Original Article

Proprotein convertase subtilisin and kexin type 9 in Sub Clinical Hypothyroidism as a Risk Factor for Cardiovascular Disease

Media Ahmed Salih[1], Sherwan Ferman Salih[2]

[1]MSc in science, Duhok polytechnic University, College of Health and Medical Technology

[2]Assistant professor in clinical biochemistry, Duhok University, College of Medicine

Abstract

A subclinical hypothyroidism characterized by s excessive amounts of thyroid-stimulating hormone despite appropriate levels of free thyroxine and free triiodothyronine. Subclinical hypothyroidism is linked to a higher risk of coronary artery disease and its mortalities, as it is associated with increased atherosclerosis. The presented study aimed to evaluate serum Proprotein convertase subtilisin/Kexin type 9 level among patients with subclinical hypothyroidism. A cross-sectional study was conducted at Azadi Teaching Hospital in Duhok, Kurdistan Region-Iraq. The study was performed from November 2021 to January 2022. A total of 160 participants, including 80 patients with newly diagnosed subclinical hypothyroidism and 80 healthy subjects as a control group. Blood samples were taken from studied groups after overnight fasting for measurement of different parameters such as thyroid stimulating hommos, Free thyroxin, Free triiodothyronine, Anti-thyroid peroxidase antibody, Lipid profiles and Proprotein convertase subtilisin/Kexin type 9. A total of 160 participants were recruited in this study, 63(78%) of subclinical hypothyroid patients were females, and 48(60%) had a positive family history of hypothyroidism. The mean level of Proprotein convertase subtilisin/Kexin type 9. was significantly higher in subclinical hypothyroid patients in comparison with control (4.03±2.96, 2.74±0.96, p= <0.001), respectively. There was insignificant higher mean level of atherogenic indices, lipid profile and serum Proprotein convertase subtilisin/Kexin type 9 among subclinical hypothyroid patients with Thyroid stimulating hormones level of more than 7.00 IU/ml. In conclusion, our research revealed a statistically significant increase in the mean circulating levels of protein convertase subtilisin/kexin type 9 in individuals who had just been diagnosed with subclinical hypothyroidism.

Keywords: Proprotein convertase subtilisin/Kexin type 9, Subclinical hypothyroidism, Atherosclerosis.

INTRODUCTION

Subclinical hypothyroidism has a biochemical definition and is characterized by slightly elevated amounts of thyroid-stimulating hormone accompanied with normal levels of free thyroxine and free triiodothyronine. It is rather prevalent, affecting about 10% of women and the elderly of the adult population (Redford and Vaidya, 2017). Thyroid hormones have an important role in the regulation of carbohydrates, lipids, and protein metabolism, which are macro-metabolic constituents of energy; thus, it has a role in growth and development (Sinha et al., 2018).

Subclinical hypothyroidism is linked to a higher risk of coronary artery disease and its mortalities, as it is associated with blood pressure changes and increased atherosclerosis (Biondi et al., 2019; Delitala et al., 2017)

Address for correspondence: Media Ahmed Salih
MSc in science, Duhok polytechnic University, College of Health and Medical Technology
Email: midyasalih@dpu.krd

Access this article online

Quick Response Code:

Website: www.pnrjournal.com

DOI: 10.47750/pnr.2022.13.03.155

How to cite this article: Media Ahmed Salih, Sherwan Ferman Salih, Proprotein convertase subtilisin and kexin type 9 in Sub Clinical Hypothyroidism as a Risk Factor for Cardiovascular Disease, J PHARM NEGATIVE RESULTS 2022;13: 994-999.

The protein enzyme proprotein convertase subtilisin/Kexin type 9 is expressed in the liver, kidney, gut, and central nervous system (Werner et al., 2014). It reduces LDLR levels on the plasma membrane and prevents LDL-R recycling to the cell surface as it promotes the degradation of LDL receptors into amino acids and cholesterol, therefore; it inhibits low-density lipoprotein cholesterol clearance from plasma (correlate positively with low-density lipoproteins) (Alborn et al., 2007).

The exact impact of elevated TSH levels among patients with subclinical hypothyroidism on cardiovascular diseases risk factors such as dyslipidemia and serum Proprotein convertase subtilisin/kexin type 9 level remain undetermined, therefor ; The presented study was aimed to evaluate serum Proprotein convertase subtilisin/kexin type 9 level among patients with subclinical hypothyroidism and ascertain the association of lipid profiles, atherogenic indices and serum Proprotein convertase subtilisin/kexin type 9 level with thyroid stimulating hormone level among patients with subclinical hypothyroidism.

Materials and Methods

A cross-sectional study was conducted at Azadi Teaching Hospital in Duhok, Kurdistan Region-Iraq. The study was performed from November 2021 to January 2022. A total of 160 participants, including 80 patients with newly diagnosed subclinical hypothyroidism and 80 healthy subjects as a control group. Participants with liver diseases, kidney diseases, muscular, neurological disorders, and diabetes mellitus, as well as patients who took medications affecting thyroid function levels, were excluded.

Subclinical hypothyroidism was diagnosed with high TSH, more than 4.2 IU/mL, normal, FT4 and FT3 levels according to the reference range taken from the institutional reference range (Singal et al., 2022). Anthropometric parameters include the measurement of a person's waist circumference, as well as their weight, height, and body mass index. The body mass index was determined by dividing a person's weight in kilograms by their height in meters squared (weight kg /height m2) (Delitala et al., 2017). The body mass index was categorized as normal weight between 18 -24.9 kg/m2, overweight 25.0 - 29.9 kg/m2 and ≥ 30 kg/m2 obsess (Nuttall, 2015).

In order to fill out a questionnaire form that was tailored to fulfil the requirements of the study, a meeting and interview were carried out. Questions concerning the respondent's name, age, gender, and family history of hypothyroidism are included in the questionnaire. Before being enrolled in the trial, each patient provided their permission after receiving enough information. Both the Ethical Committee of Duhok Polytechnic University and the Duhok General Health Directorate, both located in the Kurdistan Region of Iraq, gave their stamps of approval to the research proposal after reviewing it. (18082021 -8-20).

Blood samples were taken from studied groups after overnight fasting to appropriate gel vacutainer tubes, then centrifuged and frozen at (–80 C) for further measurement of different parameters. Measurements of lipid profile by Cobas (6000 – Hitachi, Roch) depending on Enzymatic, colourimetric method, and their reference range by National Cholesterol Education Program (Jacobson et al., 2014). Free thyroxin, Free triiodothyronine, Thyroid stimulating hormone, and Anti-thyroid peroxidase antibody were measured by Cobas (6000- Hitachi, Roch) depending on the Immunochemiluminescent method. PCSK9 was estimated by enzyme-linked immunosorbent assay with sandwich immunoassay. Atherogenic indices including Cholesterol /HDL-c ratio (normal range <4.5), Triglyceride/ HDL -c (normal ratio <3.00), LDL-c/HDL-c (normal range of less than 2.5), and non-HDL-c (< 130 mg/dl) (Ballantyne,2020).

Statistical methods

IBM Statistical Package for the Social Sciences (SPSS) version 23 was implemented to encode and input the data. Then, two methods are used, descriptive analysis as frequency, per cent, Mean, and standard deviation. In addition, the inferential analysis method is applied as independent samples T-test and One way ANOVA test in order to compare the study variables. On the other hand, the Chi-square and Pearson correlation coefficient tests are used to find relationships between different parameters.

Results

A total of 160 participants recruited in this study, 63(78%) of subclinical hypothyroid patients were female and 48(60%) had positive family history of hypothyroidism. There was significance difference in mean ± SD of Thyroid stimulating hormone and antithyroid peroxidase in subclinical hypothyroid patients comparing to control group. The mean level of PCSK9 was significantly higher in subclinical hypothyroid patients in comparison with control (4.03±2.96, 2.74±0.96, p= <0.001) respectively. Moreover, the lipid profile among studied group shown significantly high level of cholesterol and LDL-c, p= <0.001, with low level of HDL-c p= 0.002.

Table 1 Baseline characteristics and biochemical measurement between subclinical hypothyroid patients and control subjects.

Characteristics	Studied groups		p-value
	Patients (n=80)	Control (n=80)	
Gender **male** **female**	17(21.25%) 63(78.75%)	38(47.5%) 42(52.5%)	<0.001
Age (yrs.) **≤40** **> 40**	56(70%) 24(30%)	57(71.3%) 23(28.7%)	0.862
Family history of hypothyroidism **Yes** **NO**	48(60%) 32(40%)	16(20%) 64(80%)	<0.001
BMI (kg/m$^{2)}$ **Normal** **Overweight** **Obese**	26.79±5.83 28(35%) 28(35%) 24(30%)	24.84±5.21 44(55%) 20(25%) 16(20%)	0.158 0.039
WC (cm) **Male** **Female**	99.00 ± 8.139 96.57±12.64	95.95±10.37 90.67±12.79	0.006
TSH (IU/ml)	6.64 ± 1.56	2.67±1.19	< 0.001
FT4 (pmol/l)	14.33 ± 2.37	15.04±2.28	0.160
FT3(pmol/l)	5.47 ± 4.92	4.94±0.72	0.918
A-TPO (IU/ml)	63.69 ± 51.37	14.72±11.80	< 0.001
Cholesterol (mg/dl)	181.90 ± 40.36	155.86±36.46	< 0.001
Triglyceride(mg/dl)	125.85 ±63.44	118.11±45.42	0.334
HDL-C (mg/dl)	41.70 ± 2.47	43.14±3.19	< 0.001
LDL-C (mg/dl)	112.28 ± 34.25	86.89±32.02	0.002

Independent Samples T-Test and One way-ANOVA test significancy ≤0.05.

Table 2 shown a significantly high mean level of LDL -c/HDL-c ratio (2.61±0.85) (0.002), non HDL-c level (140.78± 37.33) mg/dl (<0.001), and cholesterol/HDL-c ratio (4.22 ±0.98), while there were insignificant high mean level of triglyceride/HDL-c ratio (3.05 ± 1.77).

Table 2. Mean ± SD of atherogenic indices of subclinical hypothyroid patients and control.

Atherogenic indices	Study groups Mean ± S D		P value
	Patients (n=80)	***Control (n=80)***	
CHO/HDL-c	4.22 ±0.98	3.67±0.88.22	0.009
TG/HDL-c	3.05 ± 1.77	2.83± 1.23	0.279
LDL/HDL-c	2.61±0.85	2.05± 0.79	0.002
non-HDL-c (mg/dl)	140.78± 37.33	115.27±35.05	< 0.001

Independent sample T-Test with P-Value ≤ 0.05.

The mean level of atherogenic indices, lipid profiles and Proprotein convertase subtilisin/kexin type 9 with TSH level more than 7.00 IU/mLand less than 7.00 IU/mL in subclinical hypothyroid patients shown in table 3. There was insignificant higher mean level of atherogenic indices, lipid profiles and Proprotein convertase subtilisin/kexin type 9 among subclinical hypothyroid patients with TSH level of more than 7.00 IU/ml.

Table 3: Biochemical parameters with TSH level in subclinical hypothyroid patients.

Biochemical parameters	TSH level Mean ± SD		P value
	TSH > 7 IU/mL	TSH < 7 IU/ml	
Cholesterol (mg/dl)	190.55±41.50	180.20±35.08	0.499
Triglyceride(mg/dl)	134.74±53.81	129.56±66.55	0.776
HDL-c (mg/dl)	40.44±4.15	43.05±3.18	0.901
LDL-c (mg/dl)	119.35±38.91	110.30±29.99	0.273
CH/HDL-c	4.75±1.05	4.20±0.86	0.396
TG/HDL-c	3.37±1.44	3.11± 1.35	0.403
LDL-c/HDL-c	2.96±0.90	2.55±0.83	0.229
NON-HDL-c(mg/dl)	148.78±1.44	138.48±36.43	0.472
PCSK9 ng/ml	4.20±1.2	3.7±3.3	0.278

Pearson Correlation test of P-value ≤ 0.05

Discussion

Subclinical hypothyroidism is mild thyroid dysfunction and is regarded as a critical condition because of its high prevalence rate, risk of progression to overt hypothyroidism, associated with lipid abnormalities, which all are considered as risk factors for cardiovascular disease (Rodondi et al., 2010). Proprotein convertase subtilisin/kexin type 9 represents the ninth member of the subtilisin family of kexin-like pro-convertases (Toth, 2010) . Overexpression of Proprotein convertase subtilisin/kexin type 9 impairs the function of LDLRs, resulting in a reduced clearance of LDL-c particles from plasma and accumulation of LDL-c in the circulation that involve in atherosclerotic process and prevalence of cardiovascular development (Lambert et al., 2012)

Our results observed that 70% of subclinical hypothyroid patients were less than 40 years and more than half had a positive family history of hypothyroidism (Kvetny et al., 2004). Moreover, we found an increased frequency of obese females among patients with subclinical hypothyroidism. A study done in Pakistan was consistent with our data and observed that individuals with subclinical hypothyroidism were more likely to be females and have a high body mass index (Ejaz et al., 202; Meng et al., 2015). While further studies were done in China and Brazil, inconsistencies with our results (Santin & Furlanetto, 2011) This can be explained by many factors, such as the direct effect of estrogen on thyroidal cells function and proliferation, and Thyroid stimulating hormones might upregulate the expression of hepatic 3-hydroxy-3-methyl-glutaryl co-enzyme A reductase, and Thyroid stimulating hormones receptor could play a significant role in adipocyte differentiation and adipogenesis, leading to obesity and a rising body mass index in subclinical hypothyroidism ((Lu et al., 2012; Tian et al., 2010).

The present study shows a significance elevation of mean proportion convertase subtilisin kexin type 9 level among subclinical hypothyroid patients compared to healthy groups. This is mostly related to high TSH levels among subclinical hypothyroid patients, which increase expression of PCSK9 in HepG2 cells through the stimulation of SREBP1c and SREBP2(Tsai et al., 2015). Through the increased expression of proprotein convertase subtilisin/kexin type 9 in the liver, the role of the thyrotropin-stimulating hormone in lipid metabolism was initiate. pcsk9 was called once neural apoptosis regulated convertase 1 (NARC-1) and helps break down precursor proteins like neuropeptides, prohormones, cytokines, growth factors, and different cell surfaces (Gong et al., 2017). Thus, pcsk9 increase with thyroid stimulating hormones in subclinical hypothyroidism. Many researchers studied the presence of lipid profile abnormality among subclinical hypothyroid patients with different results and data (Sadik et al., 2022; Ejaz et al., 2021)..

Our results shown slightly elevated level of serum cholesterol, LDL-c and triglyceride with low level of serum HDL -c compared to control groups. Two study done in Israel and Turkey were consistence with our study results.(Kc et al., 2015; Erem, 2006), while other study done shown contradictory results (Duntas and Wartofsky, 2007). In subclinical hypothyroidism, there is a drop in SREBP-2, which leads to a decrease in LDLRs, which reduces LDL-C clearance and produces hypercholesterolemia. (Denis et al., 2012). Moreover, Thyroid hormones stimulate cholesterol ester transferase activity, which speeds up the body's production of high-density lipoprotein . (Harvey & Ferrier, 2012). The atherogenic index of plasma is a stronger and more independent risk factor for cardiovascular disease. It is a measure of the equilibrium between components that are atherogenic and anti-atherogenic. (Cai et al., 2017; Ni et al., 2017) .In the presented study we found significant higher levels of the atherogenic indices comparing to control group.

According to some studies, there was a significant increase in cardiovascular development risk at TSH levels > 7 IU/mL.(Cooper, 2001; Pertseva & Einer, 2021)

In the current study, we observed that subclinical hypothyroid patients with TSH more than 7.00 IU/mL had an abnormality in lipid profile, atherogenic indices and high mean level of Proportion convertase subtilin kexin type 9 study done in Egypt showed the same as the found mean level of proportion convertase kexin subtilize type 9 was an increase in patients of subclinical hypothyroidism with thyroid stimulating hormones more than 7 .00 IU/mL (Sadik et al., 2022). These findings may be explained by the fact that thyroid-stimulating hormones were responsible for inducing hepatic cholesterol de novo synthesis by directly upregulating the expression of 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR), increasing hepatic and adipose triglyceride content, and stimulating lipolysis in the adipose tissue (de Jesus Garduno-Garcia et al., 2010).

Conclusion

Serum Proportion convertase subtilin Kexin type 9 level, lipids profile levels, and atherogenic index were higher among subclinical hypothyroid patients, which are regarded as a specific index for the risk of developing cardiovascular diseases. Early diagnosis and management of subclinical hypothyroidism through lowing levels of Thyroid stimulating hormones are crucial as it may associate with decreasing both serum PCSK9 and serum lipid profiles in the circulation, thus decreasing the progression risk of cardiovascular diseases in the future.

References

1. Alborn, W. E., Cao, G., Careskey, H. E., Qian, Y. W., Subramaniam, D. R., Davies, J., Conner, E. M., & Konrad, R. J. (2007). Serum proprotein convertase subtilisin kexin type 9 is correlated directly with serum LDL cholesterol. Clin Chem, 53(10), 1814-1819. https://doi.org/10.1373/clinchem.2007.091280
2. Biondi, B., Cappola, A. R., & Cooper, D. S. (2019). Subclinical Hypothyroidism: A Review. Jama, 322(2), 153-160. https://doi.org/10.1001/jama.2019.9052
3. Cai, G., Shi, G., Xue, S., & Lu, W. (2017). The atherogenic index of plasma is a strong and independent predictor for coronary artery disease in the Chinese Han population. Medicine, 96(37).
4. Cooper, D. S. (2001). Subclinical hypothyroidism. New England Journal of Medicine, 345(4), 260-265.
5. de Jesus Garduno-Garcia, J., Alvirde-Garcia, U., Lopez-Carrasco, G., Padilla Mendoza, M. E., Mehta, R., Arellano-Campos, O., Choza, R., Sauque, L., Garay-Sevilla, M. E., & Malacara, J. M. (2010). TSH and free thyroxine concentrations are associated with differing metabolic markers in euthyroid subjects. Eur. J. Endocrinol, 163, 273-278.
6. Delitala, A. P., Fanciulli, G., Maioli, M., & Delitala, G. (2017). Subclinical hypothyroidism, lipid metabolism and cardiovascular disease. Eur J Intern Med, 38, 17-24. https://doi.org/10.1016/j.ejim.2016.12.015
7. Denis, M., Marcinkiewicz, J., Zaid, A., Gauthier, D., Poirier, S., Lazure, C., Seidah, N. G., & Prat, A. (2012). Gene inactivation of proprotein convertase subtilisin/kexin type 9 reduces atherosclerosis in mice. Circulation, 125(7), 894-901.
8. Duntas, L. H., & Wartofsky, L. (2007). Cardiovascular risk and subclinical hypothyroidism: focus on lipids and new emerging risk factors. What is the evidence? Thyroid, 17(11), 1075-1084.
9. Ejaz, M., Kumar, P., Thakur, M., Bachani, P., Naz, S., Lal, K., Shahid, W., Shahid, S., Jahangir, M., & Rizwan, A. (2021). Comparison of Lipid Profile in Patients With and Without Subclinical Hypothyroidism. Cureus, 13(8), e17301. https://doi.org/10. 7759/cureus.17301
10. Erem, C. (2006). Blood coagulation, fibrinolytic activity and lipid profile in subclinical thyroid disease: subclinical hyperthyroidism increases plasma factor X activity. Clinical endocrinology, 64(3), 323-329.
11. Ference, B. A., Robinson, J. G., Brook, R. D., Catapano, A. L., Chapman, M. J., Neff, D. R., Voros, S., Giugliano, R. P., Davey Smith, G., & Fazio, S. (2016). Variation in PCSK9 and HMGCR and risk of cardiovascular disease and diabetes. New England Journal of Medicine, 375(22), 2144-2153.
12. Gong, Y., Ma, Y., Ye, Z., Fu, Z., Yang, P., Gao, B., Guo, W., Hu, D., Ye, J., & Ma, S. (2017). Thyroid stimulating hormone exhibits the impact on LDLR/LDL-c via up-regulating hepatic PCSK9 expression. Metabolism, 76, 32-41.
13. Harvey, R. A., & Ferrier, D. R. (2012). Lippincott's illustrated reviews. Pharmacology, 56.
14. Horton, J. (2007). Cohen JC, Hobbs HH. Molecular biology of PCSK9: its role in LDL metabolism. Trends Biochem Sci, 32, 71-77.
15. Jacobson, T. A., Ito, M. K., Maki, K. C., Orringer, C. E., Bays, H. E., Jones, P. H., McKenney, J. M., Grundy, S. M., Gill, E. A., Wild, R. A., Wilson, D. P., & Brown, W. V. (2014). National Lipid Association recommendations for patient-centered management of dyslipidemia: part 1 - executive summary. J Clin Lipidol, 8(5), 473-488. https://doi.org /10.1016/j.jacl.2014.07.007
16. Kc, R., Khatiwada, S., Deo Mehta, K., Pandey, P., Lamsal, M., & Majhi, S. (2015). Cardiovascular risk factors in subclinical hypothyroidism: a case control study in Nepalese population. Journal of thyroid research, 2015.
17. Kvetny, J., Heldgaard, P. E., Bladbjerg, E. M., & Gram, J. (2004). Subclinical hypothyroidism is associated with a low-grade inflammation, increased triglyceride levels and predicts cardiovascular disease in males below 50 years. Clin Endocrinol (Oxf), 61(2), 232-238. https://doi.org/10.1111/j.1365-2265.2004.02088.x
18. Lambert, G., Sjouke, B., Choque, B., Kastelein, J. J., & Hovingh, G. K. (2012). The PCSK9 decade. J Lipid Res, 53(12), 2515-2524. https://doi.org/10.1194/jlr.R026658
19. Lu, S., Guan, Q., Liu, Y., Wang, H., Xu, W., Li, X., Fu, Y., Gao, L., Zhao, J., & Wang, X. (2012). Role of extrathyroidal TSHR expression in adipocyte differentiation and its association with obesity. Lipids in health and disease, 11(1), 1-12.
20. Meng, Z., Liu, M., Zhang, Q., Liu, L., Song, K., Tan, J., Jia, Q., Zhang, G., Wang, R., He, Y., Ren, X., Zhu, M., He, Q., Wang, S., Li, X., Zheng, W., Hu, T., Liu, N., Upadhyaya, A., . . . Zhang, J. (2015). Gender and

Age Impact on the Association Between Thyroid-Stimulating Hormone and Serum Lipids. Medicine (Baltimore), 94(49), e2186. https://doi.org/10.1097/md.0000000000002186

21. Ni, W., Zhou, Z., Liu, T., Wang, H., Deng, J., Liu, X., & Xing, G. (2017). Gender-and lesion number-dependent difference in "atherogenic index of plasma" in Chinese people with coronary heart disease. Scientific reports, 7(1), 1-6.
22. Nuttall, F. Q. (2015). Body Mass Index: Obesity, BMI, and Health: A Critical Review. Nutr Today, 50(3), 117-128. https://doi.org/10.1097/nt.0000000000000092
23. Pertseva, N., & Einer, X. (2021). Metabolic changes of lipids in patient with subclinical hypothyroidism. Romanian Journal of Diabetes Nutrition and Metabolic Diseases, 21(1), 105-111.
24. Redford, C., & Vaidya, B. (2017). Subclinical hypothyroidism: Should we treat? Post reproductive health, 23(2), 55-62.
25. Rodondi, N., den Elzen, W. P., Bauer, D. C., Cappola, A. R., Razvi, S., Walsh, J. P., Asvold, B. O., Iervasi, G., Imaizumi, M., Collet, T. H., Bremner, A., Maisonneuve, P., Sgarbi, J. A., Khaw, K. T., Vanderpump, M. P., Newman, A. B., Cornuz, J., Franklyn, J. A., Westendorp, R. G., . . . Gussekloo, J. (2010). Subclinical hypothyroidism and the risk of coronary heart disease and mortality. Jama, 304(12), 1365-1374. https://doi.org/10.1001/jama.2010.1361
26. Sadik, N. A., Rashed, L. A., & El-Sawy, S. S. (2022). The Relationship of Circulating Proprotein Convertase Subtilisin/Kexin Type 9 With TSH and Lipid Profile in Newly Diagnosed Patients With Subclinical and Overt Hypothyroidism. Clinical Medicine Insights: Endocrinology and Diabetes, 15, 11795514221093317.
27. Sahebkar, A., Simental-Mendía, L., Guerrero-Romero, F., Golledge, J., & Watts, G. (2015). Effect of statin therapy on plasma proprotein convertase subtilisin kexin 9 (PCSK9) concentrations: a systematic review and meta-analysis of clinical trials. Diabetes, Obesity and Metabolism, 17(11), 1042-1055.
28. Santin, A. P., & Furlanetto, T. W. (2011). Role of estrogen in thyroid function and growth regulation. Journal of thyroid research, 2011.
29. Singal, N. P., Thakur, N., Chhabra, S., Puri, S., Hafeez, L., & Kumar, K. (2022). To Study Serum HDL Level in Subclinical Hypothyroidism and Its Association with TSH: A Case Control Study. European Journal of Molecular & Clinical Medicine, 9(3), 218-222.
30. Sinha, R. A., Singh, B. K., & Yen, P. M. (2018). Direct effects of thyroid hormones on hepatic lipid metabolism. Nat Rev Endocrinol, 14(5), 259-269. https://doi.org/10.1038/nrendo.2018.10
31. Tian, L., Song, Y., Xing, M., Zhang, W., Ning, G., Li, X., Yu, C., Qin, C., Liu, J., & Tian, X. (2010). A novel role for thyroid-stimulating hormone: Up-regulation of hepatic 3-hydroxy-3-methyl-glutaryl-coenzyme a reductase expression through the cyclic adenosine monophosphate/protein kinase A/cyclic adenosine monophosphate–responsive element binding protein pathway. Hepatology, 52(4), 1401-1409.
32. Toth, P. P. (2010). The Year in Lipid Disorders. Clinical Pub.
33. Tsai, C.-W., North, K. E., Tin, A., Haack, K., Franceschini, N., Saroja Voruganti, V., Laston, S., Zhang, Y., Best, L. G., & MacCluer, J. W. (2015). Both rare and common variants in PCSK9 influence plasma low-density lipoprotein cholesterol level in American Indians. The Journal of Clinical Endocrinology & Metabolism, 100(2), E345-E349.
34. Werner, C., Hoffmann, M. M., Böhm, M., & Laufs, U. (2014). Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) is a Novel Risk Predictor in Statin-Treated Coronary Artery Disease Patients. Circulation, 130(suppl_2), A14979-A14979.