Pacific Journal of Medical and Health Sciences
ISSN: 2456-7450 | Vol.5, No. 3, 2023, pp - 58 - 67

PJMHS
PACIFIC JOURNAL OF MEDICAL AND HEALTH SCIENCES

Review

The Present Status of Prevalence of Vitamin B12 Deficiency in Hypothyroid Individuals – A Review

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ABSTRACT

It is not uncommon to find the conglomeration of autoimmune diseases in a person. The most common autoimmune hypothyroidism is seen in general population and frequently associated with other autoimmune conditions like pernicious anaemia, celiac disease, rheumatoid arthritis etc. The present short review point towards the common association of hypothyroidism with vitamin B12 deficiency observed by different scientific groups. The symptoms of both the conditions overlap and therefore it is important to consider this common association for better patient management.

KEYWORDS: Autoimmune thyroiditis, Levothyroxin, Cobalamin, TPA

INTRODUCTION

The most prevalent endocrine disorder in developing countries is related to thyroid hormone imbalance. Hypothyroidism is a common endocrine disorder with reduced production of thyroid hormones. It is a common disease with different frequency between countries. However, the common occurrence of hypothyroidism is three times more in women than in men (12.4% versus 3.7%) in developing countries. Sex, geographical factors, age, ethnicity and iodine consumption are the determining factors for the occurrence of thyroid diseases[1]. Out of total patients of hypothyroidism, about 12% with primary autoimmune type disease experience pernicious anaemia. In hypothyroidism vitamin B12 deficiency is observed in up to 40% of patients[2].

Vitamin B12 (also known as cobalamin) is found naturally in animal foods or artificially in fortified cereals. Cobalamin has a complex mechanism of absorption in the terminal ileum that depends on the intrinsic factor (a secretory product of the gastric parietal cells) and eventually releases cobalamin in the blood linked to the plasma binding protein, transcobalamin[3].

The prevalence of B12 deficiency varies depending on the level used to define deficiency and the populations studied. In developed countries, vitamin B12 deficiency (serum B12 level <148 pmol/L) increases with age from 3% in the younger population to reach 10% in the elderly. Borderline B12 levels or subclinical cobalamin deficiency (SCCD), which is defined as a serum B12 level between 148 and 221 pmol/L, is reported in 20% of the elderly population. In developing countries, the prevalence of low and borderline B12 levels is elevated approaching 70% in adults. Furthermore, detection of B12 deficiency depends on the diagnostic strategy and the type of B12 assay used in the measurement[4,5].

In general, poor dietary intake and malabsorption conditions for example, pernicious anemia (PA), are the most common causes of B12 deficiency. The wrongheaded immune response in PA is directed against the gastric parietal cells and the gastric H/K-ATPase resulting in the deficiency of the intrinsic factor and achlorhydria. Vitamin B12 deficiency in PA is not only caused by the loss of the intrinsic factor but is also due to the associated achlorhydria because gastric acid is needed to release cobalamin from its dietary sources [6].

Primary hypothyroidism is a disease of the thyroid gland that results in a reduction of the blood levels of the thyroid hormones (thyroxine [T4] and triiodothyronine [T3]) and a subsequent compensatory rise in the thyroid-stimulating hormone (TSH) levels. Hypothyroidism can be either overt (OH), with elevated TSH and low free T4 levels, or subclinical (SCH), with a normal free T4 level despite the elevated TSH level. Hypothyroidism affects 3% to 5% of adults and is more common in women and the elderly[7].

In iodine-sufficient regions, autoimmune thyroiditis is the most common cause of primary hypothyroidism, and it is usually associated with the antithyroid peroxidase (TPO) and the antithyroglobulin (TG) autoantibodies[8].

The prevalence of B12 deficiency is 10% to 40% among hypothyroid patients. Previous studies showed that 5% to 10% of patients with primary hypothyroidism have pernicious anaemia, whereas 24% of pernicious anaemia patients have thyroid disease[1].

The link between hypothyroidism and PA is related to the common autoimmune aetiology of both disorders. In addition to PA, hypothyroid patients may have other abnormalities that may cause vitamin B12 deficiency such as inadequate dietary intake or decreased intestinal absorption due to slow gut motility and bacterial overgrowth[2].

Another condition that may coexist with hypothyroidism and can cause B12 deficiency is celiac disease which is an autoimmune disease of the gut that occurs in genetically susceptible individuals due to gluten sensitivity. Twenty-six percent of celiac disease patients have autoimmune thyroid disease (AITD). Low serum level of vitamin B12 is seen in about 40% of untreated celiac disease patients[9].

Both B12 deficiency and hypothyroidism can present with symptoms such as depression, memory impairment, dementia, fatigue, numbness, and paresthesia. Due to the non-specificity of symptoms, B12 deficiency may be overlooked in hypothyroid patients[10].

The early recognition and appropriate treatment of B12 deficiency in hypothyroid patients are crucial because it is a reversible cause of peripheral neuropathy (PN), myelopathy, cognitive defects, anaemia, and pancytopenia. However, the significance of B12 deficiency in hypothyroidism and the need to screen hypothyroid patients with serum B12 level measurement is a subject of controversy. Some studies reported a prevalence of B12 deficiency among hypothyroid patients similar to euthyroid patients, while other studies reported a high prevalence of B12 deficiency among hypothyroid patients[11]. The present paper will review the facts concerned with hypothyroidism and B12 deficiency association

REVIEW OF LITERATURE

Hypothyroidism

Hypothyroidism is a chronic disease associated with deficiency in the thyroid hormones, thyroxine (T4) and triiodothyronine (T3). Untreated or inadequately treated hypothyroidism results in musculoskeletal and nurological symptoms, , cardiovascular disease, and infertility[12]. Environmental iodine deficiency is the most common cause of hypothyroidism, worldwide, while in areas of iodine sufficiency, the most common cause of primary hypothyroidism is autoimmune thyroiditis (Hashimoto's disease)[13].

The full implications of hypothyroidism in the population are not completely appreciated or defined. Hypothyroidism affects up to 5% of the population according to European prevalence estimates, while as many as 5% of the population may have undiagnosed thyroid failure[14]. Among the patients who are treated, up to one-third are not receiving adequate treatment. The economic impact of undiagnosed, untreated or undertreated hypothyroidism is therefore not inconsequential, especially with regard to costs associated with maternal and congenital hypothyroidism, or with hypothyroid patients having comorbid conditions such as diabetes mellitus[15].

Hypothyroidism is also associated with decreased quality of life, increased number of sick leave days and even increased mortality[16]. Levothyroxine is the mainstay of treatment for hypothyroidism, and is one of the World Health Organization's essential medicines required for basic health care[17].

Epidemiology and Risk Factors

The prevalence of overt hypothyroidism in the general population varies between 0- 3% and 3-7% in the USA and between 0-2% and 5-3% in Europe, depending on the definition used[14].

A meta-analysis[7] of studies across nine European countries estimated the prevalence of undiagnosed hypothyroidism, including both overt and mild cases, at around 5%. Differences in iodine status affect the prevalence of hypothyroidism, which occurs more frequently both in populations with a relatively high iodine intake and in severely iodine-deficient populations[18].

Hypothyroidism occurs more frequently in women, in older people (>65 years), and in white individuals, although data on ethnic differences are scarce[19].

Hypothyroidism is more common in patients with autoimmune diseases, such as type 1 diabetes, autoimmune gastric atrophy, and coeliac disease, and can occur as part of multiple autoimmune endocrinopathies. Individuals with Downs'

syndrome or Turners' syndrome have an increased risk of hypothyroidism. By contrast, tobacco smoking and moderate alcohol intake are associated with a reduced risk of hypothyroidism[20].

The heritability of TSH and free thyroxine concentrations in serum is estimated to be 65% and 23-65%, respectively[21]. Results from genome-wide association studies have so far explained only a small proportion of thyroid function variability and only three studies have focused on hypothyroidism specifically. The loci most consistently implicated in hypothyroidism include autoimmunity-related genes and thyroid-specific regulatory genes (panel). Most of these loci are also associated with serum TSH concentrations within the reference range[22]. Monogenetic disorders leading to congenital hypothyroidism are rare and include TSH resistance (due to an inactivating mutation in the TSH receptor), thyroid dysgenesis, and thyroid dyshormonogenesis[23].

Causes and Classification

Hypothyroidism can be classified as:

1. Primary (due to thyroid hormone deficiency);
2. Secondary (due to TSH deficiency);
3. Tertiary (due to thyrotropin-releasing hormone deficiency); and
4. Peripheral (extra-thyroidal; panel)

Central hypothyroidism (including both secondary and tertiary) and peripheral hypothyroidism are rare and account for less than 1% of cases[24].

In iodine-sufficient areas, the most common cause of hypothyroidism is chronic autoimmune thyroiditis (also known as Hashimoto's disease). High concentrations of anti-thyroid antibodies (predominantly thyroid peroxidase antibodies and anti-thyroglobulin antibodies) are present in most patients with autoimmune thyroiditis. Raised concentrations of thyroid peroxidase antibodies are also detected in about 11% of the general population[25].

In patients with subclinical hypothyroidism, thyroid peroxidase antibody measurements help to predict progression to overt disease. The exact mechanisms underlying autoimmune thyroiditis are not known, but both genetic and environmental factors are involved. A higher genetic risk score-calculated using five genetic variants for thyroid peroxidase antibodies identified by genome-wide association studies- showed a graded association with higher TSH concentrations and clinical hypothyroidism[26].

Smokers have lower thyroid peroxidase antibody concentrations than non-smokers, and incidence of autoimmune thyroiditis increases after smoking cessation. Other environmental factors implicated in autoimmune thyroiditis are vitamin D and selenium deficiency, and moderate alcohol intake[27].

Central hypothyroidism is rare and affects both sexes equally. It is more often associated with pituitary than hypothalamic disorders but frequently involves both[24].

Biochemically, central hypothyroidism is defined by low or low-to-normal TSH concentrations and a disproportionately low concentration of free thyroxine. Occasionally, TSH concentration is mildly elevated, probably because of decreased bioactivity[28].

Over half of central hypothyroidism cases are caused by pituitary adenomas. Other causes of central hypothyroidism include pituitary or hypothalamic dysfunction due to head trauma, pituitary apoplexy, Sheehan's syndrome, surgery, radiotherapy, genetic, and infiltrative disease. Several drugs are known to affect the hypothalamic-pituitary- thyroid axis (panel)[29].

Consumptive hypothyroidism is caused by aberrant expression of the deiodinase 3 enzyme (which inactivates thyroid hormone) in tumour tissues. Although very rare, such over-expression can induce severe hypothyroidism. Elevated concentration of deiodinase 3 was first described in a newborn baby with infantile hepatic haemangiomatosis, but can also occur in patients with vascular and fibrotic tumours and gastrointestinal stromal tumours[30].

Patients with rare genetic syndromes that lead to a reduced sensitivity to thyroid hormone (panel) usually have normal TSH concentrations, but can also present with tissue-specific hypothyroidism[31].

Clinical Presentations

The clinical manifestations of hypothyroidism range from asymptomatic presentation to life threatening- myxedema coma. Myxedema coma, which was first described in the late 1900s as an outcome of long-standing untreated and severe hypothyroidism, has become a rare condition. Nevertheless, because the disease course is striking, with mortality of 40% despite treatment, early recognition is vital[32].

Myxedema coma leads to an altered mental status, hypothermia, progressive lethargy, and bradycardia and can eventually result in multiple organ dysfunction syndrome and death. Therefore, early initiation of thyroid hormone therapy and other supportive measures is crucial[33].

Although very rare, severe primary hypothyroidism can lead to pituitary hyperplasia with concomitant pituitary pathology (e.g., secondary adrenal insufficiency) and symptoms (e.g., amenorrhoea)[34].

The most common symptoms of hypothyroidism in adults are fatigue, lethargy, cold intolerance, weight gain, constipation, change in voice, and dry skin, but the clinical presentation can include a wide variety of symptoms that differ with age, sex, and time between onset and diagnosis (Table 1)[35].

The symptoms for the diagnosis of hypothyroidism are non-specific, especially in elderly patients who present with fewer and less classic signs and symptoms than younger individuals.

An increase in the severity of symptoms might predict hypothyroidism, since a change in seven or more symptoms in the past year increases the likelihood of hypothyroidism (likelihood ratio 8-7) [36].

However, in a case-control study, none of 34 hypothyroidism-related symptoms could be used to identify patients with hypothyroidism. Furthermore, 15% of patients with autoimmune hypothyroidism are asymptomatic or report only one hypothyroidism- associated symptom, whereas 70% of euthyroid controls have one or more thyroid- associated complaints[37].

Table 1: Clinical presentation and implications of hypothyroidism[35]

	Presentation	Signs and implications
General Metabolism	Weight gain, cold intolerance, fatigue	Increase in body-mass index, low metabolic rate, myxedema*, hypothermia
Cardiovascular	Fatigue on exertion, shortness of breath	Dyslipidemia, bradycardia, hypertension, endothelial dysfunction or increased intima-media thickness*, diastolicdysfunction*,Pericardialeffusion*,hyperhomocysteinemia*, electrocardiogram changes*
Neurosensory	Hoarseness of voice, decreased taste, vision or hearing	Neuropathy, cochlear dysfunction, decreased olfactory and gustatory sensitivity
Neurological and Psychiatric	Impaired memory, paresthesia, mood impairment	Impaired cognitive function, delayed relaxation of tendon reflexes, depression*, dementia*, ataxia*, Carpal tunnel syndrome and other nerve entrapment syndromes*,myxedema coma*
Gastrointestinal	Constipation	Reduced oesophageal motility, non- alcoholic fatty liver disease*, ascites (very rare)
Endocrinological	Infertility and sub-fertility, menstrual disturbance, galactorrhoea	Goiter, glucose metabolism dysregulation, infertility, sexual dysfunction, increased prolactin, pituitary hyperplasia*

Musculoskeletal	Muscle weakness, muscle cramps, arthralgia	Creatine phosphokinase elevation, Hoffman's syndrome*, osteoporotic fracture* (most probably caused by overtreatment)
Haemostasis and Haematological	Bleeding, fatigue	Mild anaemia, acquired von Willebrand disease*, decreased protein C and S*, increased red cell distribution width*, increased mean platelet volume*
Skin and Hair	Dry skin, hair loss	Coarse skin, loss of lateral eyebrows*. yellow palms of the hand", alopecia areata*
Electrolytes and Kidney Function	Deterioration of kidney function	Decreased estimated glomerular filtration rate, hyponatraemia*

*Uncommon Presentation

Vitamin B12

Vitamin B12 (B12) also known as cobalamin has a chemically complex structure. It is the largest of all vitamins[38]. At the centre of a coring ring, it contains an atom of cobalt and is the only active substance in the body. In the mitochondria it exists in 2-deoxyadenosyl (ado) form which is the cofactor for the enzyme L-methyl malonylcoenzymeA (COA) mutase. Methyl cobalamin which is the cofactor of methionine synthase is the other major cobalamin occurring naturally. Purine and pyrimidines synthesis requires methionine synthase. The reaction in which methyl group of methyl tetrahydrofolate is transferred to homocysteine to form tetrahydrofolate and methionine. Megaloblastic anaemia develops due to interruption of this reaction. Transcobalamin II is the active transport protein for vitamin B12. The endogenous forms consist of cobalamin and holotranscobalamin. The reduced state is treated with cyanocobalamin.

Availability

Vitamin B12 is synthesised solely by anaerobic microorganisms. The food of animal origin is the only source available for humans which include fish, meat, poultry, dairy and eggs. There are no naturally occurring active forms of vitamin B12 from plant sources. It is also available in the supplements and fortified foods in crystalline form[39]. The bioavailability of vitamin B12 depends on individual's gastrointestinal absorption capacity. The supplements contain cyano form, which is also found in trace amounts in food. Deficiency results from reduced consumption, reduced absorption, autoimmune states or genetic disorders.

Absorption

Cobalamin absorption consists of two mechanisms, active and passive. Passive mechanism occurs via the buccal, duodenal and ileal mucosa but is inefficient. The active mechanism is the normal physiologic mechanism, occurs through ileum and is mediated by the intrinsic factor (IF). Hydrochloric acid which is produced by the gastric mucosa is required to separate the vitamin B12 which is bound to the protein. This released cobalamin binds to R protein and reaches duodenum where R protein gets separated. Intrinsic factor binds to the free cobalamin and is absorbed by distal ileum. Vitamin B12 is secreted in bile which via the ileal receptors gets reabsorbed into enterohepatic circulation. This process requires intrinsic factor. Intrinsic factor deficiency leads to pernicious anaemia. About 0.1% gets excreted per day. Excess vitamin B12 gets excreted in urine.

Vitamin B12 Deficiency in General Population

3-4% of the general population have vitamin B12 deficiency. The reduced state is very rare in kids and adolescents. Vitamin B12 helps in central nervous system myelination, synthesis of nucleic acids and erythropoiesis. A sufficient contribution of B12 is necessary to support the function[40]. Malabsorption and reduced consumption through diet are not the uncommon reasons for reduced state of B12, which is usually seen in the elderly[41]. Strict vegetarians are prone to B12 deficiency and can meet their requirements from supplements and fortified foods. Vegetarian pregnant and lactating women are at high risk of deficiency and require adequate intake of vitamin B12 supplements. Under nutrition is common among the elderly due to physical capacity, illnesses and inflammation of gastric mucosa. Malabsorption usually occurs due to inability to break free B12 which is present bound to protein. Bariatric surgery patients are at increased risk of developing vitamin B12 deficiency and also require lifelong supplementation through diet.

Patients with both hypothyroidism and vitamin B12 deficiency

also have similar symptoms such as fatigue, dementia, weakness, memory loss, depression, lethargy and tingling. Thus, vitamin B12 deficiency may be ignored in hypothyroidism. Macrocytosis occurs commonly in patients having underactive thyroid. The relationship between TSH and B12 vitamin is not studied in detail. Due to inadequate intake, sluggish bowel motility, bacterial overgrowth, vitamin B12 deficiency can occur in hypothyroidism. Hypothyroid patients on thyroid hormone replacement therapy may not fully recover at times due to vitamin B12 deficiency.

Vitamin B12 Deficiency in Hypothyroidism

The prevalence and clinical features of B12 deficiency in hypothyroid patients were evaluated in one hundred and sixteen hypothyroid patients[2]. Laboratory parameters including Haemoglobin, MCV, Vitamin B12 levels and presence of anti-thyroid antibodies were analyzed. Patients with low B12 levels were treated with parenteral intramuscular vitamin B12 monthly, and monitored for improvement of symptoms. In this study there were 95 females and 21 males.

Forty six (39.6%) hypothyroid patients had low vitamin B12 levels. Males and females had the same prevalence of B12 deficiency. Generalized weakness, impaired memory, depression, numbness and decreased reflexes were more frequently noted in B12 deficient patients, but failed to achieve statistical significance when compared with B12 sufficient patients. The mean Hb was 11.9+/- 1.6 mg/dl in B12 deficient group and 12.4 +/- 1.7 mg/dl in the B12 sufficient group, however the mean MCV did not differ in the two groups. Patients with B12 deficiency did not have a higher prevalence of anaemia. Thyroid antibodies were checked in half the patients and 67% had positive titres for anti thyroid antibodies. Prevalence of vitamin B12 deficiency did not differ in patients with positive antibodies (43.2%) compared to those with negative antibodies (38.9%) (p= 0.759). Twenty four hypothyroid patients with B12 deficiency received intramuscular vitamin B12 injections monthly and improvement in symptoms was noted in 58.3% .Additionally, 21 subjects complained of symptoms consistent with B12deficiency but who had normal range B12, levels and were prescribed monthlyB12 injections and 8 (40%) had good subjective clinical response at 6 months.

The study concluded that there was a high (approx 40%) prevalence of B12 deficiency in hypothyroid patients. Traditional symptoms were not a good guide to determine the presence of B12 deficiency. Screening for vitamin B12 levels should be undertaken in all hypothyroid patients, irrespective of their thyroid antibody status. Replacement of B12 led to improvement in symptoms, although a placebo effect could not be excluded, as a number of patients without B12 deficiency also appeared to respond to B12, administration[2].

A literature search was conducted using multiple electronic databases to assess the prevalence of vitamin B-12 deficiency in thyroid dysfunction. Only original studies assessing the prevalence of vitamin B-12 deficiency in thyroid dysfunction that reported their findings as percentages of the sample were eligible for inclusion. From a total of 7091 manuscripts generated, 6 were included in this review. The prevalence of vitamin B-12 deficiency in hypothyroidism was reported as 10, 18.6, and 40.5% in three separate studies. The prevalence of deficiency in autoimmune thyroid disease was reported as 6.3, 28, and 55.5% in three studies. The prevalence of vitamin B-12 deficiency in hypothyroidism and autoimmune thyroid disease were reflective of the nutrition status of the population. Autoimmune thyroid disease was also associated with the autoimmune disorders pernicious anaemia and atrophic gastritis which might lead to malabsorption of vitamin B-12. Vitamin B-12 screening was recommended upon initial diagnosis with autoimmune thyroid disease and then periodically thereafter. There was not enough evidence to recommend regular screening for patients with hypothyroidism unless the underlying cause was autoimmune thyroid disease[42].

Siddique and associate from Pakistan determined the prevalence of vitamin B12 deficiency in hypothyroid patients. Two hundred and twenty five hypothyroid patients with age range of 30-70 years of either sex willing to participate in study were selected. Estimation of serum vitamin B12 was carried out. Cut off value for vitamin B12 was taken <148 pmol/L. In this study 103 patients (45.8%) were female and rest 122 (54.2%) were males. 54 patients (24%) had Vitamin B12 deficiency while rest 171 (76%) showed negative results. Female gender, malnutrition, lower BMI and socioeconomic status were risk factors linked with vitamin B12 deficiency. Age was not among the risk factors. It was concluded that prevalence of vitamin B12 deficiency was high (24%) in Pakistani patients with hypothyroidism. Female patients with malnutrition and lower BMI should be screened periodically to reduce the complications associated with vitamin B12 deficiency[43].

In another study by Tripathi and associate compared the vitamin B12, Folate and Ferritin with thyroid hormones in hypothyroid individuals. In this study, total 350 samples were included in which 175 were hypothyroid patients and 175 were normal individuals of age group between 15-65 years. Measurements of serum concentrations of Total T3, Total T4, TSH, Vitamin B12, Folate and Ferritin were done using Chemiluminiscence Immunosorbant Assay. Serum TSH levels were significantly increased in Hypothyroidism as compared to normal individual (7.42±1.75 vs. 2.72±1.28, p< 0001*). The total T3 level was significantly decreased in Hypothyroidism in comparison to normal individual (0.43±0.41 vs. 1.30±0.29, p<0001*). Similarly, total T4 level was significantly decrease in Hypothyroidism in comparison to normal individual (3.60±1.38 vs. 6.62±1.11, p<0001*). Level of Vitamin B12 was significantly decreased in Hypothyroidism in comparison to normal individual (210.45±129.30 vs. 483.93+264.74, p< 0001). Folate was significantly decreased in Hypothyroidism as compared to normal (2.51±0.99 vs. 6.67±0.83, p< 0001*). Ferritin was also observed significantly decreased in Hypothyroidism in comparison to normal (23.08±1.18 vs. 63.43±3.30, p< 0001). TSH was observed significantly correlated with Folate (r=0.187* p=0.013). The study

concluded that the lower values of above these parameters in hypothyroidism interpret that thyroid hormones were metabolic hormones and produced impact on metabolic and hormonal balance in which hemopoietic system was highly affected[44].

An observational study was conducted to assess prevalence of anaemia in hypothyroidism and to see if there is any association between vitamin B12 deficiency and anaemia in these patients. All hypothyroid patients attending the medicine OPD or admitted to medicine wards were enrolled for the study. Total 60 patients were included. Data was analyzed to assess the burden of anaemia and B12 deficiency in hypothyroid and to find out any correlation between TSH level, anaemia and vitamin B12 deficiency). About one third of hypothyroid had decreased vitamin B12 levels. TSH level showed significant positive correlation with haemoglobin value. 28% of the hypothyroid patients had vitamin B12 deficiency, but TSH levels itself did not correlate with vitamin B12 level. However, it was seen that those who had combined thyroid and B12 deficiency had significantly higher chances of developing generalized swelling and breathlessness. The study concluded that although there was no correlation between TSH level and B12 deficiency, it might be helpful to determine B12 level in hypothyroid patients who presented with anaemia, generalized swelling and/or breathlessness as B12 supplementation might give better symptomatic relief in them as compared to treating with thyroxine alone. More elaborative studies with larger sample size were required to explore this rather unattended relation of anaemia in hypothyroidism with B12 deficiency[45].

Kumar and associate compared the levels of vitamin B12, Folate and ferritin with thyroid hormones in hypothyroidism patients. The study was carried out among 400 persons in which 200 individuals were normal and 200 were hypothyroid patients. Measurements of serum concentrations of Total T3, Total T4, TSH, Vitamin B12, Folate and Ferritin were estimated using Chemiluminiscence Immunosorbant Assay. In normal individual group, all the serum values were in normal range. The levels of TSH of hypothyroid patients show a significant increase in comparison to normal individuals. Hypothryroid patients had significantly lower levels of serum total T3 and T4. The mean serum vitamin B12 and Folate were also significantly decreased as compared to normal. Serum ferritin level was observed lower in comparison to normal. TSH was observed significantly correlated with Folate. There was no correlation found of TSH with vitamin B12 and ferritin. There was no correlation found between total T3 and Vitamin B12. A negative correlation was observed between total T3 and Folate but it was not significant. No association was found between total T3 and ferritin. Total T4 was observed negatively associated with Vitamin B12 and ferritin but both are not significant. There was no correlation found between Total T4 and Folate. The study concluded that hypothyroid patients were observed to have lower levels of serum Vitamin B12, Folate and Ferritin in comparison to normal individuals[46].

A retrospective study was conducted on130 patients of hypothyroidism. They were investigated for the Vitamin D (Vit-D) and Vitamin B12 (Vit-B12) levels and their correlation with anti-thyroid peroxidase (anti-TPO) antibodies. The patients were divided into two groups as those having Vit- B12 levels below 200 pg/mL (n=60) and Vit-B12 levels equal to or above 200 pg/mL (n=70). These two groups were compared in terms of age, sex, thyroid-stimulating hormone (TSH), free-T4 (FT4), Vit-D, and anti-TPO. The correlation between Vit-B12 and anti-TPO levels was also investigated in these groups. Patients were then divided into four groups according to their Vit-D levels. Patients with normal Vit-D levels (25[OH] D>30 ng/mL; n = 5), those with Vit-D insufficiency (20-30 mg/mL; n=9), those with Vit-D deficiency (10-20 ng/mL; n=43), and those with severe Vit-D deficiency (<10 ng/mL; n=73). These four groups were compared in terms of age, gender, TSH, FT4, Vit-B12, and anti-TPO levels. In addition, the correlation between levels of Vit-D and anti-TPO was also investigated. It was found that Vit-B12 deficiency and Vit-D deficiency were associated with autoimmune hypothyroidism, and that there was a negative correlation between Vit-B12 and Vit-D levels and anti-TPO antibodies in these patients. The study concluded that in patients with autoimmune hypothyroidism, Vit-D and Vit-B12 deficiency should be investigated at the time of diagnosis and periodically on follow-ups[47].

In a prospective study the prevalence of vitamin B12 deficiency in hypothyroid patients was determined. The study was conducted at Medicine / Endocrinology department Lady Reading Hospital Peshawar from January to December 2019. 225 hypothyroid patients from IPD & OPD with age range of 30-70 years of either sex willing to participate in study were included in study. Estimation of serum vitamin B12 was carried out. Cut off value for vitamin B12 was taken < 148 pmol/L. 225 patients were included in our sampled population with mean age 47.15 + 7.210 ranging from 40 to 66 years of age. 103 patients (45.8%) were female and rest of 122 (54.2%) were males. In the study 54 patients (24%) had Vitamin B12 Deficiency and rest of 171 (76%) showed negative results. Female gender, malnutrition, lower BMI and socioeconomic status were risk factors linked with vitamin B12 deficiency, while age was not among the risk factors. The study concluded that prevalence of vitamin B12 deficiency was high 24% in Pakistani patients with hypothyroidism[48].

A hospital-based study was done on patients of hypothyroidism to determine the prevalence of vitamin B12 deficiency (<200 pg/mL). Most of the hypothyroid patients were <50 of age; out of these, 24.5% of patients had vitamin B12 deficiency. While in the age group >50 years, 27.3% of patients had vitamin B12 deficiency. The study concluded that Vitamin B12 deficiency was common in hypothyroid patients. Screening for vitamin B12 deficiency should be undertaken routinely in the diagnosis of hypothyroidism and regularly thereafter[49].

In a retrospective review of patients who presented with memory complaints were assessed in a study conducted at Peru. They were subjected for correlation of thyroid dysfunction, vitamin B12 and Folate deficiencies. Patients had either subjective cognitive decline (SCD), MCI, or dementia. They included 720 patients (330 SCD, 154 MCI, and 236

dementia); the dementia group was significantly older [mean age SCD 69.7 ±4.1, dementia 72.4±3.7 (p = 0.000)] and had lower Folate levels than SCD patients. The MCI group had higher free 13 levels compared with SCD patients. Those with lower TSH had greater dementia risk (OR = 2.91, 95%CI: 1.15-6.86) but not MCI risk in unadjusted models. B12 deficiency or borderline B12 deficiency was present in 34% of the dementia group, yet no clear correlation was seen between neuropsychological test results and B12 levels. There was no association between MCI or dementia and thyroid hormone, B12 or Folate levels in adjusted models. The study concluded that the findings did not support an association between metabolic and endocrine disorders and cognitive impairment in older Peruvians from Lima despite a high prevalence of B12 deficiency[50].

A prospective study on 50 newly detected hypothyroid patients was conducted by Raju and Kumar to evaluate vitamin B12 deficiency. Lab parameters analysed included haemoglobin, thyroid function tests (TFT), vitamin B12 levels and antithyroid peroxidase (anti-TPO) antibody levels. Of the 50 hypothyroid patients evaluated, 23 were males and 27 were females between the age of 18 to 70 years. Anti TPO antibodies were present in 24 patients (48%) out of 50, out of which 17 (70%) patients had vitamin B12 deficiency. Out of 50 hypothyroid patients, 26 patients (52%) had vitamin B12 deficiency. Statistically significant association between autoimmune hypothyroidism and vitamin B12 deficiency was detected. It was found that 26 of 50 (52%) patients had low B 12 levels. Incidence in females (54%) was more than in males (46%). The study distinctly showed association between hypothyroidism and vitamin B12 deficiency and also autoimmune thyroid disease[51].

Prevalence of auto immune thyroid disease and vitamin B12 deficiency was assessed in patients with thyroid disorders in Himalayan region. Study population comprised of patients above 18 years of age. Thyroid function tests (T3, T4, TSH) along with anti thyroperoxidase antibody (ATA) was done by chemiluminescence and vitamin B12 levels were done by chemiluminiscent enzyme immunoassay after serum separation of 120 subjects. ATA level >50ulU/ml was taken as positive and Vitamin B12 deficiency was taken as a value less than 160 pg/ml. Mean age of study population was 42.48 (±12.32) years. Forty hypothyroid and forty hyperthyroid and 40 controls were recruited. ATA positivity was reported in 52.5% (63/120) of the samples. In the present study more than 50% of cases with thyroid disorder and ATA positivity showed deficiency of vitamin B12 (hypothyroidism 63.3% hyperthyroidism, 51.8%). The study concluded that all patients with thyroid dysfunction should be screened for vitamin B12 status and treated accordingly[52].

In another recent study, Aon and associate assessed the prevalence of B12 deficiency among hypothyroid patients and evaluated for pernicious anemia and celiac disease as etiologies. A total 133 patients were included. Thyroid hormones and thyroid peroxidase (TPO) autoantibodies were measured. Serum B12 was measured and if deficient, intrinsic factor antibodies (IFAB) and tissue transglutaminase (tTG) antibodies were evaluated. The study included 45 patients with overt hypothyroidism (OH), 48 patients with subclinical hypothyroidism (SCH), and 40 patients as controls. Mean age was 34.3 years and 82% were females, TPO antibodies were positive in 73.5% of OH and 51.1% of SCH patients. B12 deficiency was detected in 33.3%, 47.9%, and 37.5% of OH, SCH, and controls, respectively with no significant difference (P.334). Borderline-to- low B12 level was more prevalent in the OH and the SCH groups compared to controls (68.9%, 85.4%, and 57.5%, respectively; P=.014). Among B12- deficient hypothyroid patients, 7.5% had positive IFAB and 13.3% had positive tTG antibodies. We did not find a significant association of TPO positivity and B12 deficiency (OR, 0.69; 95% CI 0.3-1.57; P.147). The study concluded that they did not find a higher prevalence of B12 deficiency among hypothyroid patients nor an association with TPO positivity. Borderline B12 levels were more prevalent among hypothyroid patients[53].

The prevalence of vitamin B12 deficiency in cases of subclinical hypothyroidism (SCH) was studied. One hundred patients of subclinical hypothyroidism (26 males and 74 females) and equal number of age and sex matched controls were included in the study. The serum levels of TSH, T3 and T4 were estimated through chemiluminescence by fully automated analyzer (Vitros 5600) to identify cases of SCH. The serum level of Vitamin B12 was estimated through ELISA technique. The collected data were analyzed statistically using unpaired student t-test and were compared by using Pearson correlation coefficient. In SCH patients, both T3 and T4 levels were within normal range, whereas TSH levels were in the range of 4.9-11.2 mlU/lit. Significantly low levels of serum Vitamin B12 were found in cases of subclinical hypothyroidism ($p < .0001$). These levels showed a highly significant negative correlation ($r = -0.2536$; p-value -0.01109) with serum TSH levels. The study concluded that there was a higher prevalence of Vitamin B12 deficiency in SCH patients. Hence, they hypothesized that by routine laboratory testing, early detection of vitamin B12 deficiency, and appropriate therapeutic measures could be helpful[54].

Singh and associate assessed the prevalence of vitamin B12 deficiency, the spectrum of clinical features and to draw attention to the possibility of rare hidden characteristics. The study was a multicenter retrospective, and prospective. All cases of vitamin B12 deficiency of either sex or age were enrolled in this study. Parenteral vitamin B12 was given, and cases were evaluated for the response on follow-up for more than three months. Of 220 cases, 52.27% were males. Maximum cases were reported from the age group 50 to 65 years (27.27%) and belonged to urban areas (59.1%). The majority were strict vegetarian (86.36%). Among comorbidities, diabetes (20.91%) followed by malabsorption (10.45%) were most common. The cutaneous manifestations were revealed at 38.18%. The most frequent neurological manifestation was paraesthesia (98.18%). Head heaviness/ache was the most frequent (95%) psychiatric manifestation. Anemia was revealed in 87.73% of cases with 88.64% macrocytosis. Axonal sensorimotor (52.63%)

neuropathy was a prevalent finding of NCV study. The study concluded that a high index of clinical suspicion was needed in cases with vague manifestations, especially in the pure vegetarian population. Early recognition could prevent further damage as most of its related disorders were generally reversible with treatment[55].

In a nutshell, there still needs larger studies in this direction to know the exact correlation between vitamin B12 levels in hypothyroid individuals. However, at the present time one should be vigilant regarding vitamin B12 deficiency in such patients, because clinically the symptoms of both diseases are common. Treating one condition without consideration of other may not benefit the patient.

CONFLICTS OF INTEREST: None

FINANCIAL SUPPORT: None

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