ORIGINAL ARTICLE

ASSOCIATION OF METABOLIC SYNDROME WITH INCREASED CARDIOVASCULAR RISK IN HYPOTHYROIDISM PATIENTS: EVIDENCE FROM A NEPALESE POPULATION

Bipin Kumar Jha[1,2], Anit Lamichhane[2], Saguna Laxmi Tandukar Shrestha[3], Sabindra Maharjan[2], Govardhan Joshi[2], Nitesh Adhikari[2], Anil Khadka[2], Pabitra Bista[4], Rajesh Kumar Thakur[2], Sudip Khanal[5], Sujan Gautam[5], Aashish Acharya[5], Mahendra Prasad Bhatt[2]*

[1]Department of Biochemistry, National Academy of Medical Sciences, Bir Hospital, Kathmandu, Nepal
[2]Department of Laboratory Medicine, Manmohan Memorial Institute of Health Sciences, Kathmandu, Nepal
[3]Department of Medicine, Manmohan Memorial Teaching Hospital, Kathmandu, Nepal
[4]Shahid Gangalal National Heart Centre, Kathmanndu, Nepal
[5]Department of Public Health, Manmohan Memorial Institute of Health Sciences, Kathmandu, Nepal

ABSTRACT

Introduction: Hypothyroidism is associated with metabolic syndrome and increased cardiovascular disease (CVD) risk worldwide. This study is conducted to assess hs-CRP as a CVD risk marker in hypothyroidism patients with and without metabolic syndrome.

Method: A cross-sectional study was conducted at Manmohan Memorial Teaching Hospital, Kathmandu, Nepal involving 244 participants where 122 euthyroid controls and 122 with hypothyroidism cases. Anthropometric data, blood pressure, fasting glucose, lipid profile, thyroid hormones, and hs-CRP were analyzed.

Results: Individual with hypothyroidism showed significantly increased level of DBP, WC, FBS, TC, TG, LDL, and hs-CRP, and lower HDL levels ($p<0.001$) as compared to euthyroid controls. Level of hs-CRP showed positive and significant correlation with SBP, DBP, TC, and LDL whereas negative and significant correlation with HDL. The incidence of MetS among primary hypothyroidism was 28% and 15.8% among sub clinical hypothyroidism. SBP ($p<0.001$), DBP ($p<0.001$), WC ($p<0.001$), FBS ($p<0.001$), TG ($p<0.001$), TC ($p<0.001$), and hs-CRP were significantly ($p<0.01$) higher among hypothyroidism cases with MetS as compared to hypothyroidism without MetS. Similarly HDL ($p<0.01$) was significantly lower in hypothyroidism cases with MetS as compared to hypothyroidism without MetS. Hypothyroidism cases with MetS were more prone to CVD risk as compared to the cases without MetS where majority (60%) of them were under high CVD risk followed by intermediate (28%) and low risk (12%).

Conclusion: Significant elevation of hs-CRP in hypothyroidism with metabolic syndrome shows higher CVD risk as compared to hypothyroidism without MetS which revealed that MetS exacerbate CVD risk in hypothyroidism cases. hs-CRP can also be a useful screening marker for CVD risk management.

Key words: ***Thyroid dysfunction, Hypothyroidism, Metabolic syndrome, hs-CRP, CVD risk***

https://doi.org/10.3126/jmmihs.v10i1.77977

**Corresponding Author: Dr. Mahendra Prasad Bhatt,*
Professor and Head, Department of Clinical Biochemistry and Laboratory Medicine, Manmohan Memorial Institute of Health Sciences, Kathmandu, Nepal
Email: mahendramlt@gmail.com
Received 18 february 2025 ; Received in Revised from 27 february 2025; Accepted 21 April 2025

INTRODUCTION

Cardiovascular diseases (CVDs) remain the top cause of death globally, claiming an estimated 17.9 million deaths annually[1]. Among the many contributing factors, thyroid disorders and metabolic syndrome (MetS) have also been associated with CVDs. The triads formed by these conditions create an interconnected network that significantly aggravates overall healthoutcomes[2].

Thyroid dysfunction encompasses a spectrum of conditions affecting the thyroid gland, ranging from asymptomatic abnormalities to overt thyroid disease. Based on laboratory results, thyroid dysfunction can be categorized into two categories: overt or subclinical[3]. Hypothyroidism is comparatively a common condition with a global prevalence of approximately 4.6%. Compared to overt hypothyroidism, subclinical hypothyroidism is more common[4]. Subclinical hypothyroidism (SCH) is defined by high TSH levels with normal free thyroxine levels[5].

When untreated, hypothyroidism can result in a wide range of health issues, possible consequences include myxedema coma, miscarriage, infertility, difficulty conceiving, impaired fertility, recurrent pregnancy loss, mental retardation, heart failure, cardiomyopathy, psychological disturbances, elevated LDL cholesterol levels, cardiovascular diseases, and depression[6]. People with hypothyroidism are linked to the increased rate of obesity, insulin resistance, dyslipidemia, and an increased possibility of metabolic syndrome [7-8].

Metabolic syndrome (MetS) is a major global health concern, affecting approximately 20-25% of the world's population which includes hypertension, endothelial dysfunction, low-grade chronic inflammation, dyslipidemia and insulin resistance[9-10]. Those with metabolic syndrome have a five-fold increased risk of type 2 diabetes mellitus (T2DM) and a two-fold increased risk of cardiovascular disease (CVD) when compared to healthy controls[11].

Several studies have recommended high-sensitivity C-reactive protein (hs-CRP) as a reliable marker for predicting cardiovascular events[12] as compared to other traditional markers like Framingham Risk Score, Systematic Coronary Risk Evaluation (SCORE), and Reynolds Risk Score[13].

Understanding the relationships between thyroid dysfunction, metabolic syndrome (MetS), and cardiovascular disease (CVD) is essential because these conditions are becoming more common in Nepalese people due to lifestyle changes. To better understand the implications of thyroid dysfunction and promote better therapeutic management methods, this study intends to evaluate high-sensitivity C-reactive protein (hs-CRP) levels and MetS components in Nepalese population with thyroid dysfunction.

METHODS

This laboratory-based cross-sectional study was performed in

How to Cite

Jha, B. K., Lamichhane, A., Shrestha, S. L. T., Maharjan, S., Joshi, G., Adhikari, N., ... Bhatt, M. P. Association of Metabolic Syndrome with Increased Cardiovascular Risk in Hypothyroid Patients: Evidence From a Nepalese Population. Journal of Manmohan Memorial Institute of Health Sciences, 10(1), 58–61. https://doi.org/10.3126/jmmihs.v10i1.77977

Manmohan Memorial Teaching Hospital (MMTH), Kathmandu, Nepal, from April 2023 to September 2023. Ethical approval (Ref no: NEHCO-IRC: 080/016) was taken from NEHCO Institutional Review Committee, MMIHS, Kathmandu.

Inclusion and Exclusion criteria: Patients diagnosed with hypothyroidism at Manmohan Memorial Teaching Hospital throughout the study period were included in the study. The study involved 244 participants: 122 were hypothyroidism and 122 were euthyroid control. The study included participants over 18 years. To minimize potential confounding factors, however, pregnant women, those on steroid therapy, and those on medication for diabetes mellitus, hypertension, or dyslipidemia were excluded.

Informed consent: All participants provided written informed consent in their languages after being fully informed about the study's purpose, procedures, potential risks, and benefits.

Experimental protocol: This cross-sectional observational study was conducted at Manmohan Memorial Teaching Hospital after receiving approval from the Institutional Review Committee of Manmohan Memorial Institute of Health Sciences. The 1964 Declaration of Helsinki and its later revisions' ethical guidelines were followed in this investigation. All subjects provided written informed consent following a Nepali explanation of the procedures.

A pre-tested, self-administered questionnaire was used to collect data. A 5 ml fasting blood sample (8-12 hours fasting) was collected by venipuncture in a serum tube (BD Vacutainer® SST™ Tubes). Using the fully automated biochemistry analyzer (VITROS® 350 Chemistry System, USA), the biochemical parameters, fasting blood sugar (FBS), total cholesterol (TC), triglycerides (TG) and HDL-C (high-density lipoprotein cholesterol were analyzed). LDL-C (low-density lipoprotein cholesterol), and VLDL (very low-density lipoprotein) were calculated using Friedewald equation (VLDL=TG/5; LDL-C=TC-TG/5+ HDL-C)[14]. All biochemical parameters were expressed in mg/dL. Thyroid function tests, free T3 (fT3), free T4 (fT4), thyroid-stimulating hormone (TSH) and hs-CRP were conducted using the MAGLUMI® 2000 Chemiluminescence Immunoassay (CLIA) System (Snibe, China). fT3, fT4, TSH, and hs-CRP were expressed in pg/mL, ng/dL, µIU/mL, and mg/L, respectively.

Subjects were diagnosed as Metabolic syndrome using "The National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III)" criteria. The NCEP ATP III states that five parameters are utilized for diagnosis: blood pressure (≥130/85 mmHg), fasting blood glucose (≥100 mg/dL), triglyceride levels (≥150 mg/dL), HDL cholesterol (≤40 mg/dL for males and ≤50 mg/dL for women), and waist circumference (≥102 cm for men and ≥88 cm for women). If a person satisfies three of these five requirements, they are diagnosed with metabolic syndrome[15].

Further CVD risk assessment was done by using serum hs-CRP levels according to American Heart Association/Centers for Disease Control (AHD/CDC) guideline. On the basis of serum hs-CRP levels, subjects were divided into three categories to anticipate and prevent cardiovascular risk: low risk (<1.0 mg/L), intermediate risk (1.0–3.0 mg/L), and high risk (>3.0 mg/L)[16].

Statistical Analysis: A database was constructed using Microsoft Excel 2013 and analyzed by SPSS version 18 (IBM Corporation, Armonk, NY, USA). Independent t-test and Pearson's correlation were applied in SPSS. Statistical significance was set at a p value less than 0.05.

RESULTS

This study was conducted among 244 participants including 122 euthyroid subjects and 122 cases with hypothyroidism attending Manmohan Memorial Teaching Hospital, Kathmandu, Nepal. Hypothyroidism cases were further divided into two sub groups i.e., primary hypothyroidism and sub clinical hypothyroidism. The distribution of participants into different groups is shown in figure 1.

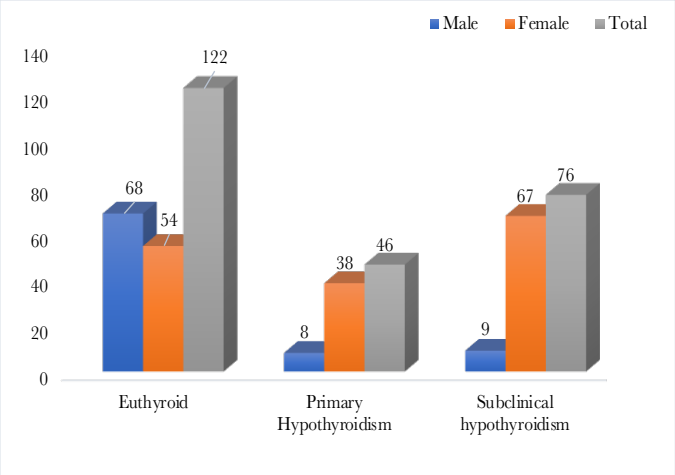

Figure 1: Distribution of participants in the study

The association of anthropometric and biochemical parameters between euthyroid and hypothyroidism cases showed that SBP, DBP, WC, FBS, TG, TC, LDL, VLDL and hs-CRP levels were significantly higher and HDL was significantly lower in hypothyroidism cases as compared to euthyroid group as shown in Table 1.

Table 1: Comparison of biochemical parameters between Euthyroid and hypothyroidism cases

Parameters	Euthyroid (Mean ± SD)	Hypothyroidism (Mean ± SD)	p-value
Age (Years)	46.95±16.42	47.07±15.04	0.951
SBP (mm/Hg)	114.01±13.10	117.40±14.81	0.062
DBP (mm/Hg)	74.18±7.31	78.57±12.02	0.001***
WC (Cm)	82.50±6.07	90.83±8.73	0.000***
FBS (mg/dl)	82.28±9.41	90.89±31.98	0.005**
CHOL (mg/dl)	172.59±53.21	206.92±92.03	0.000***
TG (mg/dl)	93.13±28.82	218.62±154.12	0.000***
HDL (mg/dl)	56.12±9.83	37.75±10.06	0.000***
LDL (mg/dl)	99.72±48.69	125.39±82.68	0.004**
VLDL (mg/dl)	27.80±17.64	43.99±30.78	0.000***
Hs-CRP (mg/L)	0.47±0.25	2.78±2.99	0.000***
FT3 (pg/ml)	3.21±0.50	3.42±1.56	0.166
FT4 (ng/dl)	12.85±2.00	08.24±4.93	0.000***
TSH (µIU/ml)	2.92±1.36	7.96±3.39	0.000***

t-test; *: Significance at 0.05, **: Significance at 0.01, ***: Significance at 0.001 level.

The correlation between hs-CRP level and other variables in hypothyroidism cases showed the positive and significant correlation with SBP, DBP, TG and LDL level whereas negative and significant correlation with HDL level as shown in Table 2.

Table 2: Correlation between hs-CRP and other parameters among hypothyroidism cases

Parameters	R	p-value
Age (Years)	0.058	0.534
SBP (mmHg)	0.303	<0.001***
DBP (mmHg)	0.236	0.010**
WC (cm)	0.135	0.144
FBS (mg/dl)	0.117	0.205
T. CHOL (mg/dl)	0.215	0.019*
TG (mg/dl)	0.135	0.145
HDL (mg/dl)	-0.231	0.011*
LDL (mg/dl)	0.251	0.006**
VLDL (mg/dl)	0.055	0.552
FT3 (pg/ml)	-0.074	0.424
FT4 (ng/dl)	-0.222	0.015*
TSH (µIU/ml)	0.079	0.393

Pearson's correlation; *: Significant at 0.05, **: Significance at 0.01, ***: Significance at 0.001 level.

Among the entire hypothyroidism cases metabolic syndrome was seen in 20.49% cases. The incidence of MetS among primary hypothyroidism was 28% and the incidence of MetS among subclinical hypothyroidism was 15.8% as shown in Figure 2.

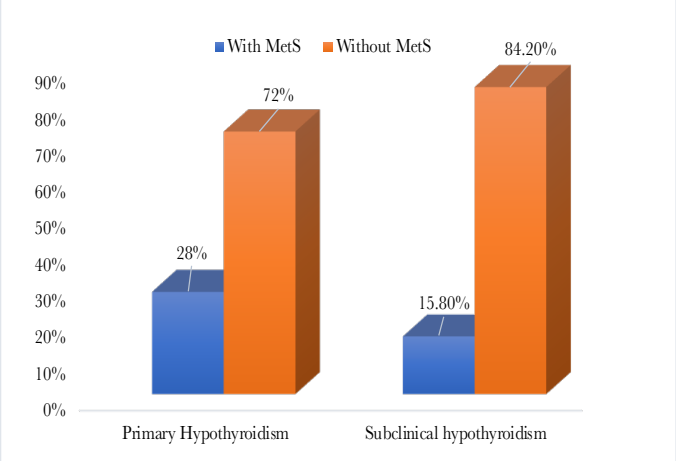

Figure 2: Incidence of Metabolic syndrome among hypothyroidism cases

The association of variables revealed significantly higher level of SBP, DBP, WC, FBS, TG, TC, LDL, VLDL, hs-CRP and TSH level and lower HDL level in hypothyroidism cases with metabolic syndrome as compared to hypothyroidism cases without metabolic syndrome as shown in Table 3.

Among the hypothyroidism cases along with MetS majority (60%) of them were under high CVD risk followed by intermediate (28%) and low risk (12%). Whereas; among hypothyroidism cases without MetS, majority (69.07%) were under low risk followed by intermediate (21.65%) and high risk (9.28%) as shown in figure 3.

Table 3: Comparison of biochemical parameters between hypothyroidism cases with and without metabolic syndrome

Parameters	Hypothyroidism		p-value
	Without MetS (Mean ± SD)	With MetS (Mean ± SD)	
Age (Years)	47.09±15.17	47.04±14.83	0.989
SBP(mmHg)	115.95±16.56	132.60±14.65	<0.001***
DBP(mmHg)	75.74±10.42	90.80±13.20	<0.001***
WC(cm)	89.16±8.51	97.12±6.45	<0.001***
FBS(mg/dl)	79.15±8.08	148.44±53.26	<0.001***
TG(mg/dl)	178.72±95.12	368.64±228.29	<0.001***
TC(mg/dl)	182.51±40.53	291.56±155.31	<0.001***
HDL(mg/dl)	39.25±8.90	33.56±11.78	0.009**
LDL(mg/dl)	107.32±31.11	194.00±153.48	<0.001***
VLDL(mg/dl)	35.39±18.37	76.32±44.39	<0.001***
Hs-CRP(mg/L)	2.39±1.93	4.06±5.08	0.011*
FT3 (pg/dl)	3.21±1.37	4.19±1.99	0.005**
FT4 (ng/dl)	8.46±4.82	7.39±5.32	0.339
TSH(µIU/ml)	9.48±3.86	13.00±2.40	<0.001***

t-test; * significance at 0.05, ** significance at 0.01, *** significance at 0.001 level.

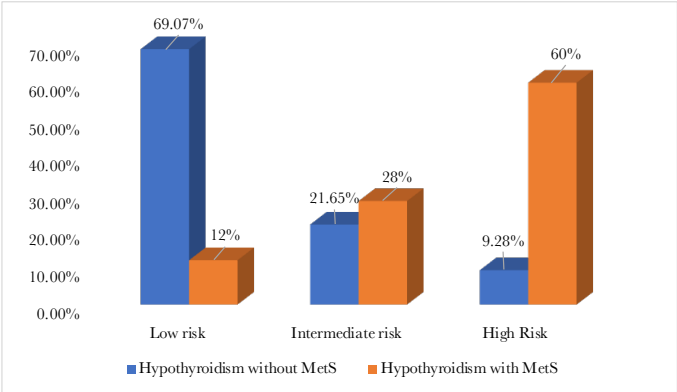

Figure 3: Distribution of cases into different CVD risk groups

DISCUSSION

The outcomes of this research have provided insights into the exacerbation of biochemical parameters in the development of cardiovascular disease risk in thyroid disorder cases associated with metabolic syndrome.

Our results showed that hypothyroid patients had significantly higher levels of diastolic blood pressure (DBP), waist circumference (WC), fasting blood sugar (FBS), total cholesterol (TC), triglycerides (TG), LDL, and hs-CRP. HDL levels were significantly lower. These findings indicate a higher risk of cardiovascular complications in thyroid disorder patients, consistent with previous studies by KC et al., Sharma et al., and Yeo et al[17–19]. Which demonstrated similar disruptions in lipid profiles and glucose metabolism among hypothyroid patients.

High-sensitivity C-reactive protein (hs-CRP) is an unshakable marker of systemic inflammation and cardiovascular risk. In our study, hs-CRP levels were significantly elevated in hypothyroid patients, particularly in those with MetS. We found that hs-CRP positively correlated with blood pressure, LDL, and total cholesterol, and negatively with HDL. These results suggest that hs-CRP is a sensitive marker of cardiovascular inflammation in patients with thyroid dysfunction.

Mainly, we found no significant correlation between hs-CRP and TSH levels. This is in line with several large-scale studies, such as those using NHANES data, which also found no strong association between TSH and hs-CRP[20]. However; some studies have reported contrasting results[21-22]. These differences may be due to variations in population size, ethnicity, or diagnostic criteria.

Among thyroid disorder patients diagnosed with metabolic syndrome (MetS), significantly worse biochemical and anthropometric parameters were observed. These included elevated blood pressure, fasting blood sugar (FBS), triglycerides (TG), total cholesterol (TC), low-density lipoprotein (LDL), and high-sensitivity C-reactive protein (hs-CRP), along with reduced levels of high-density lipoprotein (HDL) as compared to hypothyroidism cases without MetS. This subgroup demonstrated a markedly increased cardiovascular risk, consistent with findings by Wang et al. and Deshmukh et al., similarly reported that the coexistence of hypothyroidism and MetS substantially heightens the risk of cardiovascular disease (CVD)[21,23].

Using hs-CRP for cardiovascular risk prediction is highly beneficial in thyroid disorder patients, especially when traditional risk scores fall short. This study revealed that hypothyroidism associated with metabolic syndrome is more prone to CVD risk as compared to hypothyroidism without MetS. Majority (60%) of the hypothyroidism cases with MetS were under high risk of CVD followed by intermediate risk (28%) and low risk (12%). This supports the recommendation from the American Heart Association and other bodies to include hs-CRP in routine assessments for better cardiovascular risk stratification

CONCLUSION

In this study, significant elevation of hs-CRP in hypothyroidism with metabolic syndrome shows higher CVD risk in adults. Thus, evaluation of hs-CRP levels in patients with hypothyroidism can be useful screening marker of CVD risk and may help prevention of CVD in early stage.

REFERENCES

1. Cardiovascular disease. https:// www.who.int/health-topics/cardiovascular diseases.
2. PingitoreA, Gaggini M, Mastorci F, Sabatino L, Cordiviola L, Vassalle C. Metabolic Syndrome, Thyroid Dysfunction, and Cardiovascular Risk: The Triptych of Evil. Int J Mol Sci. 2024 Oct 2;25(19):10628. doi: 10.3390/ijms251910628. PMID: 39408957; PMCID: PMC11477096.
3. 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 [Internet]. 2023 Jan 1;2023(1):4440275. Available from: https://doi.org/10.1155/2023/4440275
4. Services H, Northwest P, Health O, Rugge JB, Bougatsos C, Chou R. Number 118 Screening for and Treatment of Thyroid Dysfunction : An Evidence Review for the U . S . Preventive Services Task Force. 2007;(118).
5. Hashimoto K. Update on subclinical thyroid dysfunction. Endocr J. 2022;69(7):725–38.
6. Abid M, Kumar Sharma K, Salman Ali S, Chandra P, Verma A, Ali Khan N. Complication and Management of Hypothyrodism. Indian J Drugs. 2016;(May 2018):42–56.
7. Gutch M, Rungta S, Kumar S, Agarwal A, Bhattacharya A, Razi SM. Thyroid functions and serum lipid profile in metabolic syndrome. Biomed J [Internet]. 2017;40(3):147–53. Available from: https://www.sciencedirect.com/science/article/pii/S231941701730152X
8. Ruhla S, Weickert MO, Arafat AM, Osterhoff M, Isken F, Spranger J, et al. A high normal TSH is associated with the metabolic syndrome. Clin Endocrinol (Oxf) [Internet]. 2010;72(5):696–701. Available from: https://doi.org/10.1111/j.1365-2265.2009.03698.x
9. Singh J, Rajput M, Rajput R, Bairwa M. Prevalence and Predictors of Metabolic Syndrome in a North Indian Rural Population: A Community Based Study. J Glob Diabetes Clin Metab [Internet]. 2016;1(2):007. Available from: www.scientonline.org
10. Kaur J. [Retracted] A Comprehensive Review on Metabolic Syndrome. Cardiol Res Pract [Internet]. 2014 Jan 1;2014(1):943162. Available from: https://doi.org/10.1155/2014/943162
11. Brenta G. Why Can Insulin Resistance Be a Natural Consequence of Thyroid Dysfunction? J Thyroid Res [Internet]. 2011 Jan 1;2011(1):152850. Available from: https://doi.org/10.4061/2011/152850
12. Clearfield MB. C-Reactive Protein: A New Risk Assessment Tool for Cardiovascular Disease. 2005;105(9):409–16. Available from: https://doi.org/10.7556/jaoa.2005.105.9.409
13. Davis JF, Vidyasagar S, Maiya GA. C-reactive protein and coronary heart disease - risk marker or risk factor? J Clin Sci Res [Internet]. 2012;1(4). Available from: https://journals.lww.com/jcsr/fulltext/2012/01040/c_reactive_protein_and_coronary_heart_disease__.5.aspx
14. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma without the use of the preparative ultracentrifuge. Clin Chem. 1972; 18: 499–502
15. Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection. Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). JAMA. 2001; 285: 2486–2497
16. Pearson T, Mensah G, Alexander RW, and others. Markers of in flammation and cardiovascular disease. AHD/CDC Scientific State ment. Circ 2003;107:499-511.
17. Kc R, Khatiwada S, Deo Mehta K, Pandey P, Lamsal M, Majhi S. Cardiovascular Risk Factors in Subclinical Hypothyroidism: A Case Control Study in Nepalese Population. J Thyroid Res. 2015;2015:305241.
18. Sharma P, Prashar N, Sharma G, Singh H, Sharma R. Lipid profile and hs-CRP levels in patients with subclinical hypothyroidism. Int J Med Sci Public Heal. 2016;5(6):1233.
19. Yeo HJ, Jo AR, Lee HW, Yi DW, Kang YH, Son SM. Effect of Short-Term Hypothyroid State on Lipid Profile and Cardiovascular Risk Markers in Subjects Preparing Radioactive Iodine Therapy. J Korean Thyroid Assoc. 2014;7(2):172.
20. Hueston WJ, King DE, Geesey ME. Serum biomarkers for cardiovascular inflammation in subclinical hypothyroidism. Clin Endocrinol (Oxf). 2005 Nov;63(5):582–7.
21. Wang CY, Chang TC, Chen MF. Associations between subclinical thyroid disease and metabolic syndrome. Endocr J. 2012;59(10):911–7.
22. Ganesan A, Sethulekshmi SG. Relationship between hsCRP and TSH in patients with subclinical hypothyroidism. Romanian Journal of Diabetes Nutrition and Metabolic Diseases. 2021 Dec 10;28(4):391-4.
23. Deshmukh V, Farishta F, Bhole M. Thyroid Dysfunction in Patients with Metabolic Syndrome: A Cross-Sectional, Epidemiological, Pan-India Study. Int J Endocrinol [Internet]. 2018 Jan 1;2018(1):2930251. Available from: https://doi.org/10.1155/2018/2930251

ACKNOWLEDEMENTS

We would like to acknowledge all the participants involved and MMTH staff for their support in this study. Special thanks to Mr. Gopal Rauniyar from Axis Medibiz Pvt. Ltd., Kathmandu for reagent support.

AUTHOR CONTRIBUTIONS

All authors contributed significantly to the study. Bipin Jha, Anit Lamichhane, Mahendra P. Bhatt, Saguna Laxmi Tandukar Shrestha conceived and designed the study. Bipin Jha, Sabindra Maharjan, Govardhan Joshi and Nitesh Adhikari, conducted the experiments and collected data. Sudip Khanal, Aashish Acharya and Sujan Gautam performed data analysis and interpretation. Bipin Jha, Anil Khadka, Pabitra Bista and Rajesh Kumar Thakur drafted the manuscript, and all authors reviewed and approved the final version. Each author agrees to be accountable for all aspect of work.

CONFLICT OF INTEREST

Authors declare no any conflict of interests