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Cause of Hypothyroidism in Post Universal salt iodization era in Nepal.

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Abstract:

Introduction: Iodine deficiency remains the most common cause of hypothyroidism worldwide, but in areas of iodine sufficiency autoimmune disease(Hashimoto's thyroiditis) is most common. After implementation of Universal Salt Iodization(USI) to control Iodine Deficiency Disorder(IDD), Nepal is heading towards iodine sufficiency but the prevalence of clinical and subclinical hypothyroidism is still high. So this study was done to find out either chronic autoimmune thyroiditis is the cause of clinical hypothyroidism in post universal salt iodization era of Nepal by measuring Anti-TPO antibody.

Method: Newly diagnosed patients with Clinical or Sub clinical hypothyroidism by thyroid function test were included in this study. Anti-TPO antibody was measured by Elisa method, Anti-TPO >34 was considered positive. All the data's were analyzed using SPSS software.

Result: In this study 1000 patients were included, male to female ratio was 5:1. 270 patients had clinical hypothyroidism among which 230(85.1%) patients had Anti-TPO antibody positive. Among 730 patients with subclinical hypothyroidism only 220(30.1%) patients had antibody positive. Our result showed that TPO antibody was positive in clinical hypothyroidism compared to subclinical hypothyroidism with statistical significance ($p<0.001$). Our result also showed that clinical hypothyroidism had higher TPO value (mean 225.14) compared to subclinical hypothyroidism (74.34) with statistical significance $p<0.001$.

Conclusion: The cause of hypothyroidism in present day Nepal is chronic autoimmune thyroiditis (Hashimoto's thyroiditis). As we are moving from iodine deficiency status to iodine adequate or iodine excess status there might be an increased burden of thyroid disorders in Nepal due to the increased prevalence of autoimmune thyroiditis.

Key Words: Universal Salt Iodization(USI), Iodine Deficiency Disorder(IDD), Clinical Hypothyroidism, Sub-Clinical Hypothyroidism, Anti-TPO antibody.

Introduction:

Hypothyroidism is defined as the hypo functioning of the thyroid gland. It not only causes cretinism and goiter but also leads to impaired mental and physical development in children and adolescents, impaired mental function and reduced productivity in adults and an increased risk of spontaneous abortion, stillbirths, and congenital abnormalities in pregnancy. Hypothyroidism may be either Subclinical or Clinical. Subclinical hypothyroidism is characterized by a serum TSH above the upper reference limit in combination with a normal free thyroxine (FT4).[1] An elevated TSH, usually above 10 mIU/L, in combination with a subnormal free T4 characterizes Clinical hypothyroidism.[1]

Iodine deficiency remains the most common cause of hypothyroidism worldwide, but in areas of iodine sufficiency, autoimmune disease(Hashimoto's thyroiditis) is most common.[2] World Health Organization's epidemiological criteria for assessing iodine nutrition is defined as median urinary iodine excretion of <100µg/l as insufficient, 100-199 µg/l as adequate, 200-299 µg/l as more than adequate and >300 µg/l as excessive.[3] 1998 Nepal micronutrient status survey showed that prevalence of goiter and insufficient urinary iodine excretion among school aged children were 40%

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and 35.1% respectively. This survey showed that 17.2% household of Nepal were using salt with no iodine content and as the iodine content in household salt decreases, the prevalence of low urinary iodine excretion increases.[4] So Nepal government has implemented universal salt iodization(50ppm) as a sole policy to control IDD in Nepal after late nineties. After universal salt iodization, NSISIDD 2007 result showed that national median urinary iodine excretion was 202µg/l[5] and the 2011 NDHS[6] results showed that more than 95 percent of households were using iodized salt showing that Nepal was heading towards iodine sufficiency. But 2016 Nepal National Micronutrient Status Survey showed that median UIC of children 6-9 years was 314.1 µg/l, among nonpregnant women of 15-49 years median UIC was 286.2 µg/l and among pregnant it was 241.3 µg/l.[7]

Although there is no national data available about the actual prevalence of clinical and sub clinical hypothyroidism in general population in Nepal. Mahato et al[8] in a hospital based retrospective study done in central Nepal showed that the prevalence of thyroid disorders were 29.0% with Subclinical hypothyroidism 17%, clinical hypothyroidism 8%, clinical hyperthyroidism 3% and Sub-clinical hyperthyroidism 1%. The authors concluded that as this study was done in hospital setup so there might have been higher prevalence of thyroid disorders. While in a similar kind of study done in Eastern Nepal by Rohil V et al[9] showed the prevalence of subclinical hypothyroidism was 20.42 % . Despite the implementation of USI program for almost two decades and the results showing elimination of Iodine deficiency disorder in Nepal, the prevalence of clinical and subclinical hypothyroidism is still high. 2016 National Micronutrient Status Survey[7] showed that Nepal is on transition from iodine deficiency to iodine excess status so the increased prevalence of thyroid disorders in Nepal might be due to chronic autoimmune thyroiditis(Hashimoto's thyroiditis). Approximately 75% of patients with chronic autoimmune thyroiditis have elevated anti-thyroid antibody titers[10] whereas in general population anti-TPO-Ab is positive in only 3.4%, with a female to male ratio of 2.7:1[10]. Once present, these antibodies generally persist, with spontaneous disappearance occurring infrequently. So this study was done to find out either chronic autoimmune thyroiditis is the cause of sub-clinical and clinical hypothyroidism in post universal salt iodization era of Nepal by measuring Anti-TPO antibody.

Method:

This study was done in adult patients (excluding pregnant women) who came to different endocrine clinics at Lalitpur district in the last six months. Patients who were newly diagnosed as having Clinical or Sub clinical hypothyroidism by their thyroid function test were included in this study and vocal consent was taken. All the thyroid function test and Anti-TPO tests were done inside one lab to have a uniform results. TFT was done in ADVIA Centaur CP CLIA Siemens. The normal range for TSH was 0.35-5.50µIU/ml, Free T4 was 0.89-1.76ng/dl, and Free T3 was 2.3-4.2pg/ml. Subclinical hypothyroidism was diagnosed by a serum TSH above the upper reference limit(5.5µIU/ml) in combination with a normal free thyroxine (FT4). Clinical hypothyroidism was diagnosed as an elevated TSH, usually above 10 mIU/L, in combination with a low free T4(<0.89ng/dl) Patients with TSH above 10 but normal FT4 were diagnosed as having sub clinical hypothyroidism and patients with TSH below 10 with low FT4 were excluded from the study considering the possibility of Secondary hypothyroidism. Anti-TPO antibody was measured by Elisa method with Anti-TPO level >34 was considered positive with Anti-TPO level>600 was considered highly positive. All the data's were analyzed using SPSS software.

Result:

In this study, a total of 1003 patients were included. 3 patients were excluded from the study suspecting secondary hypothyroidism with normal serum TSH and low FT4 level, among which two had empty sella syndrome and the third patient was lost in follow up. So from the remaining 1000 patients who were included in this study there were 164(16.4%) male patients with

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the remaining 836(83.6%) female patients. There were 270 patients with clinical hypothyroidism among which 230(85.1%) patients had Anti-TPO antibody positive and among 730 patients with subclinical hypothyroidism only 220(30.1%) patients had antibody positive. Pearson Chi square test was done for statistical analysis and it was found that TPO antibody was seen positive more in clinical hypothyroidism compared to subclinical hypothyroidism with statistical significance ($p<0.001$). Independent sample t test was done to find out the difference in TPO values between clinical and subclinical hypothyroid patients and it showed that clinical hypothyroidism had higher TPO value (mean 225.14) compared to subclinical hypothyroidism (74.34) with statistical significance $p<0.001$. There was no statistical significance in age group between these two hypothyroid patients. TPO antibody positive group had higher TSH value (mean 32.68) compared to negative TPO antibody group patients (mean 13.42). Independent sample t test was done and it showed statistical difference between two groups with $p<0.001$. Likewise TPO positive group had lower FT3 and FT4 value (mean 2.11 and 0.73) compared to negative antibody group (2.50 and 1.16) with statistical significance $p=0.005$ and $p<0.001$ respectively. There was no statistical significance in age in between the above two groups.

Table-1: Demography.

Total patients	Male	Female
1000(100%)	164(16.4%)	836(83.6%)

Table-2: Antibody Crosstabulation

Type	Anti-TPO Antibody		Total
	Positive	Negative	
Clinical	230(85.1%)	40(14.9%)	270(100%)
Sub-Clinical	220(30.1%)	510(69.9%)	730(100%)
Total	450(45%)	550(55%)	1000(100%)

Table-2: Antibody Crosstabulation: Result showed that TPO antibody is seen positive more in clinical hypothyroidism compared to subclinical hypothyroidism with statistical significance ($p<0.001$).

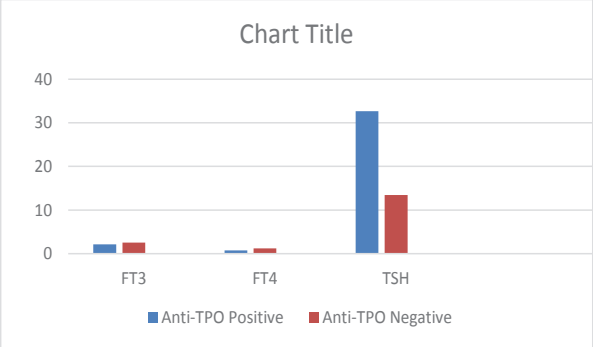

Fig-1: Result showed that TPO antibody positive group had higher TSH value (mean 32.68) compared to negative (mean 13.42) with statistical significance ($p<0.001$).
Likewise TPO positive group had lower FT3 and FT4 value (mean 2.11 and 0.73) compared to negative antibody group (2.50 and 1.16) with statistical significance $p=0.005$ and $p<0.001$ respectively.

Discussion:

Iodine deficiency is the most common cause of hypothyroidism worldwide. Two decades ago Iodine deficiency disorders were very common in Nepal with goiter and low urinary iodine excretion(<100 µg/l) prevalence of 40% and 35.1% respectively.[4] After the government of Nepal implemented Universal Salt Iodization(U.S.I) program in late nineties Nepal is already on track to eliminate Iodine Deficiency Disorder(IDD). 2016 Nepal National Micronutrient Status Survey result showed elimination of IDD with more than adequate or excess level of median urinary iodine concentration but hypothyroidism prevalence is still high in Nepal.

Our result showed that anti-TPO antibody was positive in more than two third of patients with clinical hypothyroidism but only one third of patients with sub clinical hypothyroidism had anti-TPO

antibody positive. We found that TPO antibody was seen positive more in clinical hypothyroidism compared to subclinical hypothyroidism with statistical significance ($p<0.001$). Patients with Clinical hypothyroidism had higher TPO value (mean 225.14) compared to subclinical hypothyroidism (74.34) with statistical significance $p<0.001$. TPO antibody positive group had higher TSH value (mean 32.68) compared to negative TPO antibody group patients (mean 13.42). It has been argued in the literature that introduction of iodine in a previously iodine deficient population may precipitate the emergence of thyroid autoimmunity.[11] According to some studies, iodine supplementation in iodine deficient areas increases the prevalence of thyroid autoantibody positivity and lymphocytic infiltration of thyroid gland.[12-14] Also, the prevalence of thyroid autoantibody positivity in such areas rises to over 40% within 5 years of initiating supplementation.[15] In a study by Wei Ping Teng et al[16] in China, incidence of both overt and subclinical hypothyroidism were higher in regions where iodine intake increased from being mildly deficient before salt iodization to more than adequate and excess level afterward. This study also suggest that more than adequate or excessive levels of iodine intake can increase the prevalence of autoimmune thyroiditis and hypothyroidism. A prospective study done in two areas of Denmark with moderate and mild iodine deficiency showed that after iodine fortification there was an increased incidence of overt hypothyroidism.[17] Our result also showed that chronic autoimmune thyroiditis might be the cause of clinical hypothyroidism in Nepal in this post universal salt iodization Era as Nepal has already eliminated IDD.

The relationship between iodine intake and thyroid disorders is a U shaped curve, as both low and high intake of iodine is associated with increased thyroid disorders.[18] As low iodine intake can cause cretinism, hypothyroidism and goiter, more than adequate or excess iodine intake can also increase the prevalence hypothyroidism, graves' disease and goiter.[18] Several studies have shown that higher iodine intake is associated with higher prevalence of sub clinical hypothyroidism in the general population.[16,17] In one study in Eastern Nepal[19], Median UIE of Dhankuta and Sunsari were more than adequate with 238.00 µg/L and 294.96 µg/L respectively with Relatively higher percentage (31.8%) of subclinical hypothyroid cases in Sunsari than Dhankuta (29.59%) where UIE was more. In another community based study done in Tehrathum and Morang districts of Nepal the median UIE were 345.65 and 270.36 µg/L with prevalence of sub-clinical hypothyroidism of 19.5% and 16.5%respectively.[20] In a study by Unnikrishnan AG et. al in India in the post iodization era, prevalence of hypothyroidism was 10.95%(self-reported +newly diagnosed), in the same study anti - TPO antibodies were detected in 21.85% of the study population suggesting autoimmunity.[21] In a study by Christos Zois et al there was three times higher prevalence of Autoimmune Thyroiditis in schoolchildren after elimination of Iodine deficiency in Northwestern Greece.[22]

After Universal Salt Iodization, which was initiated in Nepal almost two decades ago, we are successful in reducing the prevalence of cretinism and goiter in our society but the prevalence of thyroid disorders are still high in our country. Our study clearly showed that Hashimoto's thyroiditis is the cause of hypothyroidism in this post USI era in Nepal, as Nepal has already eliminated iodine deficiency disorder.

Conclusion:

It's time for Nepal government to reevaluate our two decade old universal salt iodization program as we are moving from iodine deficiency status to iodine adequate or iodine excess status. If we don't act now there might be increased burden of thyroid disorders(especially hypothyroidism) in Nepal due to increased prevalence of autoimmune thyroiditis due to excess Iodine supplementation. This study shows that maybe it's high time for the government of Nepal to change it's universal salt iodization policy accordingly.

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