ORIGINAL ARTICLE

UTILITY OF ATHEROGENIC INDEX OF PLASMA AS A CARDIOVASCULAR RISK FACTOR IN SUB-CLINICAL HYPOTHYROID PATIENTS

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Background: Atherogenic index of plasma (AIP) is a reliable indicator of the likelihood of developing atherosclerosis and coronary heart disease. The objective of this study was to assess the AIP as a cardiovascular risk factor in subclinical hypothyroid patients, in predicting cardiovascular risk in patients of subclinical hypothyroidism. **Methods:** This prospective, cross-sectional study was conducted at a tertiary care hospital-based laboratory. Patients with Thyroid Stimulating Hormone (TSH) values between 4.5–10 IU/L and normal T_4 were enrolled in the study. The participants were tested after fasting 8–10 hours and at least 3 days of fat-free diet for lipid profile analyzed on an automated chemistry analyzer. Data were analysed using SPSS-22. The odds ratio test was used to assess the risk of outcome keeping 1 as a positive measure to encounter outcome. **Results:** A total of 170 patients were enrolled in the study. Their mean age was 44.7±10.8 years. The AIP results indicated 118 (69.4%) as high risk, 41 (24.1%) as intermediate risk, and 11 (6.4%) as low risk (p<0.001). The assessment of outcome risk results indicated a positive association of exposure to outcome in TSH value of 6–7 mIU/L as OR 2.15 (CI: 1.81–4.13) while TSH value of 8–9 mIU/L as OR 1.08 (CI: 0.71–2.16). **Conclusion:** Sub-clinical hypothyroidism is associated with a higher risk of AIP especially with TSH levels of 4–8 mIU/L and age group of <50 years.

Keywords: AIP, Subclinical hypothyroidism, cardiovascular disease, T_3, T_4, TSH

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INTRODUCTION

Cardiovascular disorder (CVD) and CVS-associated mortality has become a global public health problem. Developing countries have higher prevalence due to delayed diagnosis and improper long-term management. The prevalence has reportedly increased from 271 million to 523 million between 1990 and 2019. CVD-associated mortality increased from 12.1 million to 18.6 million during this period.[1] Type II diabetes mellitus, higher basal metabolic index (BMI), central obesity, hypertension, and dyslipidemia are known as indecent risk factors for CVD. Within endocrine disorders thyroid disorders are most frequently reported with 11% incidence of hypothyroidism in the female population. Hypothyroidism is known to enhance cholesterol levels, resulting in a higher risk of cardiovascular disorders.[2]

An elevated blood Thyroid Stimulating Hormone (TSH) level (5–10 mIU/L) in the presence of normal free peripheral thyroid hormone concentrations is referred to as subclinical hypothyroidism (SCH). This is a laboratory diagnosis, as the name 'subclinical' suggests, and it affects 4–11% of the adult population. Although subclinical hypothyroidism is thought to affect 1–11% of all dyslipidemic individuals, its consequences on blood lipid levels are not understood well. Heart failure, coronary artery disease events, and death from coronary heart disease are all associated with SCH. Patients with SCH in their middle years may also experience mood swings, and non-specific symptoms including fatigue, and cognitive impairment.[3,4]

Levothyroxine therapy can restore these detrimental cardiovascular consequences which have long been recognized in overt hypothyroidism.[5] Even when thyroid hormone levels are normal, elevated TSH levels by themselves might cause a rise in cholesterol. By enhancing the function of cholesteryl ester transfer protein (CETP), which facilitates the exchange of cholesteryl esters between HDL and very low-density lipoproteins (VLDL) and triglycerides in the other way, thyroid hormones can influence the metabolism of high-density lipoprotein (HDL). TSH might enhance lipolysis and cholesterol production, but it hinders the clearance of cholesterol on its own.[6] One of the numerous cardiovascular risk factors that have been linked to subclinical hypothyroidism is elevated blood lipid levels.[7] Patients with subclinical hypothyroidism are likely to have reduced systolic and diastolic heart function. While recent comprehensive analyses have indicated a potential connection between subclinical hypothyroidism and a slight elevation in cardiovascular risk, particularly among younger individuals, findings from prospective cohort studies investigating the correlation between initial subclinical hypothyroidism and the likelihood of coronary disease, as well as overall and cardiovascular mortality, have yielded conflicting results.[8] Elevated TSH levels might cause hypertension and high cholesterol if left untreated. In a study on older

men and women, those with blood TSH level of 7 mIU/L or more had a doubled risk of developing congestive heart failure compared to those with a normal TSH level. For the diagnosis and prognosis of cardiovascular disease (CVD), several markers have been employed. The atherogenic index of plasma (AIP) is a ratio of molar concentrations that has undergone logarithmic transformation.[9,10]

AIP is a reliable indicator of the likelihood of developing atherosclerosis and coronary heart disease. AIP correlates with the sizes of both pre-and anti-atherogenic lipoprotein particles, highlighting the authentic connection between these two types of lipoproteins. Hypothyroid people with higher TSH levels who are not treated may experience cardiovascular problems due to high cholesterol levels.[11] Due to unknowns regarding the scope of its therapeutic effectiveness, SCH management is still debatable. On one hand, current recommendations advise treating SCH in certain circumstances, such as pregnancy, infertility, individuals displaying related symptoms, or with a high risk of developing overt hypothyroidism.[12] On the other hand, some medical professionals advise treating all individuals with subclinical hypothyroidism, including those whose blood TSH level is less than 10 IU/L. Despite having a population that is prone to having an atherogenic lipid profile, thyroid function, and lipid issues have not been connected in Pakistani people.[13] Abid *et al*[14] That research investigated the correlation between the atherogenic index of plasma and lipid irregularities in individuals from Pakistan experiencing subclinical hypothyroidism across different levels of thyroid-stimulating hormone (TSH).

This study aimed to see the efficacy of AIP as a cardiovascular risk factor in subclinical hypothyroid patients in predicting cardiovascular risk in patients of subclinical hypothyroidism.

METHODOLOGY

This prospective, cross-sectional study, was conducted at a tertiary care hospital-based laboratory, Rawalpindi from Jan to June 2023. Prior approval from the Institutional Review Board was obtained. Patients with TSH values between 4.5–10 IU/L and normal T_4, both genders, and age between 35–60 years were enrolled in the study. After signing informed consent participants were called for an interview. A questionnaire was used to document complete demographic details, history, co-morbidities, and laboratory investigations. Diagnosed cases of ischemic heart disease, familial hyper-cholesterolemia, diabetes, and overt hypothyroidism, patients on steroid therapy, and those younger than 35 years or older than 60 years were excluded from the study. After an overnight fast of 8–10 hours and at least 3 days of the fat-free diet, 3 mL peripheral blood was taken in a serum gel separator tube. The lipid profile was analyzed on automated chemistry analyzer Advia-1800. Data were analysed on SPSS-22. For independent variables such as Age and gender frequency, percentages, mean and standard deviation were used. Laboratory investigation results of TSH, Cholesterol, T_4, T_3, and Triglycerides were analyzed in mean and standard deviation. AIP risk factor was assessed with the help of the AIP formula:

log (Triglyceride/High-density Lipoprotein-Cholesterol)

and risk was categorized within three categories, AIP value <0.11 was associated with a low risk of CVD, AIP value from 0.11–0.21 was associated with medium risk of CVD and AIP value >0.21 was associated with higher risk of CVD. Results were analysed as Mean±SD. The association of two mean values was measured as significant with Chi-square test keeping $p \leq 0.05$ as significant. The odds ratio was used to assess the risk of outcome keeping 1 as a positive measure to encounter outcome.

RESULTS

A total of 170 patients were enrolled in the study, their mean age was 44.7±10.8 years, (Range: 27–60 years). There were 125 (73.5%) females and 45 (26.5%) males in the participants. The mean value of TSH was 7.0±1.3 mlU/mL, T4 was 16±3 µg/dL, and T3 was 1.3±0.2 ng/dL. Total cholesterol (TC) was 4.4±0.9 mg/dL, Low-density lipoprotein (LDL) 2.3±0.89 mg/dL, high-density lipoprotein (HDL) 1.0±0.5 mg/dL, very low-density lipoprotein (VLDL) 1.0±0.5 mg/dL, and triglycerides (TG) were 2.7±1.2 mg/dL. The mean AIP value was 0.46±0.29. Upon categorizing the AIP results within Low risk (<0.11), intermediate risk (0.11–0.21), and high risk (>0.21) the results indicated 118 (69.4%) as high risk, 41 (24.1%) as intermediate risk, and only 11 (6.4%) as low risk. (Figure-1).

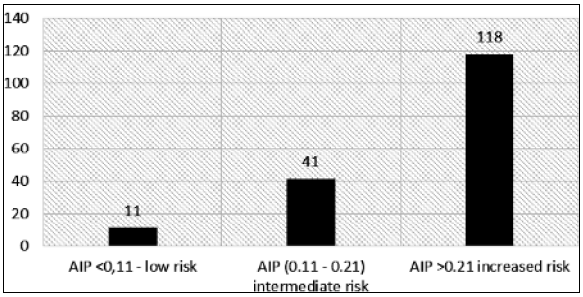

Figure-1: Categorization of AIP score in study participants

Age categories were correlated with AIP risk, and results indicated low risk in 51–60 years old participants, while younger participants reported a higher risk of AIP with 18 (10.5%) in <30 years participants, 39 (22.9%) in 31–49 years, 21 (12.3%) in 41–50 years and 40 (23.5%) in 51–60 years old participants in a high-risk category (p<0.01). The

correlation with TSH and AIP risk indicated no increased risk in a TSH value of 10, while the most frequently reported high risk was within 6–7 TSH values (p<0.001). (Table-1)

Table-1: Correlation of AIP with age and TSH level

Variables		AIP Risk			*p*
		low risk	intermediate risk	increased risk	
Age (Years)	35–40	0	17 (10%)	39 (22.9%)	<0.01
	41–50	0	12 (7%)	21 (12.3%)	
	51–60	11 (6.4%)	12 (7%)	40 (23.5%)	
TSH (mIU/L)	4–5	0	0	34 (20%)	<0.001
	6–7	6 (3.5%)	29 (17%)	56 (32.9%)	
	8–9	5 (2.9%)	6 (3.5%)	28 (16.4%)	
	10	0	6 (3.5%)	0	

The assessment of outcome risk as AIP was estimated with odds ratio, and results indicated a positive association of exposure to outcome in TSH value of 6–7 mIU/L as OR 2.15 (CI= 1.81–4.13) while TSH value of 8–9 mIU/L ad OR 1.08 (CI= 0.71–2.16), however, 4–5 mIU/L category and 10 mIU/L was not positively associated with AIP (OR 0.79, CI= 0.04–1.14, and OR 0.34, CI= 0.07–0.91 respectively). (Table-2).

Table-2: Odds of AIP incident with TSH value in study participants

Risk estimation of AIP with TSH		
Variables	**OR**	**CI (95%)**
4–5 mIU/L	0.79	0.04–1.14
6–7 mIU/L	2.15	1.81–4.13
8–9 mIU/L	1.08	0.71–2.16
10 mIU/L	0.34	0.07–0.91

DISCUSSION

This study aims to provide the efficacy of Atherogenic Index of Plasma as a cardiovascular risk factor in sub-clinical hypothyroid patients. Our results indicated independent risk factor of AIP in sub-clinical hypothyroid population, especially in young age and TSH value of 6–7 mIU/L. New research has demonstrated that HDL cholesterol levels, in addition to LDL cholesterol levels, are related to a decreased risk of obstructive coronary artery disease (CAD).[15] The triglyceride to HDL cholesterol ratio has been proposed as a more relevant metric to describe plasma atherogenicity than individual lipid levels, taking into account the intricate interconnections of lipoprotein metabolism.[16]

According to our study the prevalence of the hypothyroidism is more prominent in women as compared to the men. A study by Vanderpump *et al*[17] on the epidemiology of hypothyroidism has proved that the prevalence of overt hypothyroidism is ten times more common in women compared to men.

In our study, 118 (69.4%) participants were having high risk of CVD, 41 (24.1%) were having intermediate risk, and only 11 (6.4%) were having low risk according to the AIP category. A study by Niroumand *et al*[18] also found that on the basis of AIP category 9.7% participants were in low risk group, 12.7% were in intermediate risk and 77.5% were in increased risk of CVD. That study results showed that AIP could be an alternative screening tool for CVD in situations where all atherogenic parameter were normal and most of the participants were in the increased risk AIP category, as in our study.

Our study results concluded that the mean value of AIP in hypothyroidism patients was 0.46±0.29. James *et al*[19] performed similar study on the hypothyroidism patients and found mean AIP value 0.211. Madhura *et al*[20] also conducted a study on hypothyroidism patients and concluded the mean AIP value 0.395. The results of these studies indicated higher risk of CVD on the basis of AIP value similar to our study.

In Collet *et al* study[21] subclinical hypothyroidism was considered independently as a predictor for coronary heart disease in both cross-sectional and longitudinal analyses similar to our study.

Inoue K *et al*[22] followed a community-based cohort of 2,730 men and women in their 70s and 80s. At the time of entrance, there was no observed association between the occurrence of cardiovascular diseases, such as CHD, subclinical hypothyroidism, and congestive heart failure (CHF) at any level. Our study showing association between CVD and subclinical hypothyroidism is in contrast to their work.

The limitation of this study is the limited sample size and no follow-up, further study with longer follow-up of patients diagnosed with subclinical hypothyroidism is advised for better assessment of AIP as a risk factor for CVD.

CONCLUSION

Sub-clinical hypothyroidism is associated with a higher risk of AIP especially with Thyroid Stimulating Hormone levels of 4–8 mIU/L and age group of <50 years. This associated factor enhances the risk estimation of AIP in patients and increases the chances of timely diagnosis and better management.

REFERENCES

1. Salih MA, Salih SF. Proprotein convertase subtilisin and kexin type 9 in sub clinical hypothyroidism as a risk factor for cardiovascular disease. J Pharm Negat Res 2022;13(3):994–9.
2. Lamichhane A, Bista P, Pokhrel S, Bolakhe K, Joshi G, Aryal S, *et al.* Assessment of cardiovascular disease risk in females with subclinical hypothyroidism. J Lipids 2023;2023:4440275.
3. Luboshitzky R, Aviv A, Herer P, Lavie L. Risk factors for cardiovascular disease in women with subclinical hypothyroidism. Thyroid 2002;12(5):421–5.
4. Simlai S, Kumar P, Mohapatra TK, Sharma P. Hypothyroidism induced lipid peroxidation and coronary hazard in Lucknow. J Evid Based Med Healthc 2020;7(49):2907–12.
5. Nanda N, Bobby Z, Hamide A. Association of thyroid stimulating hormone and coronary lipid risk factors with lipid peroxidation in hypothyroidism. Clin Chem Lab Med 2008;46(5):674–9.

6. Popa CD, Arts E, Fransen J, van Riel PL. Atherogenic index and high-density lipoprotein cholesterol as cardiovascular risk determinants in rheumatoid arthritis: the impact of therapy with biologicals. Mediators Inflamm 2012;2012:785946.
7. Chaulin AM, Grigorieva YV, Suvorova GN, Duplyakov DV. Methods for modeling hypothyroidism: classification and modeling principles. Mol Med 2021;19(4):19–26. [Article in Russian].
8. Luster M, Duntas LH, Wartofsky L, (Eds). The thyroid and its diseases. Cham, Switzerland: Springer; 2019.
9. Hussain A, Elmahdawi AM, Elzeraidi NE, Nouh F, Algathafi K. The effects of dyslipidemia in subclinical hypothyroidism. Cureus 2019;11(11):e6173.
10. Ejaz M, Kumar P, Thakur M, Bachani P, Naz S, Lal K. Comparison of lipid profile in patients with and without subclinical hypothyroidism. Cureus 2021;13(8):e17301.
11. Kanthe PS, Patil BS, Bagali S, Deshpande A, Shaikh GB, Aithala M. Atherogenic index as a predictor of cardiovascular risk among women with different grades of obesity. Int J Collab Res Intern Med Public Health 2012;4(10):1767–74.
12. Dobiasova M. AIP –atherogenic index of plasma as a significant predictor of cardiovascular risk: from research to practice. Vnitr Lek 2006;52(1):64–71.
13. Nwagha UI, Ikekpeazu EJ, Ejezie FE, Neboh EE, Maduka IC. Atherogenic index of plasma as useful predictor of cardiovascular risk among postmenopausal women in Enugu, Nigeria. Afr Health Sci 2010;10(3):248–52.
14. Abid HA, Abid ZS, Abid SA. Atherogenic indices in clinical practice and biomedical research: a short review. Baghdad J Biochem Appl Biol Sci 2021;2(02):60–70.
15. Guo X, Ma L. Inflammation in coronary artery disease-clinical implications of novel HDL-cholesterol-related inflammatory parameters as predictors. Coron Artery Dis 2023;34(1):66–77.
16. Al-Tai WF, Jaffer EM, Ali ZA. Evaluating the utility of plasma Atherogenic Index among several atherogenic parameters in patients with chronic renal failure on maintenance hemodialysis. J Fac Med Baghdad 2012;54(3):259–62.
17. Vanderpump MP, Tunbridge WM. Epidemiology and prevention of clinical and subclinical hypothyroidism. Thyroid. 2002 Oct 1;12(10):839-47.
18. Niroumand S, Khajedaluee M, Khadem-Rezaiyan M, Abrishami M, Juya M, Khodaee G, Dadgarmoghaddam M. Atherogenic Index of Plasma (AIP): A marker of cardiovascular disease. Medical journal of the Islamic Republic of Iran. 2015;29:240.
19. James SR, Ray L, Ravichandran K, Nanda SK. High atherogenic index of plasma in subclinical hypothyroidism: Implications in assessment of cardiovascular disease risk. Indian Journal of Endocrinology and Metabolism. 2016 Sep 1;20(5):656-61.
20. Madhura NS, Shankar M, Narasimhappa S. Subclinical hypothyroidism (SH) and atherogenic index of plasma (AIP) in women: a case-control study from a tertiary Care Hospital in South India. Cureus. 2020 Sep 24;12(9).
21. Collet TH, Gussekloo J, Bauer DC, den Elzen WP, Cappola AR, Balmer P, *et al*. Subclinical hyperthyroidism and the risk of coronary heart disease and mortality. Arch Intern Med 2012;172(10):799–809.
22. Inoue K, Ritz B, Brent GA, Ebrahimi R, Rhee CM, Leung AM. Association of subclinical hypothyroidism and cardiovascular disease with mortality. JAMA network Open 2020;3(2):e1920745.

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