

## Original Research Article

# Prevalence of thyroid dysfunction and its association with controlled and uncontrolled type 2 diabetes mellitus in northern Andhra Pradesh population: a retrospective study

Prasad D. K. V.<sup>1</sup>, Prabhakara Rao T. S.<sup>2\*</sup>, Krishna Murthy G.<sup>3</sup>

<sup>1</sup>Department of Biochemistry, NRI Institute of Medical Sciences, Sangivalasa, Visakhapatnam, Andhra Pradesh, India

<sup>2</sup>Department of Paediatrics, NRI Institute of Medical Sciences, Sangivalasa, Visakhapatnam, Andhra Pradesh, India

<sup>3</sup>Department of Microbiology, NRI Institute of Medical Sciences, Sangivalasa, Visakhapatnam, Andhra Pradesh, India

**Received:** 15 July 2017

**Accepted:** 11 August 2017

### \*Correspondence:

Dr. Prabhakara Rao T. S.,

E-mail: drprasaddkv@yahoo.co.in

**Copyright:** © the author(s), publisher and licensee Medip Academy. This is an open-access article distributed under the terms of the Creative Commons Attribution Non-Commercial License, which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

## ABSTRACT

**Background:** The two important endocrinopathies, diabetes mellitus and thyroid dysfunction are interrelated to each other where the correlation is poorly understood. The thyroid dysfunction is more frequent in diabetics than general population. The present study was aimed to know the prevalence of thyroid dysfunction in type 2 diabetes mellitus (T2DM) and its association with controlled and uncontrolled T2DM.

**Methods:** A retrospective study of 600 T2DM patients between 13-60 years of age with known thyroid status were included and the following parameters were examined: age, sex, body mass index (BMI), fasting blood sugar (FBS), HbA1C, free triiodothyronine (fT3), free tetraiodothyronine (fT4) and thyroid stimulating hormone (TSH).

**Results:** The prevalence of thyroid dysfunction in T2DM patients was found to be 26.5% whereas 9% in healthy controls. Significantly elevated levels of FBS, HbA1C and TSH were observed whereas the levels of fT3, fT4 were found to be low in patients when compared to controls. Subclinical hypothyroidism (SCH) in diabetics (both controlled and uncontrolled) was more prevalent (15%) than it was found in healthy controls (5%). Similarly, overt hypothyroidism was also found to be high in diabetic patients (6%) as compared to healthy controls (2%). Significant difference ( $p < 0.05$ ) in the levels of TSH was found between group I (Controlled T2DM) and II (uncontrolled T2DM patients), also between groups II and III (Controls). Group II patients were found to have significant low levels of fT3 as compared to other two groups (Group I and III) ( $p < 0.005$ ).

**Conclusions:** As SCH is more frequent in T2DM diabetes mellitus and untreated SCH patients have higher rate of complications, periodical screening is advised for thyroid dysfunction to prevent micro vascular and cardiovascular complications.

**Keywords:** fT3, Overt hypothyroidism, Subclinical hypothyroidism, T2DM, TSH

## INTRODUCTION

Diabetes mellitus is a common health problem affecting millions of population worldwide and is expected to be 366 million by 2030.<sup>1</sup> The association between thyroid dysfunction and diabetes has been identified since 90's and this has accentuated the importance of screening for

thyroid dysfunction in diabetic patients.<sup>2</sup> It is well documented that uncontrolled diabetes may induce 'low T3' status that is characterized by low total T3 (tT3) and free T3 (fT3) levels, could be due to impairment in peripheral conversion of T4 to T3. The prevalence of thyroid dysfunction in type 2 diabetes mellitus (T2DM) was reported to be between 2.2-17%.<sup>3</sup> However, few

studies as high as 31% and 46.5% respectively were also observed, with the most common disorder being subclinical hypothyroidism (SH) followed by subclinical hyperthyroidism.<sup>4,5</sup> Thyroid hormones function as insulin antagonists and influence the action of insulin indirectly and probably results in low thyroid hormone status in diabetes mellitus.<sup>6</sup> Thyroid hormones regulate glucose homeostasis by exerting profound effects, which include alteration of the circulating levels of insulin and counter regulatory hormone, intestinal absorption, hepatic production and the peripheral tissue uptake of glucose.<sup>7</sup> In hypothyroidism, glucose induced insulin secretion by  $\beta$ -cells is reduced and also increased insulin resistance may influence metabolic changes.<sup>8,9</sup> However, studies exploring the association between thyroid dysfunction and diabetes mellitus are few and with differing conclusions.<sup>10</sup> Therefore, the aim of the present study was to investigate the proportion of subjects having thyroid dysfunction and its association with controlled as well as uncontrolled T2DM patients of northern Andhra Pradesh population.

## METHODS

In this retrospective study, data of 600 T2DM patients based on HbA1C value who have visited General Medicine and Paediatric outpatient departments of Anil Neerukonda Hospital between 13-60 years of age, from March 2016 to June 2017 were included, whose thyroid profile, fasting blood sugar, glycated hemoglobin (HbA1C) were analyzed.

Three hundred number of an independent control group was recruited for the study from Anil Neerukonda Hospital, who have attended General Medicine Department for either minor medical problems or for routine medical checkup. Since the analysis of both the groups is based on a preexisting data obtained from hospital information system, individual informed consent was not obtained. The study was approved by the Ethics Committee of NRI Institute of Medical Sciences.

T2DM patients with HbA1C less than or equal to 7 ( $\leq 7$ ) are named as controlled T2DM (Group I), T2DM cases with HbA1C more than 7 as uncontrolled T2DM (Group II) and finally healthy controls as Group III. The T2DM patients with a previous history of thyroid disorder and

other diseases or drugs that affected the thyroid function were excluded from the study. The difference in the levels of studied biochemical parameters between patients and controls was evaluated by student's t test, one-way analysis of variance (ANOVA) and the p-value of  $<0.05$  was considered to be significant.

## RESULTS

Six hundred T2DM patients (300 controlled and 300 uncontrolled) and 300 nondiabetic healthy controls with a mean age (in years) of  $37.7 \pm 13.6$  and  $38.8 \pm 14.1$  respectively were evaluated in this prospective study. The base line characteristics such as age, BMI, thyroid profile, FBS and HbA1c are depicted in Table 1.

**Table 1: Anthropometric and baseline biochemical characteristics of both patients and controls.**

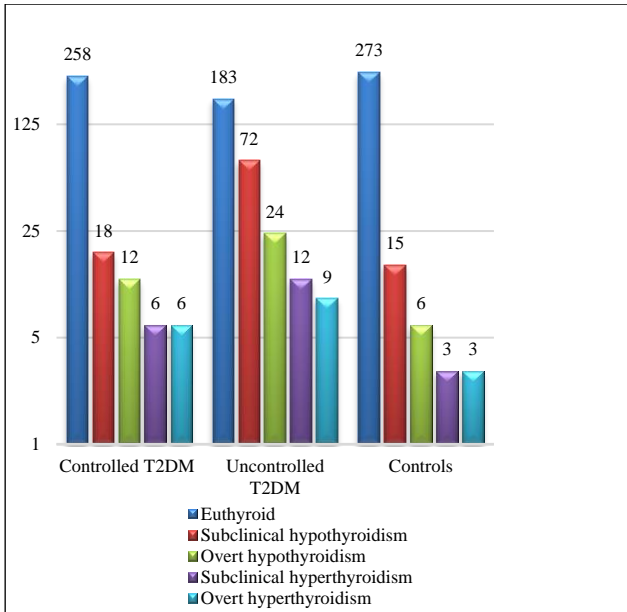
Parameter	Patients (n=600)	Controls (n=300)	p-value (<0.05* significant)
Age (in years)	$37.7 \pm 13.6$	$38.8 \pm 14.1$	0.26
<b>Gender</b>			
Males	246 (41%)	180 (60%)	
Females	354 (59%)	120 (40%)	
BMI ( $\text{kg m}^2$ )	$28.6 \pm 2.08$	$22.3 \pm 2.02$	$<0.001^*$
FBS (mg/d)	$153 \pm 22.6$	$99.6 \pm 5.75$	$<0.001^*$
HbA1C (%)	$7.64 \pm 1.02$	$5.39 \pm 0.59$	$<0.001^*$
ft3 (pg/mL)	$2.92 \pm 0.66$	$4.18 \pm 0.76$	$<0.001^*$
ft4 (ng/dL)	$1.08 \pm 0.28$	$1.25 \pm 0.25$	$<0.001^*$
TSH ( $\mu\text{IU/mL}$ )	$3.23 \pm 1.76$	$1.85 \pm 0.84$	$<0.001^*$

The mean  $\pm$  SD of BMI ( $\text{kgm}^{-2}$ ), FBS (mg/dL), HbA1C (%) of patients and controls were  $28.6 \pm 2.08$ ,  $153 \pm 22.6$ ,  $7.64 \pm 1.02$  and  $22.3 \pm 2.02$ ,  $99.6 \pm 5.75$  and  $5.39 \pm 0.59$  respectively (Table 1). It was noticed that patients had significantly higher BMI compared to controls ( $p < 0.05$ ). Significantly higher levels of FBS were observed in patients as compared to controls ( $p < 0.05$ ) (Table 1). A significant difference was noticed in the levels of ft3, ft4 and TSH between patients and controls ( $p < 0.05$ ) (Table 1). The serum levels of ft3, ft4 and TSH in controlled (Group I), uncontrolled (Group II) and controls (Group III) has been given in Table 2.

**Table 2: Comparison of thyroid hormone levels in controlled, uncontrolled T2DM patients and controls.**

Thyroid hormone	Group I (Controlled T2DM, n=300)	Group II (Uncontrolled T2DM, n=300)	Group III (Controls, n=300)	p-value (<0.05* significant)
ft3 (pg/mL)	$3.42 \pm 0.72$	$2.92 \pm 0.66$	$4.18 \pm 0.76$	$<0.001^*$
ft4 (ng/dL)	$1.09 \pm 0.2$	$1.08 \pm 0.28$	$1.25 \pm 0.25$	$<0.001^*$
TSH ( $\mu\text{IU/mL}$ )	$1.89 \pm 0.73$	$3.23 \pm 1.76$	$1.85 \pm 0.84$	$<0.001^*$

TSH: Group I vs II,  $p < 0.001$ ; I vs III,  $p = 0.53$  and II vs III,  $p < 0.001$ ; ft3: Group I vs II,  $p < 0.001$ ; I vs III,  $p < 0.001$  and II vs III,  $p < 0.001$ ; ft4: Group I vs II,  $p = 0.62$ ; I vs III,  $p < 0.001$  and II vs III,  $p < 0.001$



**Figure 1: Comparative distribution of thyroid dysfunction between controlled, uncontrolled T2DM patients and controls in study population.**

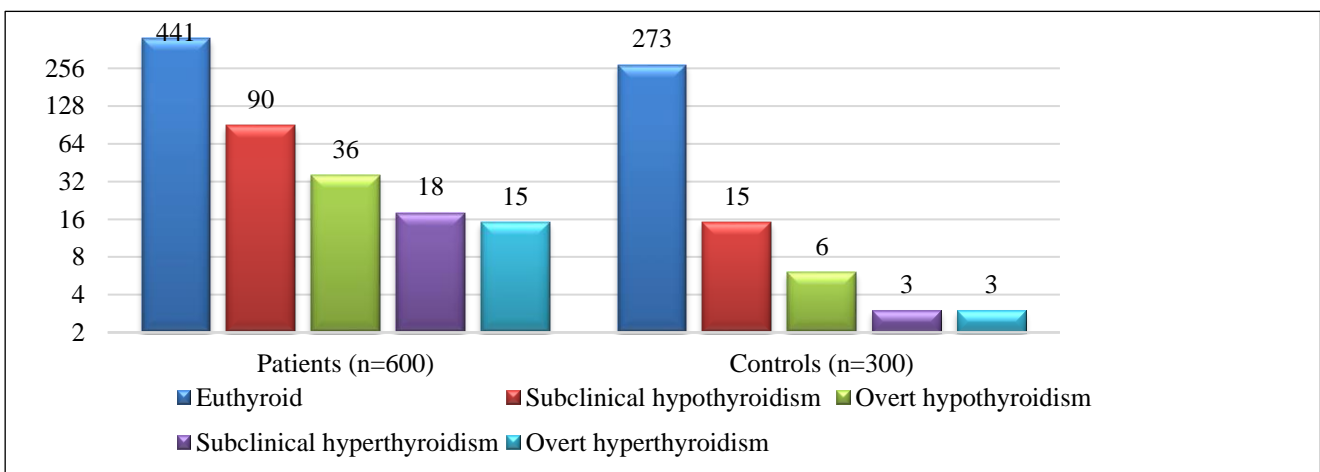
Out of 600 T2DM (controlled and uncontrolled) studied, the prevalence of thyroid dysfunction was found to be

26.5% (Table 3). According to data, the subclinical hypothyroidism was found to be 15% in patients (12 % in Group II and 3% in Group I) and 5% in controls (Group III); overt hypothyroidism 6% (4% and 2% in Group II and Group I patients respectively) and 2% in Group III controls; overt hyperthyroidism 2.5% (1.5 and 1% in Group II and Group I patients respectively) and 1% in Group III controls; and subclinical hyperthyroidism 3% (2% and 1% in Group II and Group I patients respectively) and 1% in Group III controls.

The mean±SD values of free T3 (fT3), free T4 (fT4) and TSH levels of Group I, Group II and controls were 3.42±0.72, 2.92±0.66, 4.18±0.76; 1.09±0.2, 1.08±0.28 and 1.25±0.25 and 1.89±0.73, 3.23±1.76, 1.85±0.84 respectively (Table 2). Significantly lower serum levels of fT3 were found in Group II patients compared to Group I and Group III (p<0.05). Statistically significant lower levels of serum fT4 were observed in Group II compared to Group III (p<0.05). However, no significance was noted between Group I and Group II. Similarly, significant difference in the levels of TSH was noticed among group I, II and III (p<0.05). And also, significantly increased levels were found in group II patients as compared to group I and III (p<0.05). The distribution of thyroid dysfunction in T2DM patients and healthy controls is given in Table 3.

**Table 3: Classification of thyroid dysfunction in controlled, uncontrolled T2DM patients and controls.**

Thyroid function	Group I (controlled T2DM) (n=300)	Group II (uncontrolled T2DM) (n=300)	Group III (controls) (n=300)
Euthyroid	258	183	273
Overt hypothyroidism	12	24	6
Subclinical hypothyroidism	18	72	15
Overt hyperthyroidism	6	9	3
Subclinical hyperthyroidism	6	12	3



**Figure 2: Distribution of thyroid dysfunction between patients and healthy controls.**

The euthyroids are found to be 86%, 61% and 91% in Group I, Group II and Group III respectively (Table 3 and Figure 1). The prevalence of thyroid dysfunction is more in diabetic patients as compared to healthy controls (Figure 2).

## DISCUSSION

Diabetes mellitus is a common health problem affecting millions of populations worldwide. The root cause of diabetes mellitus is defective production or ineffective action of insulin that controls glucose, fat and amino acid metabolism.<sup>11</sup> Adoption of a sedentary lifestyle, the consumption of non-traditional foods, and a genetic predisposition to the disease are some other factors contributing to the development of diabetes mellitus.<sup>12</sup> It is documented that insulin resistance has been associated with hyperthyroidism as well as hypothyroidism.<sup>13</sup> American Diabetic Association has proposed that diabetic people must be screened periodically for thyroid dysfunction.<sup>14</sup> On the other hand, patients with thyroid dysfunction may be advised to screen for the possibility of abnormal glucose metabolism, since excess of thyroid hormones can cause increased production of glucose in liver, rapid intestinal absorption of glucose, peripheral tissue uptake of glucose and increased insulin resistance.<sup>7</sup> It was also observed that patients with abnormal thyroid function have decreased renal flow, cardiac output, glomerular filtration and an increased peripheral vascular resistance contribute to renal dysfunction.<sup>15-17</sup>

Out of 600 T2DM patients studied, the prevalence of thyroid dysfunction was found to be in 159 patients (26.5%), which is three times higher than controls i.e. Group III (9%). Out of these, 117 (19.5%) were in uncontrolled T2DM (Group II) whereas 42 (7%) in controlled T2DM (Group I) patients. This is in accordance with a recent study done in Saudi Arabia, where the incidence was 28.5% as compared to controls.<sup>18</sup>

It has been observed from earlier studies that T2DM patients with SCH and hypothyroidism are more likely to develop complications such as diabetic nephropathy, diabetic retinopathy, peripheral arterial disease and diabetic peripheral neuropathy.<sup>19</sup> In a systematic review and meta-analysis, it has been noticed that the prevalence of SCH was higher in patients with T2DM as compared to healthy controls (OR = 1.93); and the similar trend was observed with studies focused on overt hypothyroidism.<sup>20</sup> In a multivariable model study, hypothyroidism and subclinical hypothyroidism correlated with increased risk for diabetes (rate ratios, 1.53 and 1.75 respectively) among statin users and nonusers.<sup>21</sup> In the present study, it was observed that SCH in diabetics was more prevalent (15%) than it was found in healthy controls (5%). Similarly, overt hypothyroidism was also found to be high in diabetic patients (6%) as compared to healthy controls (2%). However, no significant variation in the prevalence of subclinical hyperthyroidism and overt

hyperthyroidism was observed between diabetics and healthy controls (3%, 1% and 2.5%, 1% respectively).

The thyroid hormones, triiodothyronine (T3) and tetraiodothyronine (T4) are said to be insulin antagonists that enhance the action of insulin indirectly. In diabetes, synthesis of TRH decreases and this could be the possible reason for the low thyroid hormone status in diabetics.<sup>22</sup> In the present study, significant low levels of fT3 and fT4 were found in diabetic patients when compared to controls. Our results were in accordance with the results obtained by Singh et al, in which low fT3 and fT4 were noticed in T2DM patients compared to controls. Similarly, TSH levels were found to be elevated in T2DM patients compared to controls.<sup>23</sup>

Both insulin resistance and  $\beta$ -cell functions are inversely correlated with TSH levels and it may be due to insulin-antagonistic effects of thyroid hormones along with an increase in TSH. As TSH increased, T3, T4 levels decreased and insulin antagonistic effects are diluted. It shows that insulin imbalance is directly associated with thyroid dysfunction and is mediated by  $\beta$  cell dysfunction.<sup>24</sup> In the present study, statistically significant elevated levels of TSH were observed in diabetic patients as compared to healthy controls. Present data is in agreement with the earlier study carried out by Ramesh et al. where elevated TSH levels were claimed in diabetic patients compared to controls.<sup>6</sup> In contrast to the present study, no statistically significant difference in TSH levels was noticed between diabetic patients and controls.<sup>25</sup> As earlier studies suggested, leptin and hyperinsulinemia might stimulate the synthesis of TSH by affecting hypothalamic-pituitary-thyroid (HPT) axis may be the basis for TSH elevation in diabetics.<sup>26,27</sup>

In a Colorado prevalence study, 9.5% of participants were found to have elevated thyroid-stimulating hormone (TSH), and 2.2% had a low TSH.<sup>28</sup> In the present study on the contrary, we have noticed that 21% of diabetics have elevated TSH, while 5.5% had low TSH levels. This incidence may be little higher. Significant difference ( $p < 0.05$ ) in the levels of TSH was found in present study between group I and II, also between groups II and III. And also, TSH levels were higher in Group II compared to Group I and healthy controls. Similar results were also explained by Swamy et al, where higher TSH levels were noticed in uncontrolled T2DM patients compared to controlled diabetic patients.<sup>29</sup> The higher levels of TSH in uncontrolled diabetics can be attributed to interference of uncontrolled hyperglycemia with thyroid axis.<sup>30</sup>

Statistically significant difference in the levels of fT3 was found among the subject groups I, II and III. Uncontrolled T2DM patients were found to have low levels of fT3 as compared to other two groups. No significant difference was observed in the levels of fT4 between group I and II, whereas significant variation was found between groups I and III; and groups II and III. The abnormal fT3 and fT4 levels can be attributed to the

existence of thyroid hormone binding inhibitor (THBI), an inhibitor of 5'-deiodinase enzyme which converts T4 to T3, and dysfunction of the HPT axis. Such conditions may exist in diabetes mellitus and might be aggravated in uncontrolled diabetics.

## CONCLUSION

As T2DM patients with SCH and overt hypothyroidism are more prone to complications such as diabetic nephropathy, diabetic retinopathy, peripheral arterial disease and diabetic peripheral neuropathy, periodic evaluation of diabetic patients for thyroid dysfunction is essential for early diagnosis of diabetic complications. However, further studies need to be carried out to establish an association with thyroid dysfunction, and frequency of screening for thyroid dysfunction in type 2 diabetic patients.

## ACKNOWLEDGEMENTS

Authors would like to thank Professor B. Krishnamma, Superintendent of Anil Neerukonda Hospital for granting permission to retrieve the data from hospital information system, her support and encouragement to conduct this study.

*Funding: No funding sources*

*Conflict of interest: None declared*

*Ethical approval: The study was approved by the Institutional Ethics Committee*

## REFERENCES

- Vikram BV, Shubhangi AK, Krunal KT, Anu NG, Meenakshi K, Rajani RA. Thyroid dysfunction in patients with type 2 diabetes mellitus at tertiary care centre. *Natl J Med Res.* 2013;3(4):377-80.
- Swamy RM, Kumar N, Srinivas K, Manjunath GN, Prasad BDS, Venkatesh G. Evaluation of hypothyroidism as a complication of type 2 diabetes mellitus. *Biomed Res.* 2012;23(2):170-2.
- Vij V, Chitnis P, Gupta VK. Evaluation of thyroid dysfunction among type II diabetic patients. *IJPBS* 2012;2(4):150-5.
- Radaideh AR, Nusier MK, Amari FL, Bateiha AE, El-Khateeb MP, Naser PA, et al. Thyroid dysfunction in patients with type 2 diabetes mellitus in Jordan. *Saudi Med J.* 2004;25(8):1046-50.
- Celani MF, Bonati ME, Stucci N. Prevalence of abnormal thyrotropin concentrations measured by a sensitive assay in patients with type 2 diabetes mellitus. *J Diabetes Res.* 1994;27:15-25.
- Ramesh V, Geetha R, Anitha D, Swamy NRVK, Panneerselvam TT. The study of thyroid dysfunction among type 2 diabetic patients. *Int J Curr Res Aca Rev.* 2015;3(9):17.
- Gabriela B. A view of diabetes from thyroid corner. *Thyroid Int.* 2011;3:2-15.
- Duntas LH, Orgiazzi J, Brabant G. The interface between thyroid and diabetes mellitus. *Clin Endocrinol.* 2011;75(1):1-9.
- Rezzonico J, Niepomniszcze H, Rezzonico M, Pusiol E, Alberto M, Brenta G. The association of insulin resistance with subclinical thyrotoxicosis. *Thyroid.* 2011;21(9):945-9.
- Datchinamoorthi S, Rathanavel N, Rajagopalan B, Vanaja R. Study of thyroid dysfunction in type II Diabetes mellitus. *Int J Pharm Sci Res.* 2016;7(9):3877-80.
- American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care.* 2009;32(1):S62-7.
- Shukla P, Gupta A, Sehgal VK, Kumar R. Communicable behavior of noncommunicable diseases. *Int J Basic Clin Pharmacol.* 2016;5:1711-4
- Wang C. The relationship between type 2 diabetes mellitus and related thyroid diseases. *J Diabetes Res.* 2013;2013:390534.
- Johnson JL. Diabetes control in thyroid disease. *Diabetes Spectrum.* 2006;19(3):148-53.
- Ripoli A, Pingitore A, Favilli B, Bottoni A, Turchi S, Osman NF, et al. Does subclinical hypothyroidism affect cardiac pump performance? Evidence from a magnetic resonance imaging study. *J Am Coll Cardiol.* 2005;45(3):439-45.
- Asvold BO, Bjoro T, Vatten LJ. Association of thyroid function with estimated glomerular filtration rate in a population-based study: the HUNT study. *Eur J Endocrinol.* 2011;164(1):101-5.
- Kotsis V, Alevizaki M, Stabouli S, Pitiriga V, Rizos Z, Sion M, et al. Hypertension and hypothyroidism: results from an ambulatory blood pressure monitoring study. *J Hypertens.* 2007;25(5):993-9.
- Al-Geffari M, Ahmad NA, Al-Sharqawi HA, Youssef AM, Alnaqeb D, Al-Rubeaan K. Risk factors for thyroid dysfunction among type 2 diabetic patients in a highly diabetes mellitus prevalent society. *Int J Endocrinol.* 2013.
- Han C, He X, Xia X, Li Y, Shi X, Shan Z, et al. Subclinical hypothyroidism and type 2 diabetes: a systematic review and meta-analysis. *PLoS One.* 2015;10(8):e0135233.
- Tamez-Perez HE, Martinez E, Quintanilla-Flores DL, Tamez-Pena AL, Gutierrez-Hermosillo H, Diaz de Leon-Gonzalez E. The rate of primary hypothyroidism in diabetic patients is greater than in the non-diabetic population. An observational study. *Med Clin (Barc).* 2012;138(11):475-7.
- Chaker L, Ligthart S, Korevaar TIM, Hofman A, Franco OH, Peeters RP, et al. Thyroid Function and risk of type 2 diabetes: a population-based prospective cohort study. *BMC Med.* 2016;14:150.
- Perros RJP, Shaw MG, Frier BM. Frequency of thyroid dysfunction in diabetic patients: value of annual screening. *Diabetic Med.* 1995;12(7):622-7.
- Singh G, Gupta V, Sharma AK, Gupta N. Frequency of thyroid dysfunction among diabetes in Punjabi population. *Adv Biores.* 2011;2:3-9.

24. Chen G, Wu J, Lin Y, Huang B, Yao J, Jiang Q, et al. Associations between cardiovascular risk, insulin resistance,  $\beta$ -cell function and thyroid dysfunction: a cross-sectional study in She ethnic minority group of Fujian Province in China. *Eur J Endocrinol.* 2010;163(5):775-82.
25. Islam S, Yesmine S, Khan AS, Alam NH. A comparative study of thyroid hormone levels in diabetic and non-diabetic patients. *South East Asian J Trop Med Public Health.* 2008;39(5):913-6.
26. Ortega-Carvalho TM, Oliveira KJ, Soares BA, Pazos-Moura CC. The role of leptin in the regulation of TSH secretion in the fed state: in vivo and in vitro studies. *J Endocrinol.* 2002;174(1):121-5.
27. Reusch CE, Tomsa K. Serum fructosamine concentration in cats with overt hyperthyroidism. *J Am Vet Med Assoc.* 1999;215(9):1297-300.
28. Canaris GJ, Manowitz NR, Mayor G, Ridgway EC. The Colorado thyroid disease prevalence study. *Arch Intern Med.* 2000;160(4):526-34.
29. Swamy RM, Kumar N, Srinivasa K, Manjunath GN, Byrav PDS, Venkatesh G. Evaluation of hypothyroidism as a complication in Type II Diabetes Mellitus. *Biomed Res.* 2012;23(2):170-2.
30. Badman MK, Chowdhury TA. Should thyroid function tests be done annually in all patients with diabetes?. *Diabetes UK J Diab Med.* 2000;19(3):7-9.

**Cite this article as:** Prasad DKV, Rao PTS, Murthy KG. Prevalence of thyroid dysfunction and its association with controlled and uncontrolled type 2 diabetes mellitus in northern Andhra Pradesh population: a retrospective study. *Int J Res Med Sci* 2017;5:3954-9.