WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 7.523
Volume 6, Issue 4, 1671-1685. Research Article ISSN 2277–7105

INCIDENCE AND PHARMACOLOGICAL MANAGEMENT OF HYPOTHYROIDISM IN PATIENT SUFFERING FROM DIABETES MELLITUS (Type-II)

[1*]Bidhan Chand Mahato, Sabyata Gautam[2] and Bimbishar Bhattrai[3]

[1]National Model College for Advance Learning, Tribhuvan University, Kathmandu, Nepal.
[2]Sabyata Gautam: PhD Scholar, Department of Pharmacy; Shri JJT University, Rajasthan, India.
[3]Bimbishar Bhattarai: Lecturer, Department of Pharmacy; National Model College for Advance Learning, Tribhuvan University, Kathmandu, Nepal.

Article Received on
20 Feb. 2017,
Revised on 12 Mar. 2017,
Accepted on 02 April. 2017
DOI: 10.20959/wjpr20174-8299

***Corresponding Author**
Bidhan Chand Mahato
National Model College for Advance Learning, Tribhuvan University, Kathmandu, Nepal.

ABSTRACT

Diabetes mellitus is a group of metabolic disease characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. Hypothyroidism is failure of the thyroid gland to produce sufficient thyroid hormone to meet the metabolic demands of the body. The coexistence of diabetes mellitus (DM) with hypothyroidism is a known clinical observation. This is a hospital based prospective cross-sectional study carried out in OPD of Alka Hospital Pvt. Ltd. A total of 208 patients with known or newly detected cases of Type-II DM aged of any group were selected randomly and subjected to evaluation for thyroid function-clinically and biochemically and other relevant investigations were done. Data evaluation was based upon SPSS 20.0 for descriptive and correlation analysis. Out of total 208 Type II DM patients, hypothyroidism (clinical and subclinical) in diabetes was observed to occur in 42(20.19%) patients. Majority of subjects were found to be females. The mean age group at diagnosis of Type-II DM was 60-69 years. Out of 69 patients, 56.52% of diabetes and thyroid status patients were found to be overweight. Metformin was the most commonly prescribed medication. Losartan was the drug of choice in the treatment of diabetic hypertension. Atorvastatin was the most common anti-hyperlipidemics drug prescribed to the patient. Thyroxin was the drug of choice in the treatment of diabetic hypothyroidism. Subclinical

hypothyroidism was more common in female age group 60-69. Majority of patient were overweight.

KEYWORDS: Diabetes Mellitus, Subclinical Hypothyroidism, Prescription Pattern, Incidence.

INTRODUCTION

Diabetes mellitus (DM) is one of the leading causes of death in developing countries like our country Nepal. Thyroid disorders (TD) and DM are the two main common endocrine disorders encountered in clinical practice.[1] The association between DM and TD is widely known, with the first studies published in 1979.[2] Most cases of diabetes mellitus can be separated into two groups, Type 1 (formerly called insulin dependent diabetes mellitus and Type 2 (formerly called noninsulin-dependent diabetes mellitus). Diabetes Mellitus, the most common endocrine disease, is characterized by metabolic abnormalities and by long term complications involving the eyes, kidneys, nerves and blood vessels.[3] Primary hypothyroidism, by contrast, frequently results from autoimmune destruction of thyroid follicles by circulating auto-antibodies (autoimmune thyroiditis). [4] Untreated hypothyroid-ism can contribute to hypertension, dyslipidemia, infertility, cognitive impairment, and neuromuscular dysfunction. [5] Wide ranging changes in carbohydrate metabolism are seen in hypothyroidism, clinical manifestations of these abnormalities are seldom conspicuous. The reduced rate of insulin degradation in hypothyroidism may lower the exogenous insulin requirements. The occurrence of hypoglycemic states is uncommon in isolated thyroid hormone deficiency and should raise the doubt of hypopituitarism in a patient with hypothyroidism. [6] Hypothyroidism is by far the most common thyroid disorder in the adult population and is more common in older women. It is usually autoimmune in origin, presenting as either primary atrophic Hypothyroidism or hashimotos thyroiditis. Diabetic patients have higher prevalence of hypothyroidism because the patients with one organ specific autoimmune diseases are at risk of developing other autoimmune disorders. Hypothyroidism in humans is caused by insufficient production of thyroid hormone by thyroid gland.[7] Thyroid hormones have profound effects in the regulation of glucose homeostasis. These effects include modifications of circulating insulin levels and counter regulatory hormones, intestinal absorption, hepatic production and peripheral tissues uptake of glucose. Thyroid hormones oppose the action of insulin and stimulate gluconeogenesis and glycogenolysis.[1] Hypothyroidism may be either subclinical or overt. Subclinical

hypothyroidism is characterized by a serum TSH above the upper reference limit in combination with a normal free thyroxine (T4). This designation is only applicable when thyroid function has been stable for weeks or more, the hypothalamic-pituitary-thyroid axis is normal, and there is no recent or ongoing severe illness. An elevated TSH, usually above 10 mI U/L, in combination with a subnormal free T4 characterizes overt hypothyroidism. [8]

MATERIALS AND METHODS

Materials

Structured questionnaire and laboratory reports were used as a tool for the collection of information through interview and lab reports.

Study Design

The study was ahospital based prospective cross-sectional study. All the patients who were diagnosed as type-II diabetes mellitus were taken in the study. The study was based on purposive random sampling technique.

Inclusion Criteria

1. Newly diagnosed or follow up patients of hypothyroidism with a history of impaired blood glucose before the onset of treatment.
2. Patients with thyroid disorder.
3. Abnormal blood glucose (Raised Fasting, Random blood glucose or OGTT)
4. Thyroid function showing increased or decreased FT3, FT4, and TSH.

Exclusion Criteria

1. Patients diagnosed with hypothyroidism in Type-I diabetes mellitus.
2. Patients diagnosed with thyroid cancer.
3. Patients unwilling to co-operate.

Statistical Analysis

The statistical analysis of the results was performed by using the SPSS 20 version.

Ethical Consideration

An ethical approval for this research was sought from Alka hospital and then after the permission from hospital the data were accessed accordingly. However, a written consent from the patient/patient party was obtained prior to collecting the data. The identity of the patient and any information which causes harm to patient's reputation was not disclosed.

Each patient were explained about the nature and purpose of study well before recording the data from his or her prescription. All the research activities were carried out under the close guidance of the supervisor. All patients who were diagnosed as type-II diabetes mellitus were evaluated for thyroid status; assessment of FT3, FT4 and TSH levels. The laboratory evaluation of thyroid functions was done by estimation of FT3, FT4 and TSH levels.

The normal readings are

FT3:- 3.10-6.80pmol/L

FT4:- 12.0-22.0pmol/L

TSH: -0.27-4.20 mIU/L

RESULTS

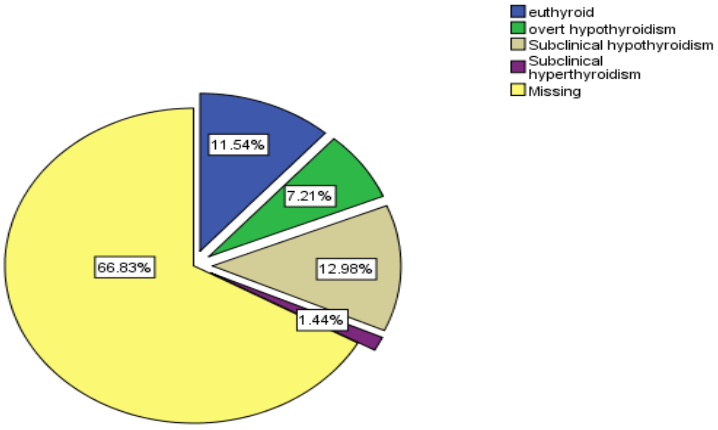

Figure 1: Incidence of Hypothyroidism in Type-II Diabetes Mellitus

Demographic Characteristics

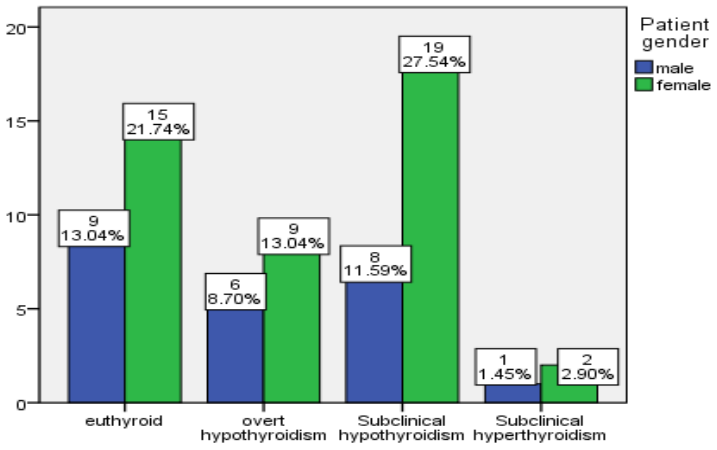

Figure 2: Gender-wise distribution of the Patients

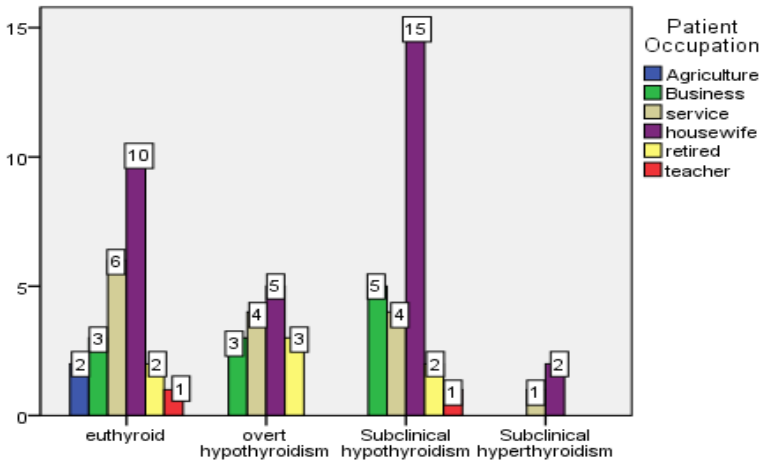

Figure 3: Occupation-wise distribution of the Patients.

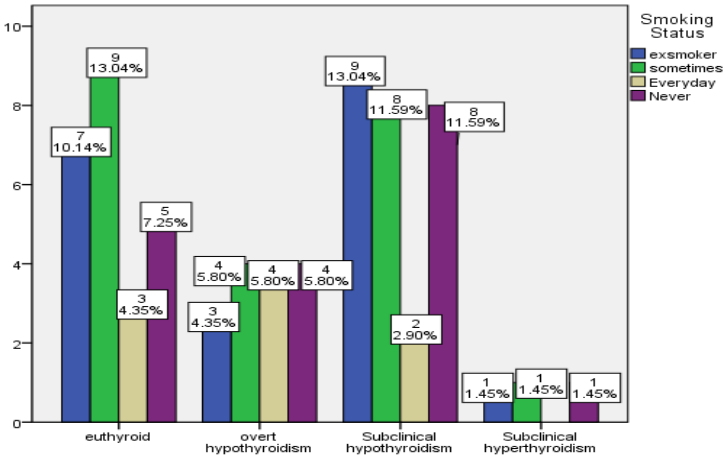

Figure 4: Smoking status-wise distribution of the Patients

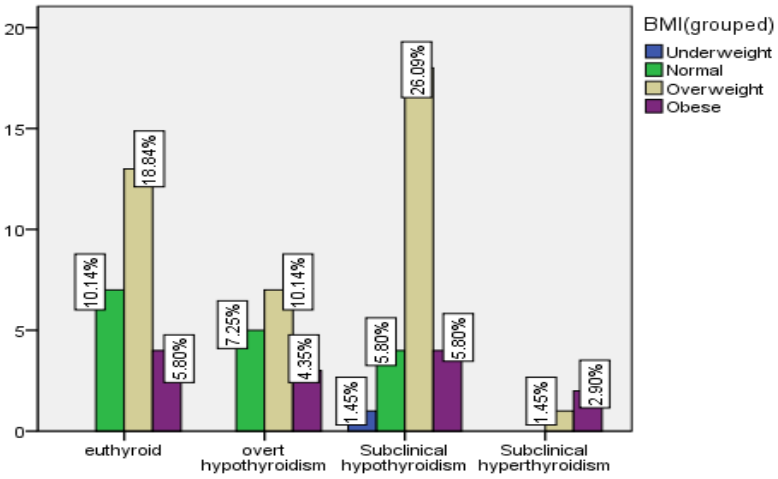

Figure 5: BMI-wise distribution of the Patients

Table 1: Age-wise distribution of the Patients

Thyroid Status	Age(grouped)					Total
	30-39	40-49	50-59	60-69	70-79	
Euthyroid	2	7	3	10	2	24
overt hypothyroidism	1	5	3	3	3	15
Subclinical hypothyroidism	1	2	12	7	5	27
Subclinical hyperthyroidism	1	0	1	0	1	3
Total	**5**	**14**	**19**	**20**	**11**	**69**
Percentage	**7.25%**	**20.29%**	**27.54%**	**28.98%**	**15.94%**	**100%**

Table 2: Educational Status of the Patients

Thyroid Status	Level of Education					
	Illiterate	Primary level (1-5)	Secondary level (6-10)	intermediate & equivalent	Graduate & equivalent	post graduate equivalent & above
Euthyroid	5	2	6	3	4	4
overt hypothyroidism	5	1	2	3	3	1
Subclinical hypothyroidism	13	4	2	4	4	0
Subclinical hyperthyroidism	1	1	0	1	0	0
Total	**24**	**8**	**10**	**11**	**11**	**5**

Out of total 208 subjects, hypothyroidism (Clinical and subclinical) and diabetes was observed to occur in 42(20.19%) patients, of which 24(11.5%) were euthyroid, 15(7.2%) were overt hypothyroidism, 27(13.0%) were subclinical hypothyroidism and 3(1.4%) were subclinical hyperthyroidism. Majority of subjects were found to be females. Out of the total 208 Type-II DM subjects, hypothyroidism and diabetes was observed in 69 patients of which 45(65.22%) were female and 24(34.78%) were male in which female preponderance. Out of 69 patients; 32(46.38%) were found to be housewife, 15(21.74%) were found to be service, 11(15.94%) were found to be businessmen, 7(10.14%) were found to be retired, 2(2.9%) were found to be farmers and 2(2.9%) were found to be teachers. Out of 208 Type-II DM patients, thyroid status and diabetes was observed in 69 patients of which the highest number of smoking status was found in patients who smoke occasionally n=22(31.88%) followed by ex-smoker n=20(28.98%). The number of patient who didn't smoke n=18(26.09%) and n=9(13.04%) who smoke regularly. Out of total 208 Type-II DM patients, diabetes and hypothyroidism was observed in 69 patients; 18.84% of euthyroid diabetics patient were found to be overweight, 5.80% were obese whereas 26.09% were overweight among diabetics with subclinical hypothyroidism.

Out of 69 subjects, the highest number of patients were from age group 60-69 years i.e. n= 20 and followed by age group 50-59 years i.e. n=19 respectively. Most of the patients are found to have subclinical hypothyroidism 27 and followed by euthyroid 24. This study showed that the highest number of patients were illiterate i.e. 24(34.78%), followed by intermediate and graduate & its equivalent 11 (15.94%). Most of the patients were suffering from subclinical hypothyroidism among Type-II DM.

Pharmacological Management

Table 3: Prescription Pattern of Anti-Diabetic Drugs

Drugs	Frequency	Percentage
Metformin	30	14.42%
Metformin+Glimeperide	47	22.59%
Metformin+Sitagliptin	12	5.76%
Metformin + Glipizide	5	2.4%
Metformin+Gliclazide	1	0.49%
Metformin+Acarbose	1	0.4%9
Metformin+Glimeperide+Sitagliptin	22	10.58%
Metformin+Glimeperide+Glipizide	8	3.84%
Metformin+Glimeperide+Acarbose	3	1.44%
Metformin+Glimeperide+Pioglitazone	1	0.49%
Metformin+Glimeperide+Voglibose	4	1.92%
Metformin+Glimeperide+Sitagliptin+Acarbose	2	0.96%
Metformin+Sitagliptin+Glibenclamide+Acarbose	3	1.44%
Metformin+Glimeperide+Sitagliptin+Repaglinide	2	0.96%
Glimeperide	1	0.49%
Glimeperide+Sitagliptin	2	0.96%
Glipizide	2	0.96%
Glipizide+Glibenclamide	1	0.49%
Glimeperide+Rosiglitazone	1	0.49%
Glimeperide+Sitagliptin+Repaglinide	2	0.96%
Insulin	17	8.17%
Insulin+Metformin	20	9.62%
Insulin+Acarbose	4	1.92%
Insulin+Sitagliptin	3	1.44%
Insulin+Metformin+Glimeperide	4	1.92%
Insulin+Metformin+Acarbose	4	1.92%
Insulin+Sitagliptin+Metformin	3	1.44%
Insulin+Metformin+Sitagliptin+Acarbose	3	1.44%
Total	**208**	**100%**

Table 4: Prescription Pattern of Anti-Hyperlipidemic Drugs

Drugs	Frequency	Percentage
Atorvastatin	55	56.7%
Rosuvastatin	31	31.96%
Fenofibrates	11	11.34%
Total	**97**	**100%**

Table 5: Prescription Pattern of Anti-Hypertensive Drugs.

Drugs	Frequency	Percentage
Losartan	29	38.15%
Telmisartan	5	6.58%
Amlodipine	3	3.95%
Irbesartan	2	2.63%
Atenolol	2	2.63%
Enalapril	1	1.32%
Amlodipine+Losartan	13	17.1%
Losartan+Hydrochlorothiazide	6	7.89%
Amlodipine+Telmisartan	3	3.95%
Amlodipine+Irbesartan	2	2.63%
Losartan+Telmisartan	1	1.32%
Irbesartan+Hydrochlorothiazide	1	1.32%
Amlodipine+Losartan+atenolol	5	6.58%
Amlodipine+Atenolol+Telmisartan	2	2.63%
Amlodipine+Irbesartan+Atenolol	1	1.32%
Total	**76**	**100%**

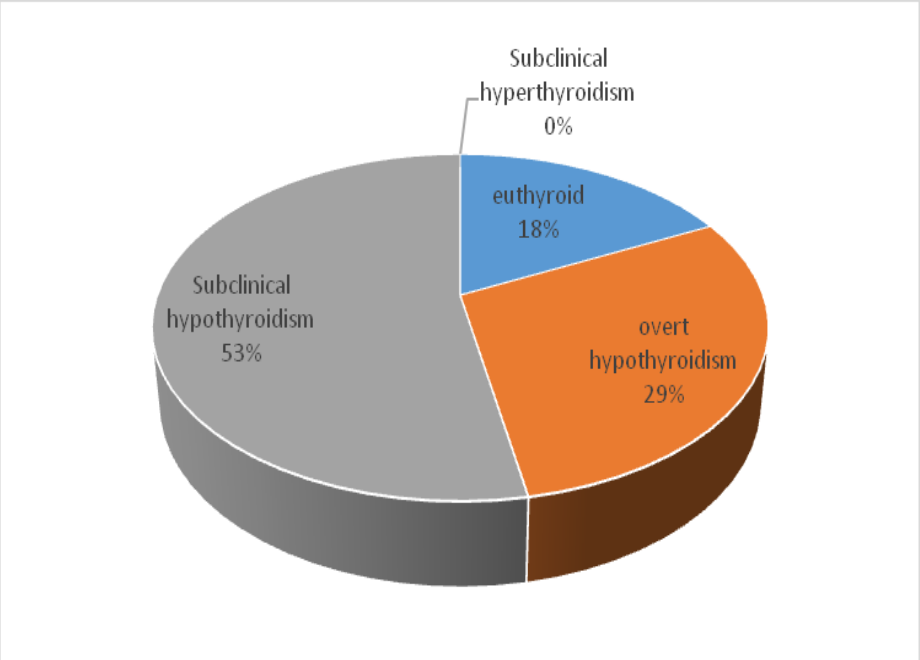

Figure 6: Use of Insulin.

Table 6: Characteristics of Thyroid Status with Type-II Diabetes Mellitus

Thyroid Status with T2DM (N=69)		[N (%)]
Age	60-69	20(28.98%)
Gender	Female	45(65.22%)
Occupation	Housewife	22(46.38%)
Educational level	Illiterate	24(34.78%)
Smoking habit	Sometimes	22(31.88%)
BMI	Overweight	39(56.52%)
Insulin	(-)	52(75.36%)

Table 7: Clinical Parameters (mean ± SD) in 208 patients under evaluation.

Parameters	Mean	SD
Age (Years)	54.44	11.403
Height (m^2)	2.493	0.286
Weight (kg)	65.68	10.347
BMI (Kg/m^2)	26.458	3.798
FBS (mg/dl)	142.802	47.372
PPBS (mg/dl)	206.723	79.525
HbA1c (%)	8.612	5.619
TC (mg/dl)	206.723	50.622
TG (mg/dl)	179.214	113.830
HDL (mg/dl)	47.913	29.797
LDL (mg/dl)	91.205	37.638
FT_3 (µIU/ml)	12.091	29.625
FT_4 (µIU/ml)	8.549	14.923
TSH (µIU/ml)	6.032	11.319
SBP (mmHg)	126.418	16.360
DBP (mmHg)	81.86	9.522

DISCUSSION

Among the endocrinal metabolic diseases, diabetes mellitus occupies the major share. Large numbers of people are suffering from diabetes mellitus in our country, Nepal. The disease is responsible for significant mortality and morbidity due to the complications.

This study was conducted to analyze the incidence and pharmacological management pattern of hypothyroidism in Type II Diabetes Mellitus in an outpatient setting. Drug utilization study will help for the improvement in usage of drug. Selecting proper and a cost effective brand will help in improving the quality of drug usage, cost reduction and improve health outcomes. The study of incidence will also help to know the occurring of diseases in worldwide and the risk factors. People with DM have been reported to suffer from thyroid dysfunction twice as much as the non-diabetic population. The presence of abnormal thyroid hormone levels in diabetic subjects without symptoms of thyroid gland dysfunction has been

reported by many researchers. The need to carry out routine thyroid function test on diabetics has also been recommended particularly on diabetic subjects whose conditions are difficult to manage.[9] A study reported that incidence of thyroid status was found to be more in T2DM patients i.e.33.2% in which euthyroid was found to be 11.5%, 7.2% were overt hypothyroidism, 13.0% were subclinical hypothyroidism and 1.4% were Subclinical hyperthyroidism. Majority of subjects were found to be female patients than that of male patients of age group 60-69. In this study it was found that female patients with thyroid dysfunction in T2DM were more compared with male patients in all age groups. The study shows that majority of patient were found to be illiterate and are housewife. Numerous studies have been done on the prevalence of hypothyroidism in diabetics and relation between them regarding various parameters. Pasupathi et al., the prevalence of thyroid disorder was 45% among type 2 diabetics. Hypothyroidism was present in 28% and 17% had hyperthyroidism.[10] In a study carried out in B.P. Koirala Institute of Health Sciences, Nepal, conducted in a total of 271 patients, hypothyroidism and diabetes was observed in 11 patients, of which 7(30.4%) were clinically hypothyroid and 4 (17.4%) were subclinical hypothyroid was not much remarkable.[11] However in another prospective study conducted in Bangalore, Ravishankar et al., the prevalence of thyroid disorders were present in 29%. [10] The studies done by Domala Prasad, 40.7% (44 no.) of the studied population were males and 59.3% (64 no.) were females. Female to male ratio was 1.45.[12] In the study of 120 T2DM patients at Hyderabad, hypothyroidism was seen in 32%, of which 80% were females. 70% of patients with hypothyroidism were between 40 and 60 years of age which is different from my study. The study carried out in B.P. Koirala Institute of Health Sciences, Nepal, conducted in a total of 271 patients, majority of patients were between 51 and 60 years of age group with female preponderance.[11] The study showed that administration workers increased metabolic risks compared to academics.[13] The study shows that subclinical hypothyroidism had high smoking status than euthyroid in Type II Diabetes Mellitus which differ from other study and shown higher in occasionally smoking patients. The study done by Furukawa et al, the smoking status has shown less in subclinical hypothyroidism than euthyroidism.[14] Smoking has been reported to be a risk for thyroid dysfunction, where higher T4 levels and lower TSH levels were reported among smokers but not among nonsmokers or former smokers. This may be explained by the toxicological effect of smoking on increasing levels of thyroxin binding globulin among smokers.[15] It is worthwhile noting that in the study, FT3 was also associated with smoking habits. In the present study, 26.09% were overweight among diabetics with subclinical hypothyroids, and 34.78% had normal

whereas in previous study done by Prasad D. et al, 59.2% (64/108) were overweight and obese; 38.9% (42/108) had normal BMI.[12]

Pharmacological Management

Prescription of Anti-Diabetic Drugs

In this study, among the total anti-diabetic drugs prescribed (n=437), Oral Anti-Hyperglycemics accounted for 86.73% of the anti-hyperglycemics used. Metformin was the commonly used drugs and prescribed upto 40.04% of the total anti-hyperglycemics drugs, followed by sulfonylureas (27.46%), DPP-4 (12.36%) and AGI (5.49%). Insulin was prescribed upto 13.27% of the total anti-diabetic drugs. Similarly, in combination therapy metformin plus glimepiride or sitagliptin was seemed to be more preferred. Other OAH agents such as AGI and DPP-4 inhibitors were more frequently favored as a third line agent. Our result is similar to that of study done in India on "Pattern of anti-diabetic drug used in Type II diabetic patients in a medicine outpatient clinic of a tertiary care teaching hospital", which also reported that the metformin was the most commonly prescribed drug and followed by sulfonylureas. The study also revealed that the combination of metformin and glimepiride was most frequently used as the combination therapy.**[16]** Similar study done by M.S. Alam et al., metformin consumption was 37% followed by 31.9% sulfonylureas.[17] The study shows that the 40.04% metformin was prescribed more as alone or in combination from 86.73% of total OHDs which indicates that metformin is the most important component of the anti-diabetic therapy. Metformin has a long-standing evidence base for safety and efficacy, and is cost effective. Metformin is recommended as the first line drug for the treatment of diabetes by ADA **[18],** thus the extensive use of metformin is justified. Metformin is the therapy of choice for overweight and obese patients with type 2 diabetes. Metformin acts as a peripheral sensitizer of insulin and also has beneficial effects on insulin resistance, an important factor in the pathogenesis of type 2 diabetes. It reduces cardiovascular- related mortality rates more than sulfonylurea. Metformin is unlikely to cause severe hypoglycemia, because it does not stimulate insulin release. So the endocrinologists may have preferred metformin over other OHAs.[17] AGI are associated with GI disturbances and have less glucose lowering efficacy. Similarly, DPP-4 Inhibitors is considered as safe and effective, are expensive which might be the reason for it's less used. Another of the OAHs, Pioglitazone has been linked with an increased risk of bladder cancer [19]. In this study, insulin seems to have less frequently utilized. There are several limitations for the use of insulin where patient compliance is a major factor. Generally, the patients used to take the medication orally than the parenteral. It

is also perceived as a 'last resort' therapy. The hypoglycemic effect of insulin is also a major corn for its use. Besides these reason, high cost of insulin also upset the use of insulin.

Prescription of Anti-Hyperlipidemic Drugs

HMG-CoA Reductase Inhibitors were the most commonly prescribed any-hyperlipidemic drugs. Of the total dyslipidemic patients, atorvastatin was prescribed in 56.7% of the cases, followed by Rosuvastatin 31.96% and the less frequent used medication was fenofibrates 11.34%. Patients with thyroid dysfunction and type II diabetes have an increased prevalence of lipid abnormalities and cardiovascular risk (CVR) at any age. Studies have shown that use of statins reduce CV events in patients with diabetes. ADA also recommends that statin therapy lowers the risk individual with diabetes, in addition to lifestyle therapy, if LDL-C remains above 100 mg/dl.[20] The uses of fibrates are also seen during study for the treatment of hypertriglyceridemia so as to reduce the risk of pancreatitis. For the non-severe form of hypertriglyceridemia, evidence for benefits of lowering triglyceride levels are not strong and thus ADA suggests lifestyle and dietary interventions.[18] Combination therapy of statin and fibrate was not observed in the study. The combination of statin and fibrate as compared to statin alone, has not shown the to provide additional cardiovascular benefits, and thus is generally not recommended as an option for improvement of cardiovascular outcomes in high risk individuals with Type II diabetes.[9]

Prescription of Anti-Hypertensive Drugs

The study shows that most prescribed anti-hypertensive drugs were ARBs. Losartan was prescribed in 38.15% while Telmisartan was prescribed in 6.58%. ACE inhibitors and ARBs have a renoprotective effect and slow down the progression to diabetic nephropathy.**[21]** Telmisartan also provides cardioprotective action which is very much desirable in patient with diabetes. In this study, other anti-hypertensive drugs were not commonly used as a first line agent. This might be because of the lack of efficacy of such agents in reducing proteinuria and progression of nephropathy. Amlodipine was more used as a second line agent. Clinical trial has shown the benefits of using CCBs as a second line agent to ARBs.[22]

Prescription of Hypothyroidism Drugs

Levothyroxine is the standard treatment for hypothyroidism. There is no option to prescribe other drugs than levothyroxine. Treatment with levothyroxine is usually life long, but because the dosage you need may change. The medication also gradually lowers cholesterol levels elevated by the disease and may reverse any weight gain.

CONCLUSION

Diabetes is a global problem with numerous long term complications and thyroid dysfunction is also one of the leading problems in worldwide. Even though the hallmark metabolic abnormality of hypothyroidism in diabetes is high, other features such as dyslipidemia and hypertension are common in Type-II diabetes and in thyroid status. Thus, Diabetes Mellitus and thyroid status require continuous medical care and support to prevent the complication and to reduce the risk of long term complications. This knowledge should be delivered by the pharmacist during counselling. The greater the duration of uncontrolled Type-II DM in a patient, higher is the chance of thyroid dysfunction. Thus, patient counselling plays important role.

ACKNOWLEDGEMENT

I would like to thank Dr. Ansu Mali Joshi, Consultant Endocrinologist and Dr. Mahesh Dahal, Internal Medicine for his motivation, continuous support, guidance, advice and remarks throughout the thesis work. Last but not the least, I am grateful to Mr. Sudarshan Tandukar for his continuous support and help throughout my work.

REFRENCES

1. Taksali, Reeta; Bindu, S. M.; Mulay, Smita; “Evaluation of Thyroid Dysfunction in Type II Diabetes Mellitus: A Case Control Study”; International journal of Current Medical and Applied Science, 2013; 1(1): 16-20.
2. Palma et al.; Diabetology& Metabolic Syndrome, “Prevalence of thyroid dysfunction in patients with diabetes mellitus”, 2013; 5: 8.
3. Singh, Tajinder; Kaur, Jaswant; “Evaluation of Thyroid Dysfunction in Patients Suffering From Diabetes Mellitus in a Tertiary Care Hospital”; International Journal of Bioassays, 2014; 3(12): 3574-3676.
4. Distiller A, L; Polakow S, E; Joffe I, B; “Type 2 Diabetes Melitus and Hypothyroidism: the possible influence of metformin therapy”; 18 october 2013; DOI: 10. 1111/dme.12342.
5. Gaitonde Y, David; Rowley D, Kevin; Sweeney B, Lori; American Family Physician “Hypothyroidism: An Update”, 2012; 86(3).
6. Bharadiya A, Amit ; Swati C, Aundhkar; Jaju B, Jyotsna; Bharadiya R, Rahi; “Evaluation of Thyroid Function Tests in Patients with Uncontrolled Type 2 Diabetes Mellitus”; International Journal of Health Sciences & Research, 2014; 4(5).

7. Bhavthankar, Sachin; Madole, Mahesh; Somwanshi, Sachin; Ganjewar, Vaishali; "Evaluation of Thyroid Hormones in Patients with Type II Diabetes Mellitus", Journal of Medical Education & Research, 2013; 3(2): 2249-9660.
8. Garber et al.; "Clinical practice Guidelines for Hypothyroidism In Adults: Cosponsored by the American Association of Clinical Endocrinologists and the American Thyroid Association"; 2012; 18(6).
9. Ginsberg, H.N., et al., The New England Journal of Medicine, "Effects of combination lipid therapy in type 2 diabetes mellitus", 2010; 362(17): 1563-1574.
10. C. E. J. Udiong, et al, Journal of Diabetes Mellitus, "Evaluation of BMI & lipid profile in Type 2 Diabetic Subjects with low & raised levels of thyroid hormone in Calabar, Nigeria", 2015; 5: 277-283.
11. Maskey, Robin; Shakya R, Dhana; Baranwal K, Jouslin; Lavaju, Poonam; Karki, Prahlad; Poudel k, Shyam; Indian Journal of Endocrinology and Metabolism; "Hypothyroidism in Diabetes Mellitus Patients in Eastern Nepal", 2015; 19(3): IP: 113.199.230.250.
12. Prasad Domala et al, International Journal of Scientific Research, "The Thyroid Profile in Type 2 Diabetes Mellitus and its Significance", 2014; 3(12).
13. J.C. Maureen, International Journal of Occupational Medicine and Enironmental Health, "Evaluation of the Relationship between Subclinical Hypothyroidism and metabolic Syndrome Components among workers", 2014; 27(2).
14. Furukawa et al., Endocrine Journal Advance Publication, "Association Between Subclinical Hypothyroidism and Diabetic nephropathy in patients with type 2 diabetes mellitus", EJ14-0206, doi:10.1507/endocrj
15. C. L. Fisher, D. M. Mannino, W. H. Herman, and H. Frumkin, "Cigarette smoking and thyroid hormone levels in males," *International Journal of Epidemiology*, 1997; 26(5): 972–977.
16. Patel, B., et al., International Journal of Basic and Clinical Pharmacology, "Pattern of ant-diabetic drugs used in type-2 diabetic patients in a medicine outpatient clinic of a tertiary care teaching hospital", 2013; 2(4): 485-491.
17. M. S. Alam et al, Pharmacology and Pharmacy, "Utilization Pattern of Oral Hypoglycemic Agents for Diabetes Mellitus Type 2 Patients Attending Out-Patient Department at a University Hospital in New Delhi", 5: 636-645.
18. American Diabetes Association, Standards of Medical Care in Diabetes2013. Diabetes Care, 2013; 36(supplement 1): S11-S66.

19. M. Ferwana, et al., Diabetic Medicine, "Pioglitazone and risk of bladder cnacer: a meta-analysis of controlled studies", 2013; 30(9): 1026-1032.
20. Watts L. David, Trace elements, "Hypothyroidism and Hypertension", 2015; 26(1).
21. National Kidney Foundation, KDOQI Clinical Practice guideline for diabetes and CKD: 2012 Update. American Journal of Kidney Diseases, 2012; 60(5): 850-886.
22. Wu, H.Y., et al., BMJ: British Medical Journal, "Comparative effectiveness of renin-angiotensin system blockers and other antihypertensive drugs in patients with diabetes: systematic review and bayesian network meta-analysis", 2013; 347.