was significant reduction in mean TSH from 12.09 (±1.89)mIU/L to 7.97(±1.59)mIU/L,TC from 217.12(±20.87)mg/dl to 198.47(±17.34)mg/dl and LDL from 137.16(±14.57)mg/dl to 124.62(±12.89)mg/dl was found along with significant reduction in VLDL wasfound after levothyroxine therapy, There was slight reduction in serum triglyceride was found with no significant alteration in HDL and BMIlevels. **Conclusion:** The study showed significant reduction in the lipid profile including TC, LDL and VLDL after levothyroxine therapy. There was significant reduction in the level of TSHwas also found whereas the level of free T4 and T3 were not muchaltered. Therewas no significant change found in the level of HDLand BMI.

Keywords: Dyslipidemia, Levothyroxine, Subclinical hypothyroidism, Total cholesterol

Introduction

Iodine deficiency is one of the major public health problems with 30% prevalence of thyroid dysfunction in which 10% -17% of the population are suffering from subclinical hypothyroidism in Nepal.[1] Subclinical hypothyroidism (SCH) is represented by high levels of serum thyroid stimulating hormone (TSH) concentration and normal serum total or free thyroxine (T4) and triiodothyronine (T3) with few orwithout any clinical sign and symptoms of hypothyroidism. It is more common in elderly people in which females are predominant than males.[2]

Thyroid dysfunction increases the lipid levels in which patients with TSH values between 5.1 - 10 mIU/L have significantly higher mean total cholesterol (TC) and low-density lipoprotein-cholesterol (LDL-C) levels. TSH was found to be high in 5.2% of the 49.5% of patients who were diagnosed with hyperlipidemia.3Some studies suggest that even subclinical hypothyroidism (SCH) might be the cause of hyperlipidemia

Correspondence Author
Dr. Binod Raut, Assistant Professor
Kathmandu Medical College and Teaching Hospital (KMCTH), Duwakot, Bhaktapur, Nepal
E-mail: binod14raut@gmail.com
Phone:+9779840050194

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and later linked to coronary heart diseases. In hypothyroidism, the dyslipidemia occurs due to increased synthesis and over degradation rate leading to raised levels of TC, LDL-C, and reactive oxygen species causing lipid peroxidation leading to oxidative stress.[4]

The coexistence between dyslipidemia and hypothyroidism has become one of the main risk factors for the development of atherosclerosis ,which occurs due to changes in lipid profile, arterial hypertension, inflammation and oxidative stress leading to endothelial dysfunction which is the major cause of death due to development of coronary heart diseases.[5,6] A TSH value above 2.5 mIU/L in women of child bearing age may induce oxidative damage to membrane lipids and alter the lipid profile, suggesting that TSH levels should be maintained below this value, similarly above 10 mIU/L can be considered as predictor of cardiovascular disease since lipid status worsens along with TSH levels.7Recent studies on subclinical hypothyroidism and lipid profile indicates that the serum total cholesterol, LDL-C, and total triglycerides were significantly increased in SCH patients.[8]

Levothyroxine administration to normalize the lipid profile of subclinical hypothyroidism patients depends upon the degree of disease progression and has shown its proven efficacy in reducing TC and LDL-C with TSH value < 10 mIU/L.9levothyoxine replacement in SCH patients has shown significant improvement in both lipid profile and the carotid artery intima-thickness : a well recognized index of early atherosclerosis and cardiovascular events along with significant reduction in serum TC and LDL-C levels by 5.5 and 7.3% respectively.10studies conducted in Nepal had also suggested that hypothyroidism is more prevalent which lead to elevated level of cholesterol and subclinical hypothyroidism which is one of the important risk factor for causing cardiovascular disease so its earliest prevention is utmost requirement.[11]

The aim of the present study is to observe the effect of levothyroxine substitution therapy on serum lipid profile in patients diagnosed with subclinical hypothyroidism at tertiary care hospital.

Methods

The prospective observational study involving 122 patients based on non-probability sampling was conducted in the Department of Internal Medicine of Tertiary care Teaching Hospital from July 2019 to March 2020 after obtaining ethical approval from institutional ethical committee. The study involved patients who have been diagnosed with subclinical hypothyroidism with normal level of free thyroxine (T4), Triiodothyronine (T3) and elevated levels of Thyroid Stimulating Hormone (TSH) with positive Thyroperoxidase (TPO) antibodies. Patients were advised to investigate lipid profile which includes Serum Triglyceride (STG), Total Cholesterol (TC), Low Density Lipid Cholesterol (LDL-C), Very Low-Density Lipid cholesterol (VLDL-C), and High Density Lipid (HDL). Height and weight were also recorded for BMI scale and obesity.

Patients were prescribed with levothyroxine tablet 50, 75 and 100 micrograms once a day on the basis of TSH levels. Follow up was done after 6-9 wks and again Thyroid level test andlipid profile test along BMI of the patient were recorded and the difference in the value of Thyroid level, BMI and Lipid level were compared before and after levothyroxine therapy.

Data has been recorded in customized proforma from the patient record sheets and reports during the outpatient follow up after taking consent from the patient. All the collected data were retrieved from proforma and the statistical program for the social sciences (SPSS) package version 20 was used for analysis.

Results

Among 122 diagnosed patients with subclinical hypothyroidism only 112 patients visited for follow up. The age of the patient in this study ranges from minimum 23 years to maximum 73 years with

Journal of Diabetes and Endocrinology Association of Nepal

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mean age of 46.81(±12.02) The level of BMI was 18.50 kg/m2 to 38.0 kg/m2 with mean value of 27.85 kg/m2 similarly the level of TSH was 8.25 mIU/l to 15.90 mIU/l with mean value of 11.90 mIU/l.The level of free T4 was 6.25 µg/dl to 11.05 µg/dl with mean value of 8.61 µg/dl and the level of T3 was 1.78 ng/dl to 7.42 ng/dl with mean value of 4.30 ng/dl. The lipid levels were recorded after diagnosis with sub clinical hypothyroidism. Serum Triglyceride was 140 mg/dl to 250 mg/dl with the mean value of 196.56 mg/dL,the value of TC was 178 mg/dl to 285 mg/dl with mean value of 215.45 mg/dl. The level of LDL-C was 94.68 mg/dl to 167.80 mg/dl with mean value of 134.23 mg/dl, the level of VLDL-C was 20.82 mg/dl to 55.42 mg/dl with mean value of 35.17mg/dl and the value of HDL was 36 mg/dl to 47 mg/dl with mean value of 42.08 mg/dl.

Table :1 Descriptive parameters before Levothyroxine Therapy:

	Number	Minimum	Maximum	Mean	Std. Deviation
Age	122	23	73	46.81	12.020
BMI before	122	18.50	38.00	27.85	3.601
TSH before	122	8.25	15.90	11.90	1.943
T3 before	122	1.780	7.42	4.30	1.22
T4 before	122	6.25	11.05	8.61	.999
TC before	122	178	285	215.45	20.949
TG before	122	140	250	196.56	23.067
LDL-c before	122	94.68	167.80	134.23	17.166
VLDL-c before	122	20.82	55.42	35.17	8.082
HDL-c before	122	36	47	42.08	2.031

Mean BMI of the patients before therapy was 27.85 kg/m2 which was found to be 28.21kg/m2 after therapy, there was no significant difference in the mean value of BMI before and after therapy.

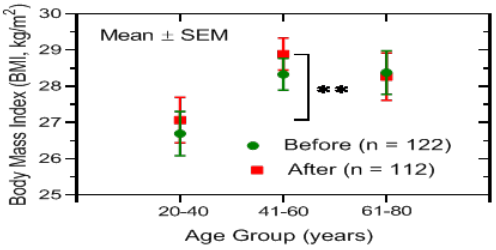

Figure 1: Age-wise BMI distribution before and after Levothyroxine therapy

Paired T-test was applied for the comparison of various parameters of thyroid and lipid profile before and after levothyroxine therapy. Mean value of TSH was found to be 7.91mIU/L with SD ±1.59. Mean value of T4 was found to be 7.11µg/dl with SD ±1.16 similarly mean value of T3 was 3.58ng/dl with SD ±.732. The mean value of STG was found to be 195.6mg/dl, the mean value of TC was found to be 198.47mg/dl, LDL-C was found to be with mean value of 124.62mg/dl, VLDL-C was found to be 29.93mg/dl and the mean value of HDL was found to be 41.15mg/dl.

Journal of Diabetes and Endocrinology Association of Nepal

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Table 2: Thyroid parameters before and after Levothyroxine therapy

Thyroid parameters	Before therapy Mean ± S.D. (n=122)	After therapy Mean ± S.D.(n=112)	correlation	P – value
TSH (mIU/L)	12.09 ±1.89	7.97 ±1.59	.680	<0.001
T4 (µg/dL)	8.63 ±1.01	7.11 ±1.16	.326	<0.001
T3 (ng/dL)	4.46 ±1.14	3.58 ±.732	.743	<0.001

The mean value of TSH was higher in SCH patients 11.90 mIU/L before levothyroxine therapy which was found to be 7.91mUI/L after therapy which was statistically significant shown in below with figure.

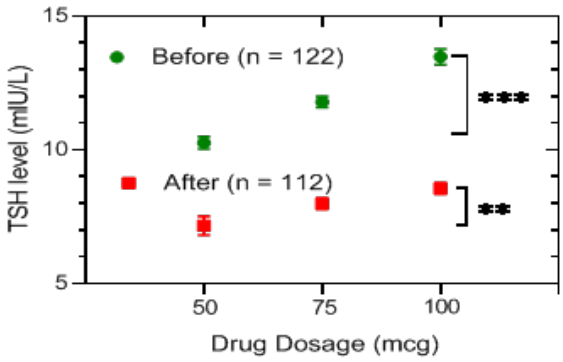

Figure: 2 Distribution of TSH value before and after Levothyroxine Therapy

The mean level of STG was 199.11(±21.93) mg/dL when compared to patients after therapy it was 195.56(±23.23) mg/dl (p: 0.001).The level of Total cholesterol was even markedly higher in patients before therapy which was 217.12(±20.87) mg/dl which was found to be 198.47(±17.34) mg/dl (p: 0.001). The mean LDL levels were significantly higher before therapy 137.16(±14.57) mg/dl compared to patients after therapy was 124.62 (±12.89) mg/dl. Similarly the mean value of VLDL was 35.98(±7.89)mg/dl before and it was found to be 29.93(±7.89)mg/dl after therapy. The mean HDL was higher in patients with SCH before therapy 42.32(±1.89) mg/dl compared to patients after therapy 41.15(±1.80)mg/dl which was not statistically significant.

Table 3: Lipid parameters before and after Levothyroxine therapy

Lipid parameters (mg/dL)	Before therapy Mean±S.D.(n=122)	After therapy Mean ±S.D.(n=112)	correlation	P – value
SerumTriglyceride	199.11 ±21.93	195.56 ±23.23	.720	<0.001
Total cholesterol	217.12 ±20.87	198.47 ±17.34	.834	<0.001
LDL-cholesterol	137.16 ±14.57	124.62 ±12.89	.833	<0.001
VLDL-cholesterol	35.98 ±7.89	29.93 ±6.1 4	.857	<0.001
HDL- cholesterol	42.32 ±1.89	41.15 ±1.80	.509	<0.001

The mean value of total cholesterol (TC) was 217.12 (±20.87)mg/dl before therapy and was found to be 198.47 (±17.34) mg/dl after therapy similarly the mean vale of LDL_C was137.16 (±14.57) mg/dl before and it was found to be 124.62(±12.89) mg/dl after therapy which was statistically significant shown below with figure.

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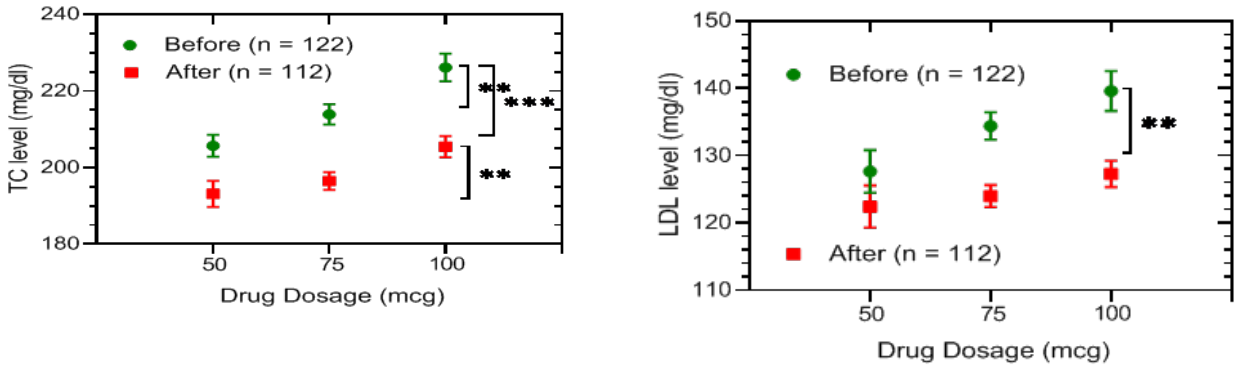

Figure: 3 Alterations in TC and LDL_C after Levothyroxine therapy

Discussion

Thyroid disorders are the most common endocrine disorders and these have major role in the alteration of lipid metabolism. Hypothyroidism is one of the most common ailment affecting patients attending endocrine outpatient department. Increase in the level of TSH is the key finding for early detection of thyroid dysfunction. Out of 122 diagnosed SCH patients 112 patients came for follow up after prescribing levothyroxine.

In the present study a predominance of female was noted in which F: M ratio is 3:1.similar other studies also reported that hypothyroidism was more prevalent among females than male.[12] The mean age of the patient in this study was 46.81 which is almost similar to the study done by Ravisekher et al with the mean age of 50.20 yrs in male and 48.02 years in female.[13]

In the present study an evaluation regarding BMI was also undertaken which was recorded based on weight on kilogram and height on meter square, the mean BMI of the patient was found to be 27.85kg/m^2 in the similar study they have observed BMI of 28.1kg/m2,[14] similar study conducted in Tehran has observed the level of BMI was 26.3 kg/m^2 . In our study we found no significant alteration in BMI after therapy it was 27.85kg/m^2 to 28.21kg/m2.Another study has also revealed there was no change in BMI after levothyroxine therapy the probable reason behind this alteration in BMI is most probably due to the fact that patient were not advised to reduce the dietary intake and change in the lifestyle which supported our study.[15]

In this study it was found that there was raised level of TSH whose mean value was 11.90 mIU/L which suggest that levothyroxine therapy was required whereas the level of free T4 and T3 was in the range of mean value with 8.63mIU/L ,and 4.46mIU/L which was in within the normal range there was significant reduction in TSH value was found after prescribing levothyroxine. The value of TSH was 7.97mIU/L, similarly there was slight reduction of mean value of free T4 and T3 was there which was 7.11mIU/L, and 3.58mIU/L. These findings were similar to the study confirmed by a recent, randomized, double blind, crossover trial in patients having SCH with a mean TSH of 6.6 mIU/L, which showed that levothyroxine treatment leads to significant improvement in many cardiovascular risk factors including total and LDL cholesterol [Razvi et al. 2007][10]

In our study it was found that there was raised level of serum triglyceride, total cholesterol and Low density lipoprotein cholesterol and very low density lipoprotein which signifies the condition of hypothyroidism causing rise in circulating cholesterol similar studies done by Pearce et al observed increased in serum triglyceride, total cholesterol, low density lipoprotein (LDL) cholesterol in subclinical hypothyroid patients which supports our findings, the reason behind the increment in the total cholesterol and LDL

Journal of Diabetes and Endocrinology Association of Nepal

cholesterol levels may be due to formation of oxidized LDL cholesterol leading to enhanced risk of atherosclerosis.[16] Another recent study has suggested that dyslipidemia was more in patients with SCH, and the levels of Total cholesterol, STG and LDL- C were also significantly high whereas HDL-C levels were lower compared to the control group.[17]

Serum triglyceride levels were also significantly high in our study Carontein et al also observed higher mean level of serum triglyceride with lower mean level of HDL levels in sub clinical hypothyroid patients .it also suggest that particularly in patient with subclinical hypothyroid there was marked raised value of STG, TC , LDL-C and VLDL-C with reduced level of HDL which has direct role in the development of complication in the formation of atherosclerosis and other cardiovascular diseases.[18] In our study the doses of levothyroxine has been prescribed based on the level of TSH from 50 microgram,75 microgram to 100 microgram once a day and patient has been reviewed for follow up after 6-9 wks duration similar studies also suggests The ETA guidelines recommend a weight-adjusted starting dose of 1.5 µg/kg daily (e.g. 100 or 125 µg/daily for a man, 75 or 100 µg for woman) for patients without cardiac disease and 25–50 µg daily for patients having heart problems and in the elderly.[16] The serum TSH should be rechecked 2–3 months after starting levothyroxine with the aim of keeping TSH in the lower half of recommended range (0.4–2.5 mIU/l), though a higher reference range (1.0–5.0 mIU/l) is acceptable in elderly patients (>70 years) [Biondi and Cooper, 2008].[19] Another study has also concluded the decrease in the TSH level from mean (±SD) 6.40±2.01 mIU/L to 3.63 mIU/L at the median dose of 50 micro gram of levothyroxine, it was mentioned that the study was underpowered to detect any effect on the incidence of cardiovascular events and mortality.[20] In our study it was found that there was significant decrease in the mean level of STG, TC, LDL-C and VLDL-C with less significant alteration in the level of HDL after replacement therapy with levothyroxine, similar studies has supported our findings in which it was clearly mentioned that after replacement therapy with levothyroxine in sub clinical hypothyroid patient there was marked reduction in STG, TC and LDL was observed which has direct role in avoiding incidence of CAD, stroke and peripheral vascular disease.[21] various other studies had also revealed the fact that there was significant reduction of total cholesterol and LDL cholesterol following levothyroxine therapy which also support our observations.[22] Monzane et al 23 also found reduction in level of STG after replacement therapy which has similar result that support our study but few studies has contradictory result in respect to STG value Ineck et al did not observed any significant change in the value of STG level following levothyroxine therapy.[24] It has been suggested in a recent Cochrane systematic review that thyroxine treatment in patients with SCH improved cardiovascular risk in terms of reducing serum cholesterol and improved cardiac function. But due to insufficient data, no clear recommendations could be stated and it was suggested that the decision either to treat or not should be on an individual basis Villar et al. 2007.[25] In another randomized trials which evaluate the effect of levothyroxine therapy in patients having mild SCH are considered insufficient to support levothyroxine treatment in this group and the benefits seen in the available trials are either very minor or of no benefit.[26]

In our study there was statistical significant decrease in STG was observed before and after levothyroxine therapy in which STG has decrease from 199.11 mg/dl to 195.56mg/dl. Similarly the mean value of total cholesterol has reduced from 217.12mg/dl to 198.47, LDL-C has reduced from 137.16mg/dl to 124.62mg/dl and VLDL from 35.98mg /dl to 29.96mg/dl , but there was reduction in the level of HDL from 42.32mg/dl to 41.15mg/dl similar studies also supported our finding in which Monzani et al reported that replacement with levothyroxine in SCH patients significantly reduced both total cholesterol (214.2 ± 37.5 mg/dL Vs 191.6 3 ± 2.5 mg/dL), and LDL cholesterol (138.9 ± 32.3 mg/dL Vs 119.2 ± 27.8 mg/dL). There was a

Journal of Diabetes and Endocrinology Association of Nepal

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reduction in the levels of triglycerides (94.0 ± 31.9 mg/dL Vs 88.1 ± 30 mg/dL) as well, these findings supported our observations.[23] In contrast to our findings, Efstathidou et al observed no significant changes in serum lipid profiles after levothyroxine therapy except for a decrease in HDL-cholesterol (59 ± 15 to 55 ± 14 mg/dL, $p < 0.05$).[3]

Conclusion

In conclusion this study has concluded that the prevalence of subclinical hypothyroidism is high and earliest management of raised level of thyroid stimulating hormone (TSH) is utmost important. Replacement therapy done by the levothyroxine has direct effect on reducing total cholesterol (TC) and low density lipoprotein cholesterol (LDL-C) and it has also effective role in reducing serum triglyceride (STG) and very low density lipoprotein cholesterol (VLDL-C). It has no significant effect regarding body mass index (BMI) and high density lipoprotein (HDL).

Recommendation

Dyslipidemia and its effects on cardiovascular system including ischemic heart disease, heart failure, stroke and peripheral vascular disease leading to increase in the mortality implies that earliest management of sub clinical hypothyroidism can prevent the alteration in the lipid levels and further control the cardiovascular complications. Therefore biochemical screening of thyroid dysfunction is recommended for the early diagnosis of dyslipidemia and sub clinical hypothyroidism.

levothyroxine replacement therapy has important role in the improvement of quality of life and prevention of cardiovascular diseases related complications by controlling the thyroid stimulating hormone levels and lipid levels.

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Use of complementary and alternative medicine in Type 2 Diabetes in Eastern Nepal

Mainali U K[1] Sigdel D[1] Sharma R[2] khatri S[3] Kathet R[4] Jha S K[1] Dahal M[1] Acharya D P[1]
[1]Department of Internal Medicine, Koshi Hospital, Biratnagar, Nepal [2]Department of Dermatology, Venereology and Leprology, Koshi Hospital, Biratnagar, Nepal [3]Student, Bachelor in public Health
[4]Department of Oncology, Koshi Hospital, Biratnagar, Nepal

Abstract

Background: The chronic and progressive nature of Diabetes Mellitus often leads people to use complementary and alternative medicines (CAMs) which may be defined as a group of medical and health care systems, practices and products that are not considered to be part of conventional medicine.

Methods: This descriptive cross-sectional study was done in a tertiary care hospital in Eastern Nepal from 15th June 2018 to 15th September 2019 to determine proportion of type 2 diabetic patients who have triedcomplementary and alternative medicines (CAMs) exclusively prior to presentation to endocrine OPD (Outpatient department).Consecutive sampling was done after informed verbal consent. **Results:** Out of 401 participants, 60.6 percent were male and 39.4 percent were female. Mean age of participants was 52.21 ± 11.42 years. Regarding use of CAMs, 11 percent sad tried some form of CAMs exclusively without any allopathic antidiabetic medicines for some period in their lifetime prior to presentation to endocrine OPD. More specifically, 10.3 percent had tried products under brand of ayurvedic medicines from local practitioners. Similarly, 0.2 percent had tried medicine from Homeopathic Practitioner and rest (0.5 percent) had tried homemade herbal remedies like garlic, fenugreek, aloe vera and bitter melon.

Conclusion: A significant proportion of type 2 diabetics in our community are still using CAMs. The associated factors behind this and long term effects of such products in diabetic patients need to be explored further in details.

Key words: Complementary and Alternative medicines (CAMs), Type 2 Diabetes

Introduction

Diabetes Mellitus is one of the most common metabolic disorders in the world and the prevalence of diabetes in adults is increasing in last few decades. An estimated 463 million adults aged 20-79 years are currently living with diabetes which represents 9.3 percent of the world's population in this age group. This number is predicted to rise to 578 million (10.2%) by 2030 and to 700 million (10.9%) by 2045. In 2019, the number of deaths resulting from diabetes and its complications is estimated to be 4.2 million. It is estimated that 79.4 percent of total people with diabetes live in low and middle income countries.[1]

The chronic and progressive nature of the disease often leads people to use complementary and alternative medicines. The National Centre for Complementary and Alternative Medicine of the United States defines CAM as "a group of medical and health care systems, practices and products that are not considered to be part of conventional medicine".CAMs include herbal remedies and other forms of therapy like acupuncture, faith healer, massage therapy, hypnosis and music therapy. [2]

Correspondence Author
Dr. Uttar Kumar Mainali, MD, Department of Internal Medicine, Koshi Hospital, Biratnagar, Nepal

Journal of Diabetes and Endocrinology Association of Nepal

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In a 2008 position statement, the American Diabetes Association (ADA) stated that there is insufficient evidence to demonstrate the efficacy of supplements in diabetes management and recognized the lack of standardization among preparations.[3]The botanical products that are commonly used for patients with diabetes and that clinicians may encounter in clinical practice are as follows[4]

Table 1. Selected Biologically Based Practices Used for Diabetes

Name	Hypothesized Effect(s) on Glucose Metabolism	Potential Adverse Effects
Allium sativum (garlic)	Insulin secretagogue	Blood thinning (To use with caution with anticoagulation or antiplatelet medications)
Aloe vera	Insulin secretagogue	Abdominal pain, diarrhea from laxative component, with subsequent electrolyte depletion
Cocciniaindica (ivy gourd)	Insulin mimetic	None reported
Gymnemasylvestre (gymnema)	Insulin secretagogue	Suppression of sweet taste
Momordicacharantia (bitter melon)	Insulin mimetic Decreased hepatic glucose production	Glucose 6 phosphate deficiency Contraindicated in pregnancy
Opuntiastreptacantha (prickly pear cactus, nopal) Panex ginseng, P. quiquefolius (ginseng)	Decreased carbohydrate absorption coagulation and anti Insulin mimetic Alters hepatic glucose metabolism	Diarrhea, nausea, abdominal fullness May interfere with effect of anti-coagulation and anti-platelet medications Estrogenic effect with breast tenderness, amenorrhea, vaginal bleeding, impotence Hypertension Insomnia
Trigonellafoenumgraecum (fenugreek)	Insulin secretagogue Decreased carbohydrate absorption	Gas, bloating, diarrhea Contraindicated in pregnancy

Around 25% to 57% of people with diabetes have been reported using complementary or alternative medicine worldwide.[5] This figure is even higher in developing countries where more than 70% of populations still depend on the complementary and alternative systems of medicine.[6]

Nepal is also one of the developing country having population of 28,981,469 (0.37% of the total world population) with only 21.4 percent population living in urban areas.There are three main domains of non conventional medicinal practices commonly available in Nepal. They are i) Scholarly Medical systems which includes Ayurveda, Homeopathy, Tibetan and Unani medicine ii) Folk medicines and iii) Shamanistic medicine (Faith healing system) that includes four different types of faith healing namely a) Dhami-jhankri, b) Jharphuke, c) Pandit-Lama-Pujari-Gubhaju and d) Jyotish.[7]

Some previous studies carried out in Nepal have shown that more than 50 percent of the population use CAM for various diseases because of culture, lack of health facility and expensiveness of modern allopathic medicine which are common in both the rural and urban areas of Nepal.[8]

In Nepal, no any studies were found till date on the prevalence of exclusive use of CAMs in diabetic population specifically. Hence, this study was designed to investigate the proportion and demographic profile of diabetic population who have tried CAMsexclusively with purpose to control or cure diabetesprior to date of presentation in endocrine OPD (Out Patient Department) of a tertiary care hospital in Eastern Nepal.

Objective

To determine the proportion of type 2 diabetic patients who have tried complementary and alternative medicines (CAMs) exclusively prior to presentation to Endocrine OPD of tertiary care hospital.

Materials and Methods

Study design: Descriptive cross sectional study

Settings:Endocrine OPD of Koshi Hospital, Biratnagar; a tertiary care Hospital of Eastern Nepal

Outcomes

outcome: Percentage of type 2 diabetic patients who have tried complementary and alternative medicines (CAMs) prior to presentation to endocrine OPD ofKoshi Hospital.

Sample size: Sample size was calculated using the formula n =z2pq/l2 on the basis of similar study on prevalence of CAM users among type 2 diabetics by N. Vishnu, G. K. Mini and K. R. Thankappan(9) which showed the 39 percent prevalence of use of CAMs in diabetes. The calculated sample size was 401 assuming 10 percent contingency error.

Inclusion criteria: Type 2 diabetes patients 18 years or older visiting Endocrine OPD during the period of 15th June 2018 to 15th September2019 who have voluntarily consented for participation.

Data collection and analysis:Data collection instrument was developed by the researchers around the objectives of the study and to suit the Nepali environment through robust review of literature on previous studies on CAM use in diabetes. Expert comments were obtained by the experts who were involved in diabetic treatment and research. The questionnaire comprised socio-demographic variables, duration of diabetes, co-morbidities, use of CAM sand types of CAM.

Operationally, adult patients were classified based on their age into young adults who were aged less than 60 years and elderly patients who were aged 60 years and more.Consent (verbal) was obtained from the participants.The data were analyzed by using SPSS version 16 software. Categorical variables were described by frequencies and percentages. Chi-square test was used to test any significant association between categorical variables. In all cases, $P < 0.05$ was considered statistically significant. Odds ratio (OR) which is an indicator of degree of association of exclusive use of CAM events with a predictor variable was estimated at 95 percent confidence limit.

Results

Four hundred and one patients were included in our study out of which 60.6 percent were male and 39.4 percent were female. Mean age of participants was 52.21± 11.42 years. Elderly population (≥60 years) occupied 28.2 percent. Out of total study population, 83.8 percent had received some level of formal education in life. Similarly, 57.4 percent had Diabetes of less than 5 years duration,18.2 percent had of 5 to 10 years and rest (24.4%) had of ≥ 10 years. Understanding of disease itself was good in 48.4 percent while only fair in 35.9 percent and rest (15.7%) had poor understanding of the disease. Regarding comorbidities, 39.9 percent had Hypertension, 5.2 percent had Ischemic heart Disease and 4.5 % had Chronic Kidney Disease.

Table 2: Background characteristics of Type 2 Diabetes Mellitus patients

Background characteristic	Number	Percentage
Age		
≥60 years	113	28.2.
<60 years	288	71.8
Sex		
Male	243	60.6
Female	158	39.4
Education		
Literate	336	83.8
Illiterate	65	16.2
Duration of Diabetes in years		
≥10 years	303	75.6
<10 years	98	24.4
Awareness of complications of diabetes		
Yes	188	46.9
No	213	53.1
Complete adherence to treatment		
Yes	55	13.7
No	346	86.3
Comorbidities		
Hypertension	160	39.9
Heart disease (IHD/CHF)	21	5.2
Chronic kidney disease	18	4.5
Complications of Diabetes		
Retinopathy	62	15.5
Peripheral neuropathy	112	27.9
Sexual problems	19	4.7

Only 13.7 percent of total population was strictly compliant to treatment while rest 86.3 percent had lost adherence in some moment of life. Out of total study population, 11.5 percent were on insulin at home. Similarly 23.6 percent were using one oral antidiabetic drug, 68.1 percent were using more than one antidiabetic drugs and 8.3 percent were on only diet and lifestyle modification.

Regarding complications, 46.9 percent were aware of macro and micro-vascular complications. Out of total patients, diabetes related ophthalmological complications were found in 15.5 percent and similarly neuropathy related problems in 27.9 percent, sexual problems in 4.7 percent and dental problems in 6.2 percent patients.

Table 3: Percentage of exclusive CAMs use and types of CAMs used

Variable	Number	Percentage
Exclusive use of CAMs for some period in their lifetime	44	11
Use of unregistered products as CAMs from local non-licensed practitioners	41	10.3
Use of homeopathic medicines as CAMs	1	0.2
Use of homemade remedies like garlic fenugreek, aloe vera juice etc as CAMs	2	0.5

Regarding use of CAM, 11 percent had tried some form of CAM. Specifically, 10.3 percent had tried medicine from local practitioner without authorized license to practice, 0.2 percent had tried medicine from Homeopathic Practitioner and rest (0.5 percent) had tried homemade herbal remedies like garlic, fenugreek, aloe vera and bitter melon.

Table 4: Percentage of exclusive CAMs use by background characteristics in Type 2 Diabetes Mellitus patients

Background characteristic	CAMs users (percentage)	Non CAMs users (percentage)	p value
Age			
≥ 60 years	10.6	89.4	
< 60 years	11.1	88.9	.887
Sex			
Male	10.7	89.3	
Female	11.4	88.6	.82
Education			
Literate	11.6	88.4	
Illiterate	7.7	92.3	.355
Duration of Diabetes in years			
≥ 10 years	10.2	89.8	
< 10 years	11.2	88.7	.779
Family history of diabetes			
Yes	12.6	87.4	
No	9.1	90.9	.26
Understanding of nature of disease itself			
Good /Fair	11.5	88.5	
Poor	7.9	92.1	.401
Awareness of complications			
Yes	12.2	87.8	
No	9.9	90.1	.448
COMORBIDITIES			
Hypertension			
Yes	10.8	89.2	
No	11.1	88.9	.945
Heart disease (IHD/CCF)			
Yes	0	100	
No	11.6	88.4	.098
Chronic Kidney Disease			
Yes	11.1	88.9	
No	11	89	.985

IHD: ischemic Heart Disease, CCF: Congestive cardiac failure

Discussion

This study identifies percentage of type 2 diabetics who have tried complementary and alternative medicines (CAMs) exclusively since diagnosis of their disease prior to presentation to endocrine OPD in 401 ambulatory type 2 diabetes patients .We didn't find any study conducted in Nepalese diabetic patients on use of CAMs till date. Many patients prefer to use alternative medicine and inevitably this interest has an effect on theoretical and clinical applications of medicine. The global rate of prevalence of use of alternative medicine by diabetic patients varies from 17-28 percent.[9,10] Percentageof patients who reported using exclusive CAMs for diabetes was 11 percent in our study which was comparable to prevalence of 9 percent reported in a similar study conducted in Kerala, India by N Vishnu and his team.[11] We did not find any other similar studies intended for studying proportion of exclusive use of CAM by diabetics though studies on use of CAM alongwith allopathic medicines have shown various results from different countries – 35.5 percent in Malaysia[9], 41 percent in Turkey[10] and 18.4 percent (Japan)[12] . The global rate of diabetic patients using alternative medicine products alongwith or without modern medicines varies from 17 to 72.8 percent.[13, 14]

Regarding the types of CAM used by participants in our study, 10.3 percent had tried medicine in the form of dust and pellets that were sold to them from local herbal shops and practitioners. They try to attract the patients with advertisement through various popular media in society like radio, television and newspapers claiming of guaranteed cure of the disease without any side effects and sell these substances to patients in the name of ayurvedic medicines. Similarly 0.2 percent had tried medicine from Homeopathic Practitioner and rest (0.5 percent) had tried homemade herbal remedies like garlic, fenugreek, bitter gourd and cinnamon. Analysis of current trends also indicates that bitter gourd and cinnamon are used most frequently worldwide, but there is a broad spectrum of herbal products in use that varies greatly between countries.15-16[15,16]All of these patients had to visit hospital or clinic for conventional anti diabetic medicines when they found that their blood sugar was not being controlled by use of these CAMs alone. Some of these patients were also using CAMs alongwith conventional medicines but our objective was only to measure percentage of those type 2 diabetics who were using CAMs exclusively either stopping their conventional medicines or were using such products exclusively after diagnosis of their disease.

Female gender, high income, monthly blood glucose tests, birthplace, education level, and living with immediate family are common demographic characteristics of patients who have a preference for alternative medicine products, according to international data.[10,13] But in this study, the patient characteristics like age, gender, duration of diabetes, positive family history,literacy status, level of understanding of the disease and level of awareness of complications of diabetes itselfdid not seem to be relevant to use of alternative medicine, nor did presence of any comorbid illness or complications create significant difference. This suggests that progression, severity of the disease, and complications developed are not meaningful factors in patients' choice to use complementary and alternative medicine products.

Strength

The strength of our study includes the relatively large sample of 401 enrollments, which provides adequate representation of diabetic population to study proportion of exclusive CAMs users among them.

Limitations of the study:

1. It is limited to only one centre and hence data may not be representative for diabetics visiting other centers.
2. It is based on self reported data. So, recall bias needs to be considered while interpreting data.
3. It includes only those diabetics who visit endocrine OPDof Koshi Hospital and thus may not be representative for whole diabetic community.

Conclusion

Life-long treatment of Diabetes Mellitus is a challenge for patients. Living with the disease of diabetes, compliance with dietary therapy, performing regular blood glucose tests, and the compulsory, regular use of antidiabetic drugs can be very demanding. Hence, patients often seek a quick cure, leading many to try alternative medicine. A significant proportion of type 2 diabetics in our community are still using CAMs. The associated factors behind this and long term effects of such products in diabetic patients need to be explored further in details.

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Psycho-sexual Disorders in Clinic Diabetes mellitus Patients of a Teaching Hospital of Eastern Nepal

Shakya DR[1], Maskey R[2], Karki P[3], Sharma SK[4]
[1]Professor, Department of Psychiatry, [2]Additional Professor, Department of Medicine, [3] Professor, Department of Cardiology, [4] Professor, Department of Medicine, B. P. Koirala Institute of Health Sciences, Dharan, Nepal

Abstract

Background: Diabetes mellitus, a chronic disease, is frequently associated with sexual dysfunctions. Identification and management of these dysfunctions are important for overall wellbeing of the patient, though usually neglected. We lack data on this regard from Nepal. **Objective:** To estimate prevalence of psycho-sexual disorders (with emphasis on erectile dysfunction) in the patients with diabetes mellitus visiting 'Diabetes clinic' of a tertiary care teaching hospital in eastern Nepal. **Method:** It is a hospital-clinic based prevalence study. This study analyzed consecutive diabetes mellitus clinic patients' response to self response questionnaires 'Arizona Sexual Experience Scale' (ASEX) for over all sexual dysfunction and '5- Item Version of the International Index of Erectile Dysfunction' (IIEF-5) for erectile dysfunction. 'Diabetes mellitus' diagnosis was made based on the ADA guidelines 2010. **Results:** Among 100 male clinic diabetes patients, majorities were married, above age 50 years and all diagnosed as type 2 diabetes mellitus. Out of total, 48% had sexual dysfunction by the ASEX and many subjects had erectile dysfunction by the IIEF-5. **Conclusion:** Psychosexual dysfunctions, mainly erectile dysfunction are common among diabetic patients. Hence, assessment should include attention to sexual problems as well during management of diabetes mellitus.

Key words: ASEX, Diabetes-mellitus, erectile dysfunction, psychosexual dysfunction

Introduction

Diabetes Mellitus (DM) is one of the most common chronic diseases, with prevalence of about 2%.[1-4] Sexual health of these patients, frequently forgotten has surfaced out with the passage of time[5-9] though many patients and their family may not express in the first instance. Cultural, societal, educational and many other factors may play a role in the manifestation, expression and help seeking for these psychosexual problems.[10] In Nepalese context, people may hesitate to seek help for the underlying sexual symptoms.[11] Psycho-sexual problem, e.g. erectile dysfunction worsens 'quality of life' of these people. Hence, its timely recognition and management is important. We lack data on this aspect.

Correspondence Author
Prof. Dhana Ratna Sakya, Department of Psychiatry, B.P. Koirala Institute of Health Sciences, Dharan, Nepal

This hospital clinic based prevalence study was conducted in 'Diabetes clinic' of B. P. Koirala Institute of Health sciences (BPKIHS), Nepal in March 2011- May 2012 to detect psychosexual problems with the focus on erectile dysfunction (ED) through the use of standard instruments called the 'Arizona Sexual Experience Scale' (ASEX) and the '5- Item Version of the International Index of Erectile Dysfunction' (IIEF-5). Overarching the project would be to draw attention to this usually concealed and forgotten problem and to facilitate management at all levels through a multi-specialty clinic for these needy people.

Materials and Methods

Design: It is Institute Hospital based prevalence/

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descriptive study conducted among diabetes mellitus patients.

Subjects: We enrolled 100 consecutive male out-patients and in-patients with diabetes mellitus coming into the contact of the investigating team during study period of March 2011- May 2012. Male outpatients and inpatients aged more than 15 years admitted through Diabetes clinic to the wards that were either previously or newly diagnosed diabetic cases in B.P.K.I.H.S., Dharan were included in the study (irrespective of marital status).

Diagnosis of diabetes mellitus was done as per the American Diabetes Association (ADA) 2010 guidelines:12

a. Fasting venous plasma glucose ≥ 126 mg/dl (7.0 mmol/L)
b. Two hour venous plasma glucose (post 75 gm glucose) ≥ 200 mg/dl (11.1mmol/L)
c. HbA1C ≥ 6.5%

Subject enrolment: Male participants diagnosed with DM providing informed written consent were enrolled. Information related to their socio-demographic profiles and illnesses were collected in semi-structured proforma. Sexual dysfunctions were screened with the use of the instrument 'Arizona Sexual Experience Scale' (ASEX)13 and erectile dysfunction with the '5- Item Version of the International Index of Erectile Dysfunction' (IIEF-5).14

- Arizona Sexual Experience Scale (ASEX): This simple scale was developed by the department of Psychiatry and Psychology, University of Arizona and department of Psychiatry and behavioral sciences, Stanford University to measure 5 items identified as core elements of sexual function. These 5 items sexual drive, arousal, penile erection/ vaginal lubrication, ability to reach orgasm and satisfaction from orgasm are rated on a 6-point Likert scale ranging from 1 (hyperfunction) to 6 (hypofunction). The scale has two versions, one for males and one for females, with difference in question 3 that references penile erections versus vaginal lubrication. The scales are easy to complete and the results may be used to assess current levels of sexual dysfunction (SD) or to monitor changes in sexual dysfunction over time following clinical interventions. A total score of more than 18 on the ASEX or a score of 5 (very difficult) or greater on any one item is associated with clinical sexual dysfunction.[13] It has an excellent internal consistency, reliability and validity.[15] It is self-rated scale and takes about 5-10 minutes. It may be completed/ rated by the interviewer.
- '5- Item Version of the International Index of Erectile Dysfunction' (IIEF-5): An abridged, 5-item version of the International Index of Erectile Function IIEF-5 is also known as the Sexual Health Inventory for Men (SHIM). The IIEF-5 is an excellent diagnostic test for erectile dysfunction (ED). This abbreviated questionnaire is a two-thirds reduction in the number of original IIEF items, from 15 to 5 providing a quick and reliable assessment tool. The IIEF-5 consists of Items 5, 15, 4, 2, and 7 from the IIEF. The items of IIEF-5 questionnaire have been rephrased to address the past six months of sexual activity. The sensitivity is reported as 0.98 and the specificity as 0.88.14 It is self-rated scale and takes about 5-10 minutes. It may be completed/ rated by the interviewer.
- Semi-structured proforma: It was designed to cover all information related to their socio-demographic profiles.

Data processing: Regular meetings and interactions were held to sort out difficulties. The coded proforma were collected at the end of the week by research staffs. On receiving proformas, the informations were entered into computer and data were analysed using 'statistical package for social studies' (SPSS 17). The output of the project provided data on the sexual dysfunction (SD) with focus on erectile dysfunction (ED). Prevalence rates were calculated as mean.

Ethical consideration: The study was initiated after the approval of the 'Ethical Review Board' of the institute (IERB Ref.- Aca. 590/067/068). Informed written consent was taken from the subjects. Strict confidentiality of information was maintained and it was utilized for the research purpose and the case management. The result was presented in institute scientific forum.

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ORIGINAL ARTICLE OPEN ACCESS

Results

Among total enrolled 100 male subjects, all had type 2 diabetes mellitus (DM).

Ethnicity distribution of the subjects showed that the top 4 common castes according to the number of subjects in the clinic of the institute were: Upper hill, disadvantaged non-dalit Terai, relatively advantaged Janajati and disadvantaged hill Janajati (Table 1).

Table 1: Caste-ethnicity Distribution of Diabetes-clinic service attenders

Ethnic groups	No./ %	Ethnic groups	No./ %
Upper hill	24	Disadvantaged nondalit Terai	24
Upper Terai	3	Disadvantaged hill Janajati	20
Relatively advantaged Janajati	21	Hill dalit	8
Religious minority	0	Disadvantaged Terai Janajati	0

Average age was 52.64 (32 minimum, 78 maximum) years. Most of the patients were above 50 of age. Most of them (50%) came from urban, some (38%) semi urban and less (12%) from rural background (Figure 1).

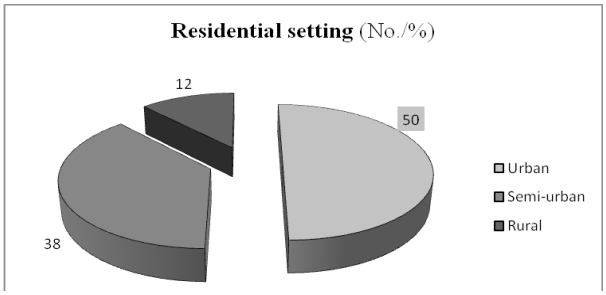

Figure 1: Residential settings

From information given by respondents, only two patients were single, rest married and 5 did not reply. As per the criteria of at least 1 item with score of 5, overall score of 18 and 3 items with 4 scores, 48% had significant sexual dysfunction (SD) (Table 2).

Table 2: Sexual dysfunction by ASEX questionnaire

Sexual dysfunction by	No./%
Total score 18	38
Item with score 5	24
3 item with score 4	40
Any of the criteria	48

Only 22% denied any and 28% had only mild erectile symptom/dysfunction. About half of the subjects had moderate or severe degree of erectile dysfunction (ED).

Table 3: Erectile dysfunction among Diabetes-clinic service users

Grading of erectile dysfunction	Number (%)
No (22- 25)	22
Mild (17- 21)	29
Mild to Moderate (12- 16)	31
Moderate (8- 11)	14
Severe (5- 7)	4

Discussion

Diabetes mellitus (DM) is the most common endocrinal disorder with the prevalence of 6- 7.6 % in the west.[1-3] The prediction of 35% increase in the worldwide prevalence of diabetes in between 1995 and 2025 and the greater rising number of people with diabetes mainly in developing countries, leading to more than 300 million globally by 2025 are alarming.[1] Nepal lies in 'diabetic zone' and has been reported with the highest prevalance of pre-diabetes among the SAARC countries.[2,3] A community survey in eastern Nepal showed the prevalence of 3- 8%.[4]

The disease may lead to various complications due to affect in the small (e.g. retinopathy, nephropathy, and neuropathy) and large vessels (e.g. ischemic heart disease and stroke). A greater prevalence of psychiatric problems has been found in our institute as in other places.[16] The disease has a tremendous impact on the 'quality of life'.

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Various studies done suggest that sexual dysfunctions (SD) are more common in DM (both type I and type II) than in the general population. Loss of/ reduced libido, erectile dysfunction, premature ejaculation are commonly reported among male diabetics and reduced sexual response among females.[5] They may arise from a variety of vascular, neurologic, and hormonal derangements. Other factors such as psycho-social stressors and comorbidities might also play a significant role. The prevalence of these SDs may differ with a number of demographic and clinical factors such as: age, duration of DM, physical complication, control of blood sugar, BMI etc.[6,17] In this study, all the cases were type II diabetes mellitus and the overall psychosexual dysfunction (SD) was found in 48% DM clinic patients by using the ASEX. We studied only among male subjects whereas females are also reported to be affected in similar fashion.[18] This rate of our study coincides with an Indian study conducted in a similar DM clinic of a hospital setting using the SCID-IV and the ASEX to diagnose SD.[17]

Erectile dysfunction (ED), one of the sexual disorders'/ dysfunctions (SD) has been reported at least 3 times more common among DM people than among general population.[7] ED is emerging as an important complication of diabetes in South Asians as revealed in a review by Gupta et al.[19] After taking into account the confounding role of age, the prevalence of ED was found to be 37% in type II and 51% in type I DM.[8] ED may also be the presenting symptom for DM and may predict later neurologic sequelae.[9] Mean age in our study was above 50, i.e. 52.64 (32 minimum, 78 maximum) years. This is relatively elder than in an Ethiopian study with relatively younger age (43.39 years) showing a lower ED rate (69.9%).[20] ED was present in many (78%) cases in our study as found through the '5- Item Version of the International Index of Erectile Dysfunction' (IIEF-5), nearly half of the subjects had moderate or severe degree of ED and 28% had mild erectile symptom/dysfunction. This finding is consistent with an Indian study conducted with same tool the IIEF-5 in similar set up and subjects of relatively similar ages.[21] This ED prevalence rate is, however higher than that reported by Kumar et al. (58%)[22] and the pooled prevalence in patients with DM in Africa reported by Shiferaw et al. (71.45%).[23]

Since this study was conducted in a diabetes clinic of a teaching institute in a sensitive issue like sexual problem where people may not open up readily and our subjects were mainly elderly above 50, the finding may not be generalized. Looking intensively into the underlying factors, like: age, duration of DM, physical complication, glycemic control, BMI, psychological, psychiatric, socio-cultural and other factors could be undertaken in future studies for comprehensive understanding. Large sample size and intensive study is warranted for the same.

Conclusion

Nearly half of the male diabetic patients had some sexual dysfunction (SD). Many of the clinic visitors with DM had erectile symptom/ dysfunction (ED). About half of them had either moderate or severe symptoms.

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Study of TSH level at the time of diagnosis of Hypothyroidism in patients with Diabetes Mellitus- A Retrospective Study

K.C.(Adhikari) I[1], Ghimire S[2], Deo R[3]
[1]Associate Prof, Department of Medicine Shree Birendra Hospital chhauni ,Nepal,
[2] Resident, Department of Medicine, Shree Birendra Hospital chhauni , Nepal
[3]Associate Prof, Department of Medicine Shree Birendra Hospital chhauni , Nepal

Abstract

Background: To evaluate the difference in the level of TSH in diabetic and non diabetic patients at the time of the diagnosis of hypothyroidism. **Methods:** 100 diagnosed cases of hypothyroidism, 50 with diabetes and 50 without diabetes were studied. The level of TSH at the time of diagnosis and other information were obtained from the medical records. **Results:** The mean TSH in patients with the history of diabetes at the diagnosis of hypothyroidism was 19.9616±26.990 and in those without the history of the diabetes was 10.4797±6.503 (p value 0.018). The females with diabetes had higher level of TSH level at the time of diagnosis of hypothyroidism than females without diabetes (p value 0.045).There was no statistically significant difference in the level of TSH in males with and without diabetes at the time of diagnosis of hypothyroidism. **Conclusion:** Patients with diabetes mellitus had higher level of TSH at the time of diagnosis of hypothyroidism in comparison to those without diabetes. Early identification of the raised TSH levels in diabetic patients and timely intervention will help to reduce the chances of adverse cardiovascular outcomes and diabetic kidney disease in this group of patients.

Key words: Diabetes Mellitus, Hypothyroidism,Thyroid stimulating hormone [TSH]

Introduction

Thyroid diseases and Diabetes Mellitus are the two endocrine disorders which are frequently encountered in the clinical practice by almost all the clinicians.[1] These two diseases have effect over each other and this mutual relationship between them has been shown in various studies.[1] Among various spectrums of the thyroid disorders, hypothyroidism is most frequently found to be associated with the diabetes mellitus.[2,3]

Hypothyroidism is a clinical condition which results from the decreased synthesis of thyroid hormone from the thyroid gland or from the impaired activity of the thyroid hormone at the tissue level.[4] Overt hypothyroidism is diagnosed when patients have low levels of thyroid hormone and high levels of thyroid-stimulating hormones (TSH). The subclinical hypothyroidism is diagnosed when there is elevated thyroid-stimulating hormone (TSH) and normal thyroid hormone level.[5]

Correspondence Author
Col Dr Indu K.C., Associate Prof, Department of Medicine Shree Birendra Hospital chhauni, Nepal,

The relationship between diabetes and hypothyroidism is a very well established. Patients with diabetes mellitus who have higher levels of TSH are found to be associated with the increased prevalence of the diabetic kidney disease.[6] Similarly a study done by Ping Zhu et al. showed the independent association of TSH level with the insulin resistance.[7]

TSH level measurement in blood is the main test used for the diagnosis of the hypothyroidism in the clinical practice.[8] The use of TSH for the hypothyroidism is preferred because of the various reasons. TSH has inverse log-linear relationship with free-thyroxine (FT4), so small linear decrease in free-thyroxine level causes exponential increase in the TSH level. Similarly, the modern test methods used for the measurement of TSH have more than 99% sensitivity and specificity. Also, most cases

of the hypothyroidism encountered in the clinical practice are due to decrease in hormone synthesis by the thyroid gland, making TSH a test of choice.[9] Within the current study, we aimed to investigate whether there is exists any significant difference in the level of TSH at the time of diagnosis of hypothyroidism among those with and without diabetes mellitus.

Methods and Methodology

We analyzed retrospectively 100 hypothyroid adult participants of age more than 18 years. 50 patients had diabetes mellitus and remaining 50 without diabetes mellitus were taken as control. All patients were either army personnel, retired armies or their families. All the data were collected on the basis of their medical records. Participants were defined as having T2DM according to self-report, clinical reports,use of anti-diabetic agents and ADA criteria. Serum TSH was estimated by immunoradiometric assay.

Continuous variables were described using means and standard deviations. Chi square test was used for categorical data comparison. ANOVA test was used to compare the means among the groups. P value of <0.05 indicates significance. The statistical analysis was conducted with SPSS version 21.0 for Windows. The data were presented and tables and charts.

Results

Among the total 100 participants in the study, 50 had history of diabetes and 50 didn't have the history of diabetes. Among 100 patients 49 patients were male and 51 patients were females. Out of the 50 patients with diabetes 31 were males and 19 were females. Among the 50 patients without diabetes 18 were males and 32 were females. The mean age of participants with diabetes mellitus was 60.50±10.42 µIU/mL and without diabetes was 52.54±15.97µIU/mL. (Table 1 and Table 2)

Table 1. History of Diabetes * Sex of Participant Cross-tabulation

		Sex of Participant		Total
		Male	Female	
History of Diabetes	Present	31	19	50
	Absent	18	32	50
Total		49	51	100

Table 2. Mean age of participants

History of Diabetes	Mean	N	Std. Deviation
Present	60.50	50	10.420
Absent	52.54	50	15.965
Total	56.52	100	13.996

The mean TSH in patients with the history of diabetes at the diagnosis of hypothyroidism was 19.9616±26.990 µIU/mL and in those without the history of the diabetes was 10.4797±6.503 µIU/mL. On comparing the mean difference between these two groups using ANOVA, the p value was found to be 0.018, which is statistically significant. (Table 3 and Figure 1)

Table 3. Relation between TSH level at diagnosis of hypothyroidism and history of diabetes mellitus

History of Diabetes	Mean	N	Std. Deviation
Present	19.9616	50	26.99041
Absent	10.4797	50	6.50346
Total	15.2207	100	20.10471
df-1; F-5.832; p value-0.018; CI-1.69-17.27			

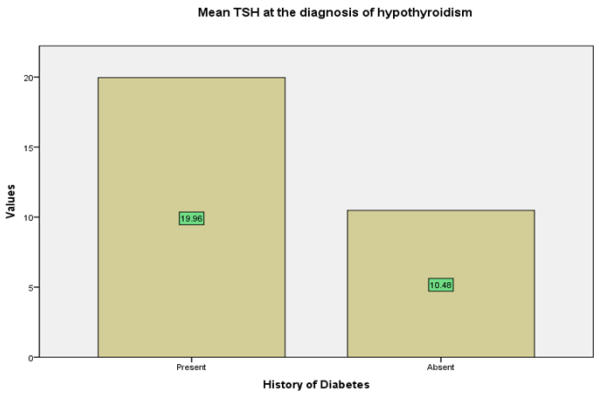

Figure 1. Bar diagram showing mean TSH level on diagnosis of hypothyroidism

In this study, while comparing the mean TSH level among the males with and without diabetes, the mean TSH level among those with diabetes was 17.315±20.99 µIU/mL and among those without

diabetes was 9.232±3.143 µIU/mL.The mean difference among these two categories was not statistically significant (p value 0.113). This implies that there was no statistically significant difference in the level of TSH in males with and without diabetes at the time of diagnosis of hypothyroidism. (Table 4)

Table 4. Difference in TSH level among males with and without diabetes at the time of diagnosis of hypothyroidism

History of Diabetes	Sex of Participant		Statistic	95% Confidence Interval	
				Upper	Lower
Present	Male	Mean	17.3152	11.1457	25.7020
		N	31	31	31
		Std. Deviation	20.98780	5.71590	31.45213
Absent					
	Male	Mean	9.2326	7.7633	10.7583
		N	18	18	18
		Std. Deviation	3.14274	1.87317	3.77188
Total	Total	Mean	14.3461	10.4281	19.7306
		N	49	49	49
		Std. Deviation	17.15522	5.04543	26.08701

df-1; F- 2.613; p value- 0.113

In this study, while comparing the mean TSH level among the females with and without diabetes, the mean TSH level among those with diabetes was 24.280±34.888 µIU/mL and among those without diabetes was 11.181±7.748 µIU/mL.The mean difference among these two categories was statistically significant (p value 0.045). This implies that there was statistically significant difference in the level of TSH in females with and without diabetes at the time of diagnosis of hypothyroidism. Thus, the females with diabetes have higher level of TSH level at the time of diagnosis of hypothyroidism than females without diabetes. (Table 5)

Table 5. Difference in TSH level among females with and without diabetes at the time of diagnosis of hypothyroidism

History of Diabetes	Sex of Participant		Statistic	95% Confidence Interval	
				Lower	Upper
Present	Female	Mean	24.2795	11.1235	42.0303
		N	19	19	19
		Std. Deviation	34.88844	7.35747	49.53283
Absent	Female	Mean	11.1813	8.7824	13.7807
		N	32	32	32
		Std. Deviation	7.74764	4.26692	10.31682
Total	Female	Mean	16.0610	10.9975	22.6109
		N	51	51	51
		Std. Deviation	22.72257	7.44397	34.08326

df-1; F-4.216; p value- 0.045

Discussion

This study was done with the purpose to evaluate the difference in the level of TSH among the hypothyroid patients with and without the history of the diabetes at the time of their diagnosis of the hypothyroidism. To our knowledge, this is the first study which has compared the TSH level at the time of diagnosis of hypothyroidism in both group of patients with and without diabetes.

Our study included 100 participants. 50 participants had diabetes when they were diagnosed of having hypothyroidism. 50 hypothyroid patients without the diabetes were taken as control. In the present study, the mean values of serum TSH was 19.9616±26.990 µIU/mL in those with history of diabetes, and was 10.4797±6.503 µIU/mL in those without the history of the diabetes mellitus. The mean TSH level was higher in those patients with diabetes during the time of their diagnosis of hypothyroidism. This difference in TSH level among those with and without diabetes was statistically significant with the p-value of 0.018. one of the study conducted by Acharya et al. in Nepal also showed statistically significant difference in the TSH level in patients with and without diabetes with the TSH level being higher in diabetic patients.[10] Similarly, in the studies done by Prasad et al. and Swamy et al., statistically significant increased level of TSH was found in diabetic patients as compared to non-diabetic patients.[11,12] These results are similar to that of our study showing increased TSH level in patient with diabetes in comparison to those without diabetes; however these studies used healthy persons as control, whereas we used hypothyroid patients without diabetes as controls in our study. However, in a study done by Islam et al there was no significant difference in the level of TSH among diabetic and non-diabetic patients.[13]

In our study, females with diabetes were found to have higher level of TSH at the time of diagnosis of hypothyroidism than females without diabetes (p value 0.045).Bharat et al. also found statistically significant higher level of TSH in diabetic females in comparison to females without diabetes mellitus.[14] However study done by Ishay et al. didn't not find the statistically significant difference in TSH between female patients with and without diabetes, which contradicts the results of our study.[15] In our study, however, there was no statistically significant difference in the TSH level among male patients at the time of diagnosis of hypothyroidism irrespective of the presence or absence of diabetes mellitus.

The elevation of TSH in the diabetic patient might be due to the effect of Hyperinsulinemia and the Leptin on the Hypothalamic-Pituitary-Thyroid Axis resulting in stimulation of TSH secretion.[16] Undiagnosed or diagnosed elevated TSH level, as seen in hypothyroidism, increases the existing cardiovascular risk and diabetic kidney disease in patients with diabetes mellitus.[6,17] So, early diagnosis of elevated TSH level in diabetic patients will help in the reduction of mortality and morbidity.

However our study has some limitations. First, this study is a retrospective and observational study and it was tough to avoid selection and confounding bias. Second, the sample size of this study was relatively small. Third, as this study was done at a tertiary referral centre, the results of this study may not be applicable at the community level.

Conclusion

Patients with diabetes mellitus had higher level of TSH at the time of diagnosis of hypothyroidism in comparison to those without diabetes. Early identification of the raised TSH levels in diabetic patients and timely intervention will help to reduce the chances of adverse cardiovascular outcomes and diabetic kidney disease in this group of patients.

Also, as elevated TSH is independently related with the insulin resistance, early identification of raised TSH and proper treatment of thyroid dysfunction can reverse the insulin resistance in diabetic patients.

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Use of parathyroid hormone analog (Teriparatide) in patients with chronic hypoparathyroidism after total thyroidectomy: a case report

[1]Rai A, [2]Karki P, [3]Paudel D, [4]Maskey R

[1]Senior resident, [4]Additonal Professor, Department of Internal Medicine, BPKIHS, Dharan, Nepal, [2]Senior Resident, [3]Assistant Professor, Department of ENT, BPKIHS, Dharan, Nepal

Abstract

Background: Hypoparathyroidism and hypocalcemia is a common postoperative complication, after total thyroidectomy due to thyroid cancer. Standard treatment with supplementation of calcium and vitamin D analogs, usually treat this condition. In some patients, hypoparathyroidism is refractory to standard treatment plus intermittent calcium infusions with persistent low serum calcium levels and associated clinical complications. Attempts have been made to add recombinant human parathormone (rhPTH) to the treatment schedule. To our knowledge, this is the first time that we encounter a patient suffering from treatment-refractory postsurgical hypoparathyroidism who was treated with teriparatide. **Case presentation:** Male (31 years) with postoperative hypoparathyroidism, after total thyroidectomy due to papillary thyroid cancer, several weeks after the surgery still required intermittent intravenous calcium infusions because of tetany symptoms. He had persistent hypocalcemia despite oral treatment with up to 1 ug calcitriol and 4 g calcium per day necessitating additional intravenous administration of calcium gluconate intermittently. This time, Teriparatide treatment was introduced at once daily 50 micrograms (mcg) subcutaneous injection, while doses of calcium and calcitriol were gradually decreased depending on the response of serum total and ionized calcium taken periodically, which resulted in total resolution of hypocalcemia symptoms and the achievement and maintenance of laboratory normocalcaemia in just 5 days. **Conclusion:** Treatment refractory chronic hypoparathyroidism may be seen in some cases after total thyroidectomy. Furthermore, the use of recombinant human parathyroid hormone analog (Teriparatide) allows for the control of recurrent hypocalcemia reducing the daily dosage of calcium and vitamin D. Finally, regular intravenous calcium administration was no more needed.

Key words: Postoperative Chronic Hypoparathyroidism, Recurrent Hypocalcemia, Teriparatide

Introduction

Hypoparathyroidism is a common complication following bilateral thyroid surgery. Post-thyroidectomy hypoparathyroidism is due to inadvertent excision, damage, or devascularization of the parathyroid gland(s). Hypocalcemia, in most cases, is transient, which usually resolves after 2-3 months with oral calcium and vitamin D supplementation alone. Meanwhile, 0.12 % - 4.6 % of cases may have chronic hypoparathyroidism extending beyond 6 months[1].

Correspondence Author
Dr. Avinash Rai, Senior Resident Department of Internal Medicine, B.P. Koirala Institute of Health Sciences, Dharan, Nepal

Hypoparathyroidism is characterized by low parathyroid hormone (PTH) and low calcium levels. The main clinical features of the disease are hypocalcemic symptoms such as perioral numbness, limb paresthesia, and carpopedal muscle spasms. Acute hypocalcemia can be a medical emergency with severe and potentially life-threatening complications such as laryngeal spasms, tetany, and seizures that may occur requiring intravenous calcium ions. Supplementation of calcium, active vitamin D, and at times, thiazide diuretics may be sufficient for most of the individuals with iatrogenic hypoparathyroidism. Despite the valiant efforts, some cases may be difficult to control

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Journal of Diabetes and Endocrinology Association of Nepal
CASE REPORT OPEN ACCESS

with conventional therapy, even after high doses are employed. Moreover, prolonged use of high doses can cause hypercalciuria, nephrocalcinosis, ectopic soft tissue calcification, and subsequent renal impairment[2]. besides, conventional therapy does not alleviate Quality of life complaints, nor does it reverse bone remodeling abnormalities of the disease[3]. To sum things up, conventional therapy does not provide benefits that a hormone replacement therapy provides for the lack of PTH in chronic hypoparathyroidism.

Hypoparathyroidism is the last remaining classic endocrine deficiency disorder for which hormone replacement therapy was not approved until recently. Over the past decade, the study of full-length natural PTH (1-84) and short active N-terminal PTH (teriparatide (PTH 1-34)) have introduced a new era of management of this disease. In 2015, the United States Food and Drug Administration (FDA) approved the use of recombinant human PTH (1-84) in treating patients with classical treatment-resistant hypoparathyroidism[4]. Regarding our clinical settings, the incidence of chronic hypoparathyroidism post-thyroid surgery is rare. Furthermore, the usage of Teriparatide (PTH 1-34) as hormone replacement therapy in such a case is itself a first of its kind here.

Case Report

A 31-year-old male, non-smoker, non-alcohol consumer, presented with bilateral upper/lower limb paresthesia and carpopedal spasm. He does not have any history of hypertension, diabetes mellitus, tuberculosis. His family history was not significant. The patient had undergone total thyroidectomy due to papillary carcinoma thyroid 8 months back. Thereafter, the patient developed postoperative hypoparathyroidism and was under calcium 3g/day and active vitamin D (calcitriol) 0.25 ug/day for hypocalcemia. The patient had been on intermittent calcium gluconate injections for recurrent tetany symptoms on an emergency basis.

This time (2020/07/08), he was admitted to the department of Internal medicine with the chief complaint of bilateral upper and lower limb tingling sensation, weakness, myalgia, and severe spasmodic pain. At the time of presentation, his physical examination results were normal, except for thyroidectomy scars and carpopedal spasm (see figure 1).

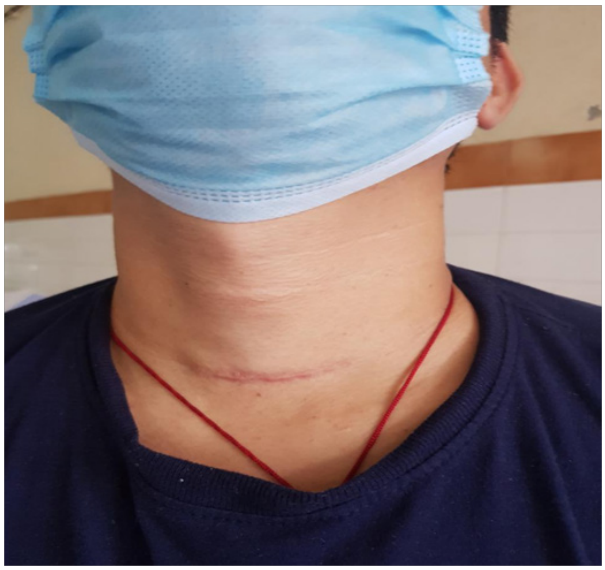

Figure 1: 31 year old male with status post total thyroidectomy, with thyroidectomy scar.

On examination, chvostek's sign and trousseau's sign were positively elicited. His vitals were: Pulse rate 90 bpm, Blood Pressure 120/70 mmHg, Respiratory rate 18/min, Temp 37.3 C.

The laboratory values of the patient after hospital admission are shown in table 1.

Jour of Diab and Endo Assoc of Nepal 2020; 4 (2): (29-35)
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Journal of Diabetes and Endocrinology Association of Nepal
CASE REPORT OPEN ACCESS

Table 1: Clinical parameters of the patient during time of admission.

Clinical parameter	Value (normal range)	Clinical parameter	Value (normal range)
Total calcium	5.5 mg/dl (8.4-10.2)	Hemoglobin	13.0 gm/dl (11-16)
Ionised calcium	0.76 mmol/L (1.05-1.27)	RBS	94 mg/dl (<140)
Phosphorus	3.6 mg/dl (2.5-4.5)	Urea	21 mg/dl (10-50)
Magnesium	0.81 mmol/L (0.66-1.07)	Creatinine	1.0 mg/dl (0.6-1.3)
Albumin	4.7 g/dL (3.5-5)	ALP	26 U/L (35-130)
TSH	0.001 uIU/ml (0.3-4.5)	Sodium	144 mmol/L (135-145)
PTH	2.426 pg/mL (6-80)	Potassium	4.6 mmol/L (3.5-5.0)
Vitamin D	64.7 ng/mL (30-80)		

Abbreviations: TSH - Thyroid stimulating hormone; PTH - Parathyroid hormone; RBS - Random blood sugar; ALP - Alkaline phosphatase.

ECG showed a normal sinus rhythm. Intravenous calcium gluconate was given at bolus dose and continued on infusion. His oral medication dose was increased to calcitriol 1 ug/day and elemental calcium 4 g/day. On intravenous calcium infusions, Serum calcium level returned to normal range, but after stopping calcium infusion hypocalcemia recurred. As hypomagnesemia is associated with hypocalcemia, correction of magnesium deficiency was done by intravenous magnesium infusion. We could not maintain normocalcemia even after continuous infusions of calcium gluconate. Symptoms of peri-oral tingling sensation, carpopedal spasm would not completely recover.

We decided to start a parathyroid hormone analog (teriparatide) replacement therapy on this patient. We initiated a once daily 50 mcg subcutaneous injection of recombinant human PTH (1-34) (Teriparatide: Terifrac (rDNA origin) 750 mcg/3ml, Intas Pharmaceuticals Ltd, India) (see figure 2).

Figure 2: Human recombinant parathyroid hormone analogue 1-34 (Teriparatide: Terifrac (r-DNA origin) 750 mcg/3ml, Intas Pharmaceuticals Ltd, India).

Using a reusable pen, teriparatide was instructed to be injected subcutaneously on the lateral aspect of the thigh. 50 mcg or 20 IU of injection was administered every day at the same time. Side effects of headache and pain on the injection site occurred for a few days but was relieved on plain paracetamol tablets. Total calcium and ionized calcium level started to rise. Thereafter, the daily dose of calcium and calcitriol was gradually decreased. Normocalcemia was restored and symptoms completely resolved. On 2020/08/02, the patient was discharged on injection Teriparatide 50 mcg (20 IU) s/c once a day, tablet calcium carbonate 3 gm/day, tablet calcitriol 0.25 mcg/day and tablet levothyroxine 150 mcg/day. At the time of discharge, patient had stable vitals and lab parameters were: serum Total calcium 10.1 (8.4-10.2) mg/dL, Ionised calcium 1.01 (1.05-1.27) mmol/L, phosphorus 3.6 (2.5-4.5) mg/dL, magnesium 0.98 (0.66-1.07) mmol/L, albumin 4.8 (3.5-5) g/dL, and TSH 14.14 (0.3-4.5) uIU/mL. (see figure 3)

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Journal of Diabetes and Endocrinology Association of Nepal
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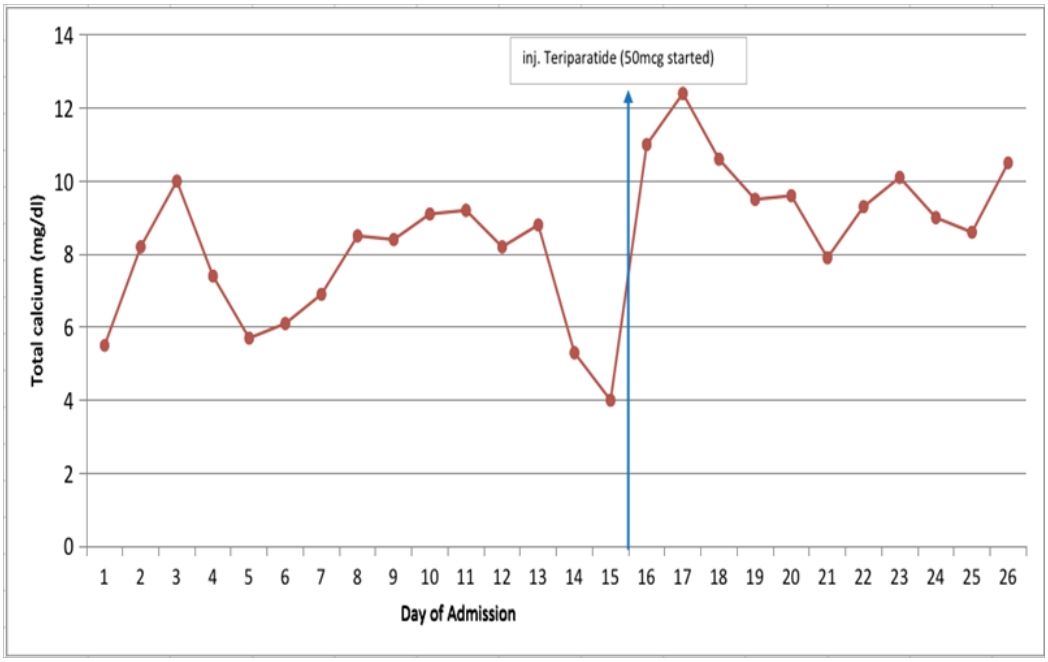

Figure 3: Total calcium measured everyday. Note the high spike in calcium level before initiation of teriparatide is due to intermittent bolus of injection calcium gluconate. After 15 days, injection teriparatide was given as 50 mcg (20 IU) subcutaneous once a day. Calcium infusions were stopped and tablet calcium and vitamin gradually decreased. When needed, serum calcium was adjusted for albumin by the following formula: (0.8 [4.0 - patient's albumin] + serum calcium)

Discussion

In the majority of patients with hypoparathyroidism secondary to post-total-thyroidectomy, hypocalcemia and its associated symptoms can be treated adequately by calcium and active vitamin D analogs. Hypoparathyroidism which does not respond to this standard management is rare. The success rate of parathyroid transplantation is very low worldwide as most trials have resulted in transplant rejections[5]. Therefore, it is reasonable to use PTH analogs (teriparatide) as hormone replacement therapy in such patients. PTH(1-34), (teriparatide) is absorbed rapidly after subcutaneous injection. It has a half-life of 1 hour, with a bioavailability of 95%. it has been observed that 4-6 hours after subcutaneous injection of teriparatide, a peak increase in serum calcium level by approx. 0.4 mg/dL occurs, and that it persists for about 6 hours and return to baseline levels after 16-24 hours[6]. Previously, teriparatide was focused more on the treatment of osteoporosis[7-8]. In recent years, after the FDA approval, PTH analogs have been started to be used for indications like iatrogenic hypoparathyroidism[7].

For 25 years, Winer et al have led a series of systemic investigations into synthetic human PTH(1-34) replacement in hypoparathyroidism irrespective of any etiology. They first investigated once daily PTH(1-34) in 10 adult hypo-parathyroid subjects in a 20-week randomized crossover study of daily PTH(1-34) vs calcium and vitamin D supplementation, which showed that PTH(1-34) achieved superior results by maintaining normal serum calcium and urinary calcium excretion levels, although diminishing effects in serum calcium were seen 12 hours after administration [9]. This can be explained by the short half-life of PTH (1-34). A 28-week study by the same group comparing once daily with twice-daily injections showed that twice-daily dosing with PTH (1-34) produced significantly higher serum calcium levels

Journal of Diabetes and Endocrinology Association of Nepal

CASE REPORT OPEN ACCESS

with less fluctuation throughout the day. Besides, twice daily injections were superior to once-daily injection in reducing the urinary calcium level as well as the total daily dose of PTH(1-34) required for stable calcium level[10]. A longer 3-year randomized study by Winer et al showed that twice-daily subcutaneous PTH(1-34) to be superior to oral calcium and calcitriol by maintaining normal urinary calcium excretion along with stable bone density scores[11]. Other studies also showed better serum calcium homeostasis in multiple dosing of teriparatide than single dosing per day.[12-13]

In 2012, a 6 month-randomized crossover trial in chronic postsurgical hypoparathyroidism cases was done. This trial compared continuous PTH(1-34) delivery by a pump with twice-daily delivery of PTH(1-34). In comparison to twice-daily injection, continuous PTH (1-34) delivery by pump resulted to a remarkable decrease in both urine calcium excretion and in the daily PTH(1-34) dose needed to maintain normal calcium level. Compared to the twice-daily injection regimen, pump delivery was more efficient in normalizing serum calcium and drastically reduced markers of bone turnover. Additionally, pump delivery reduced the excretion of magnesium level and the subsequent need for magnesium supplementation.[14] In a case of postsurgical hypoparathyroidism, few weeks of teriparatide 20 mcg once daily injection proved sufficient to achieve normocalcemia. However, in severe cases of hypoparathyroidism with associated tubulopathy thrice-daily dosing of teriparatide was needed.[13] Zafer et al reported that in a patient with treatment-resistant chronic postsurgical hypoparathyroidism, hypocalcemia was not corrected even after teriparatide usage at 60 mcg/day in three divided doses. In this case, intermittent teriparatide infusion using an insulin pump corrected hypocalcemia.[15] Similar other case reports with postsurgical hypoparathyroidism resistant to standard treatment and subcutaneous injection of teriparatide (once daily or multiple injections) were successfully treated with continuous teriparatide delivery by a pump.[16-17] In total, teriparatide therapy via pump infusion was found to have less fluctuation in serum calcium, long term stabilization of calcium and phosphate, decreased urinary calcium, and significant reduction of PTH total daily dosage as it mimicked the physiological response of natural endothelial parathyroid hormone found in the human body. Furthermore, teriparatide supplementation in chronic postsurgical hypoparathyroidism decreased "brain fog" like symptoms and improved an individual's mental and physical health[18].

In our case study, a single subcutaneous daily dose of teriparatide was sufficient to normalize serum calcium levels without needing intravenous calcium infusions. The dose of oral calcium and calcitriol was also gradually reduced. In 10 days of teriparatide administration, we had a fluctuation in serum calcium range from lower limit to higher limit normal range, but never had any episode of hypocalcemia. Further serial calcium level should be measured in the long term follow up to determine the full efficacy of subcutaneous once-daily dosing of teriparatide. We did not observe any serious adverse reactions besides minor headache and nausea for a few hours, which were attenuated by plain paracetamol and antiemetics. Concerns about carcinogenic potential have been made after the development of osteosarcoma in rats when PTH 1-34 is given for a higher dose and a longer duration[19]. However, multiple studies done on teriparatide over 2 years to 7 years have not shown any carcinogenic risk on humans.[20]

Limitations of this study: Hypocalcemia can be observed in patients with postoperative hypoparathyroidism and an underlying condition can make calcium deficiency even worse. We did not rule out those underlying conditions like impaired calcium absorption from the gastrointestinal tract (D-xylose absorption test, anti-tissue transglutaminase antibody for celiac disease), and tubulopathy associated with excessive urinary calcium loss.

Journal of Diabetes and Endocrinology Association of Nepal

CASE REPORT OPEN ACCESS

Conclusion

There is a chance of chronic hypoparathyroidism in patients with post total thyroidectomy that would present with recurrent hypocalcemia beyond 6 months, which were not managed with the standard protocol of high dose calcium and active vitamin tablets. PTH hormone analog 1-34 (Teriparatide) represents a new alternative option, with a relatively safe therapeutic profile, providing a long term calcium and phosphate homeostasis, while reducing the need of oral vitamin and calcium supplementation.

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Journal of Diabetes and Endocrinology Association of Nepal

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