IJBPAS, January, 2023, 12(1): 378-397

ISSN: 2277–4998

International Journal of Biology, Pharmacy and Allied Sciences (IJBPAS)

'A Bridge Between Laboratory and Reader'

www.ijbpas.com

IMPACT OF TYPE 2 DIABETES MELLITUS AND HYPOTHYROIDISM ON CARDIOVASCULAR OUTCOMES FOLLOWING PERCUTANEOUS CORONARY INTERVENTION

GOKILA S[1*], ANANDHI D[2], REVATHI K[3], SENTHIL KUMARAN S[4], SUBBAN V[4], MULLASARI AS[4], PHILIP DC[4] AND ANANDAN H[4]

1: MMM College of Health Sciences, Chennai, India / Meenakshi Academy of Higher Education and Research, Chennai, India

2: Meenakshi Ammal Dental College, MAHER, Chennai, India

3: Meenakshi Academy of Higher Education and Research (MAHER), Chennai, India

4: The Madras Medical Mission, Chennai, India

***Corresponding Author: Gokila.S: E Mail: gokila83@gmail.com**

Received 26th Feb. 2022; Revised 25th March 2022; Accepted 22nd June 2022; Available online 1st Jan. 2023

https://doi.org/10.31032/IJBPAS/2023/12.1.6778

ABSTRACT

The association between diabetes mellitus (DM) and hypothyroidism in cardiovascular disease (CVD) is well established. Both are associated with significant adverse impacts on patients undergoing percutaneous coronary interventions (PCI). DM is an independent predictor of adverse outcomes after drug-eluting stent (DES) implantation. Despite reasonable glycemic control in the peri-procedural period, DM is associated with worse clinical outcomes than non-diabetic patients. Hypothyroidism leads to higher cardiovascular comorbidities and is associated with an increased incidence of major adverse cardiac and cerebrovascular events (MACCE) than euthyroidism in PCI patients. Low T_3 syndrome has also been associated with adverse outcomes in PCI patients. Diagnosis and optimal management of hypothyroidism may improve outcomes in CAD patients undergoing PCI. This review focus on the impact of T2DM and hypothyroidism in patients undergoing PCI.

Keywords: Acute coronary syndrome, Coronary artery disease, Endocrine disorder, Revascularisation, Major adverse cardiac and cerebrovascular events

INTRODUCTION:

Cardiovascular disease (CVD) is the primary cause of morbidity and mortality in developed and developing countries. Hypothyroidism and diabetes mellitus (DM) are the two most common endocrine disorders seen in adults, and their co-existence increases the risk of coronary artery disease (CAD) **[1]**. Elevated glycemic status and decreased thyroid hormone level show worse cardiovascular (CV) outcomes. Recent evidence shows that reasonable glycemic control and thyroid hormone homeostasis would positively impact the outcomes of the patients undergoing percutaneous coronary interventions (PCI).

Coronary artery disease in diabetes mellitus

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder associated with higher blood glucose levels due to insufficient insulin secretion, insulin action, or both **[2]**. T2DM is highly prevalent in patients with CAD, peripheral artery disease, and cerebrovascular disease. CVD prevalence is 21.4% to 77% **[3-5]** in DM patients, and it is steadily increasing over time. Several prospective studies indicated DM as an independent risk factor for CVD, and the presence of other risk factors like smoking, hypertension and dyslipidemia, further increases the risk of CVD. The incidence of myocardial infarction (MI), acute coronary syndrome (ACS), and heart failure is increased in the presence of T2DM as comorbidity.

In patients with T2DM, an increase in adipose tissue deposits results in insulin resistance within hepatocytes, myocytes and it is mainly reported in people prone to genetic susceptibility for ectopic fat deposition **[6]**. T2DM leads to endothelial cell (EC) dysfunction, the elevation of plasminogen activator inhibitor 1 (PAI-1), fibrinogen, coagulation factor VII and inflammatory proteins, which accelerates atherosclerotic plaque formation and generate a pro-thrombotic environment and increases clot formation. The clot's structure is altered by elevated levels of thrombin and fibrinogen, which results in a denser fibrin network, which is highly resistant to fibrinolysis, thereby associated with increased CV risk **[7]**.

Plaque formation is a cascade of events triggered by the early development of EC dysfunction, leading to the genesis of unstable, lipid-rich atheromatous plaques comprising macrophages and inflammatory proteins. The nitric oxide (NO) released from EC exhibits anti-atherosclerotic properties. Altered EC function in T2DM results in impairment of NO release, which in turn leads to a reduction in the

bioavailability of NO and impairment of vasodilation, increase in inflammation, oxidative stress, smooth muscle cell proliferation, and expression of adhesion molecules such as integrins, selectins, cadherins and vascular adhesion protein 1 (VAP-1) **[8]**. These adhesion molecules facilitate infiltration of vessel walls with monocyte that later becomes macrophages. These macrophages transform into foam cells and secrete inflammatory cytokines such as tumor necrosis factor-α and interleukin-6, resulting in a fatty streak, a precursor for atherosclerotic plaques. The formation of reactive oxygen species (ROS) due to an increase in oxidative stress accelerates the oxidation of LDL particles and increases susceptibility to plaque rupture. The consequences of atherosclerotic plaque rupture are ACS, stroke, and lower limb ischemia. In patients with unstable angina, T2DM is an independent predictor of adverse plaque morphology **[9]**. Coronary atherosclerotic plaques in T2DM patients exhibit a more extensive content of lipid, thin fibrous cap, macrophage infiltration than patients without T2DM. These features increase vulnerability for coronary thrombosis in patients with T2DM **[10]**. Poor glycemic control, oxidative stress, insulin resistance, and low-grade inflammation are proposed as putative factors linking T2DM and CVD. There is an altered platelet function leading to increased platelet aggregation in the diabetic state, compromising the coronary microvascular circulation leading to increased macrovascular and microvascular disease and further exacerbating the effect of coronary artery stenosis **[11]**.

Hypercholesterolemia is a significant determinant of CAD **[12]**. One of the crucial functions of insulin in euglycemic patients is to balance the triglyceride-rich lipoprotein (TRL) derived from the liver and intestine. In T2DM, this regulation is impaired, leading to the liver's inappropriate production of very-low-density lipoprotein (VLDL) and hypertriglyceridemia. Lipoprotein lipase and endothelial enzyme initiate the catabolism of TRL, which hydrolyses triglyceride component of chylomicrons, VLDL, and releases fatty acids for energy production in muscle and storage in adipose tissue. This lipoprotein lipase enzyme activity is low in patients with T2DM. In addition, there is a delay in the passage of TRL through the lipolytic cascade due to the shortage of catalytic sites on lipoprotein lipase, and overproduction of triglycerides rapidly saturates available sites, which promotes hypertriglyceridemia. Hypertriglyceridaemia and low concentrations of high-density lipoprotein

(HDL) characterize diabetic dyslipidemia. High hepatic lipase activity is a constant feature in T2DM results in hydrolysis of triglycerides in HDL and LDL cores, resulting in small dense HDL and LDL particles. The predominance of small, dense, low-density lipoprotein (LDL) particles which are poor in lipid and enriched in protein, is associated with an increased risk of CAD and myocardial infarction **[13]**. The severity of CAD evaluated angiographically is positively related to the numbers of TRL particles in the plasma of diabetic patients. This relationship is more robust in women than in men, and it is independent of HDL and LDL **[14]**. Significant coronary artery stenosis (≥50% stenosis) per patient was higher in people with diabetes than in non-diabetic subjects ($p<0.05$) **[15]**. In another study, abnormal coronary arteries (≥50% stenosis) lead to a higher incidence of triple vessel disease with high atherosclerotic angiographic score (ATS) were observed in T2DM than non-diabetic patients **[16]**.

Revascularization outcomes in T2DM:

T2DM patients present with ACS much earlier in life. The severity of CAD and the incidence of multivessel disease in ACS were significantly higher in T2DM when compared to non-diabetic. T2DM with ACS requires coronary artery bypass graft (CABG) more often than non-diabetic patients **[17]**. In a Korean nationwide study presence of DM is associated with poor outcomes following revascularization procedure **[18]**. Glycated hemoglobin (HbA1c) < 7% measured two years after PCI was associated with a less MACCE than those with HbA1c ≥ 7 %. High HbA1c was associated with an increased incidence of repeat revascularization. Strict glycemic control after PCI may improve long-term clinical outcomes in diabetic patients **[19]**. At long-term follow-up, T2DM patients with CAD and LVD (left ventricular dysfunction) treated with CABG exhibited a significantly lower incidence of MACCE and better long-term survival over PCI, without an increased risk of stroke **[20]**. Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease (FREEDOM) trial showed that CABG is superior to PCI in T2DM patients. At one year follow-up, repeat revascularization was high among DM patients. Mortality and MI were significantly increased among PCI patients at five years of follow-up. Events were high among insulin-dependent DM patients **[21]**.

In another study, a lower incidence of target vessel failure (TVF) was seen in non-diabetic when compared to diabetic. At two year follow-up, diabetic patients experienced higher incidence of cardiac

death following PCI (3.5% vs1.0%, p = 0.048) **[22]**. Wang *et al*, observed that diabetic patients undergoing PCI for chronic total occlusion had higher mortality at longer length of follow up period (OR: 1.67, 95% CI: 1.06–2.64; p= 0.03). MACE and repeat revascularization were higher (p = 0.01) **[23]**. In SYNTAX trial, T2DM patients had higher MACCE (PCI: 46.5% vs CABG: 29.0%; p < 0.001) and repeat revascularization (PCI: 35.3% vs CABG: 14.6%; p < 0.001) in PCI as compared to CABG group at 5 year follow up **[24]**.

Maayan Konigstein *et al.* found that at 30 days, the target vessel revascularization (TVR) was more frequent in the T2DM group (1.4% vs. 0.5%, p=0.04). At one year, TLF, MACE, stent thrombosis, and TVR were all significantly more frequent among insulin-treated patients compared with non-insulin-treated patients and non-diabetic patients. A trend toward more MI events and all-cause mortality among insulin-treated patients was also observed **[25]**. Corpus *et al* found that diabetic patients with HbA1c > 7% had a significantly higher rate of TVR than those with HbA1c < 7% (34% vs 15%, p=0.02). HbA1c > 7% was a significant independent predictor of TVR **[26]**. Intensive glycemic control could improve the clinical outcome in patients undergoing PCI. Abnormal hemoglobin A1C levels (6% to 7%) were found in 30% of non-diabetic patients. Non diabetic patients with an abnormal HbA1c level had a significantly higher rate of MACE (33 % vs 22%, p= 0.04), TVR (31% vs 19%, p=0.02) and cardiac mortality (4.6% vs 0.5%, p= 0.03) compared to non diabetic patients with HbA1c < 6% **[27]**.

Coronary artery disease in hypothyroidism

The CV system is one of the main target organs for thyroid hormones that have a direct effect on it. T_3 (triiodothyronine), the essential thyroid hormone for cardiomyocytes, is mainly produced by the process of T4 deiodination. It can affect cardiomyocytes via genomic and non-genomic actions. T_3 regulates transcription by binding to thyroid hormone receptors (TRs) in the nucleus, which then binds to thyroid hormone-responsive elements (TREs) present in regulatory regions of target genes. Non-genomic actions of T_3 include thyroid hormone signaling, changes in thyroid hormone levels, and thyroid hormone receptors. Evidence has proved that the thyroid hormone receptor (TRα1) can reduce myocardial injury and post-ischemic cardiac remodeling through T_3 binding, and it controls genes related to contractile proteins, pacemaker activity and conduction, cell growth, differentiation, and metabolism. T_3 may also regulate plasma membrane ion currents, activate

survival pathways, and decrease oxidative stress in mitochondria **[28]**.

Hypothyroidism is diagnosed when low levels of the thyroid hormones result in elevated levels of thyroid stimulating hormone (TSH), and it can be primary or secondary. Whereas subclinical hypothyroidism (SCH) is diagnosed when TSH levels are elevated above the upper limit of the assay reference range with normal thyroid hormone levels, overt hypothyroidism is when TSH is increased, and T_4 level is decreased **[29]**. Hypothyroidism increases CVD risk due to the presence of thyroid hormone receptors in myocardial and vascular endothelial cells that result in alteration in heart rate, cardiac contractility, vascular smooth muscle, and endothelial function. It also increases total and LDL cholesterol in proportion to the rise in serum TSH levels **[30]**. It has been shown that the TSH receptor is expressed on vascular endothelial cells, and elevated TSH can promote endothelial dysfunction by altering gene expression in human umbilical vein endothelial cells **[31]**.TSH levels can adversely affect myocyte function. In addition, alteration in the CV system by activating the inflammatory immune response through genomic and non-genomic mechanisms **[32]**.

Clinical studies have shown that SCH increased CV risk through altered lipid profile, insulin resistance, oxidative stress, increased vascular stiffness, endothelial dysfunction, increased systemic vascular resistance, and modified coagulability. SCH manifests in the CV system in numerous ways, including increased heart rate, left ventricular mass, decrease in cardiac output, cardiac contractility, increased peripheral vascular resistance, susceptibility to endothelial dysfunction, and left ventricular diastolic dysfunction, which can cause changes in CV morphology and function. There are also significant changes in carotid intimal media thickness and endothelial-derived relaxation factor **[33]**. SCH on admission for acute decompensated heart failure (ADHF) was an independent predictor of adverse CV outcomes, suggesting a possible interaction between thyroid dysfunction and the pathophysiology of ADHF. Increased TSH level may be a marker to predict CV events in ADHF patients **[34]**. Thyroid dysfunction is highly prevalent among females and contributes to the overall coronary risk. Microvascular endothelial dysfunction is noted in women with hypothyroidism **[35]**. Low T_3 negatively affects the CV system, such as delayed diastolic filling, decreased cardiac contractility, and increased vascular resistance. Low T_3 syndrome constitutes a hormonal imbalance that may significantly

affect pathophysiological mechanism and CV hemodynamics and was found to be a strong prognostic predictor of mortality in patients with cardiac disease **[36]**. Also, mildly altered thyroid status is associated with an elevated risk of mortality in patients with cardiac disease **[37]**. SCH is associated with an increased risk of CVD events and CVD mortality in those with higher TSH levels, particularly in those with a TSH ≥ 10mlU/L **[38]**. Glucose and lipid metabolism is altered in thyroid dysfunction, leading to insulin resistance, which is an essential risk factor for CVD, and intervention in such patients may reduce CV morbidity and mortality **[39]**.

Revascularization outcomes in hypothyroidism:

Clinical studies showed that low T_3 was associated with more significant thrombus burden, increased severity of coronary artery disease, worse cardiac functions, and larger myocardial injury size in ACS patients **[32]**. In patients undergoing coronary angiography, the prevalence of thyroid dysfunction was up to 40% **[37]**. Among patients undergoing PCI, hypothyroidism is also associated with a higher risk of MACCE, cardiac death, MI, heart failure, and TVR **[40]**. The post-PCI patients with overt or SCH have more MACCE and more significant angiographic progression of CAD than euthyroid patients, even when adjusted for comorbidities such as dyslipidemia associated with hypothyroidism. Hypothyroidism is associated with an increased frequency of in-hospital cardiogenic shock and peri PCI bleeding and increases the risk of mortality up to 3 years after PCI. According to TSH, the mortality difference was achieved within the first 30 days after PCI in ST-elevation myocardial infarction (STEMI) patients and was maintained over the rest of 3 years follow-up.

Further study is needed to assess the association between TSH in the upper part of the reference range and the prognosis of patients with CAD **[41]**. SCH is largely undiagnosed among STEMI patients undergoing primary PCI. It is a significant predictor of worse in-hospital outcomes and elevated short and long-term mortality. Thyroid function tests are not regularly performed during hospitalization for acute MI. Regular testing of thyroid function before performing PCI should be considered. Large-scale prospective studies are needed to clarify the optimal management of STEMI patients with SCH undergoing primary PCI **[42]**. Additional trials are required to prove the benefit of L-thyroxine substitution in addition to conventional therapies on morbidity and mortality of CAD patients **[43]**.

CVD in T2DM and hypothyroidism:

The CVD risk further increases in patients with the combination of T2DM and hypothyroidism. T2DM patients with thyroid dysfunction exhibit significantly higher CVD risk when compared to their euthyroid counterparts. A significant positive linear association was found in T2DM subjects between TSH and CVD with elevated inflammatory markers, dyslipidemia, and poor glycemic control **[1]**. **Table-1** summarizes PCI outcomes in patients with T2DM and hypothyroidism. No prospective randomized studies so far have evaluated in patients combined with hypothyroidism and T2DM on PCI outcomes. **Figure 1** shows the mechanism of DM and hypothyroidism causing cardiac complications.

Table 1: Review of Literature

S. No	Study	Yr	Design	Condition	Sample size	Duration of Follow up	Outcomes Measured	Outcome Results
1	BK Benjamin *et al* [44]	2021	Prospective	CAD	302	12 month	MI, repeat coronary revascularzation, cardiac death	Longer DM duration [>10 Yr] is a significant independent predictor of MACE at one year after coronary Intervention using DES and DCB. Significantly higher prevalence of MI , with longer duration of diabetes vs shorter duration (7.7% vs 0.6%, p-0.001). There is no significant association between DM duration and all-cause mortality at one year following PCI.
2	Konigstein M *et al* [25]	2018	Prospective	CAD	1919	2 Yrs	MACE,TLR,TVR,TLF	DM was associated with higher rates of TLF and MACE, driven by higher rates of TLR. Insulin treated DM patients are at higher risk of adverse outcomes compared with non insulin treated DM patients. RES and ZES presented similar performance among diabetic and non diabetic
3	Hwang JK *et al*[19]	2017	Prospective	CAD	980	2 Yrs	MACE, cardiac death, MI, repeat revascularization, stroke,	Good Glycemic control (HbA1c < 7.0 %) after 2 years of PCI, was associated with improved clinical outcomes.
4	Jiang YJ *et al*[22]	2017	Retrospective	ACS	600	2 Yrs	Cardiac death, ST,TVF,TLF, MI, MACE.	DM is still an independent risk factor for worse outcomes in patients treated with PCI using DES . This study concluded that DM patients were more likely to have poor prognostic outcomes and higher incidence of adverse events after DES implantation.
5	Koskinas KC *et al*[45]	2016	Prospective	CAD	6081	2 Yrs	MACE, TLR, cardiac death, MI.	This study assessed DES outcomes in relation to diabetic status and CAD complexity as assessed by the SS. MACE in DM vs Non-DM (14.5% vs 9.9%, p-<0.001). Diabetic patients had higher SS (13.9±8.8 vs 12.9±8.7, p-<0.001) , more frequently underwent multi vessel treatment than non diabetic patients (25% vs 23%, p-0.03).
6	Sato T *et al*[46]	2012	Prospective	CAD	562	8 month	MACE, cardiac death, non fatal MI, congestive heart failure, recurrent angina pectoris.	DM patients have worse mid- term prognosis than non-diabetic patients undergoing PCI with DES.
7	Kassaian SE *et al*[47]	2012	Prospective	CAD	2884	6 Months	MACE , TVR, TLR CABG, Non fatal MI, All cause Mortality,	Good glycemic control (HbA1c levels ≤7%) was associated with a better clinical outcome after PCI.
8	Sohrabi B *et al*[48]	2011	Prospective	CAD	163	1 Yr	MACE (Death, MI, Repeat revascularization)	DM in patients undergoing successful PCI on CTO, was associated with higher in-hospital adverse events (25.8% vs 7.8%, p-0.02). However there is no significant difference in long term outcomes.
9	Ike A *et al*[49]	2011	Prospective	Excluded ACS	546	300 Days	MACE.	DM patients with HbA1c < 6.9% showed better clinical outcomes ≥ 6.9% group. Glycemic control during PCI was not associated with improvement in the clinical outcome at follow up.
10	Ruperto C *et al*[50]	2011	Retrospective	ACS	1462	3 Yr	Composite of death, non fatal MI,TVR	DM patients experienced higher 3-year rates of death, non-fatal MI or TVR (32.3 vs. 21.9%, p- 0.001).
11	Liu YS *et al* [51]	2021	Retrospective	CAD	3168	4 Yr	All cause mortality, cardiac death	In patients with age ≥ 65 undergoing PCI, SCH is not a risk factor for mortality. No significant difference in mortality rate between the SCH and euthyroid groups at 4 year follow up .

12	**Cao Q *et al*[32]**	**2020**	**Prospective**	**ACS**	**1560**	**12 Month**	**All cause mortality, cardiac mortality, non fatal reinfarction**	**Prevalence of mild thyroid dysfunction was higher in patients with ACS undergoing PCI. Low T_3 syndrome was associated with a higher rate of all cause and cardiac mortality at 12 month follow up .**
13	**Maninder Singh *et al* [52]**	**2018**	**Prospective**	**CAD**	**1317**	**1 Yr**	**Mortality and MACE.**	**Hypothyroidism was associated with higher all cause mortality after PCI (14% vs 6.7%, p=0.014) and there was no significant difference in MACE.**
14	**Desai R *et al*[53]**	**2018**	**Retrospective**	**CAD**	**9205**	**After PCI with Coronary Atherectomy for Calcified Coronary Lesions:**	**In hospital mortality and post operative complications**	**In-hospital mortality (4.1% vs. 3.2%, p<0.01), post myocardial infarction rate (9.7% vs. 8.8%, p<0.05), postoperative respiratory failure (1.6% vs. 0.9%, p<0.001) and acute kidney injury requiring dialysis (1.3% vs. 0.8%, p<0.001) were higher in the hypothyroid group as compared to the euthyroid group. Length of hospital stay (days) were more in hypothyroid group (4.8±5.3 vs. 4.2±5.9, p<0.001).**
15	**Lee Y *et al*[54]**	**2017**	**Prospective**	**CVD**	**936**	**3.1 Yrs**	**Cardiac death, non fatal MI ,repeat revascularization**	**Cardiac mortality was high in the SCH group than in the euthyroidism group. SCH was associated with worse PCI outcomes and was associated with the repeat revascularisation for in-stent restenosis rather than the de novo lesions.**
16	**Xue C *et al*[55]**	**2017**	**Prospective**	**ACS**	**613**	**1 Yr**	**MACE, stroke or repeat revascularization.**	**The incidence of low T_3 syndrome is common in ACS patients. Patients with Low freeT_3, normal thyroxine (T_4) and thyroid-stimulating hormone (TSH) had increased mortality. Low fT_3 patients had poorer Health related quality of life (HRQOL) both at baseline and 1-year follow-up (p<0.05) . In ACS patients treated with DES, Low fT_3 level is a predictor of worse HRQOL improvement.**
17	**Zhang M *et al* [40]**	**2016**	**Prospective**	**CAD**	**2430**	**10 Yr**	**MACCE, Cardiac death, MI, HF, Revascularization,Stroke.**	**Hypothyroidism is associated with a higher incidence of MACCE as compared with euthyroid patients undergoing PCI.**
18	**Ndrepepa G *et al* [41]**	**2016**	**Retrospective**	**CAD**	**8010**	**3 Yr**	**All cause of mortality.**	**Patients with TSH level ranging from 1.67 mU/L to 4.00 mU/L(tertile 3) had increased risk of mortality upto 3 years after PCI (p-<0.001) when compared with other two groups tertile 1 (0.3 mU/L to <1.02 mU/L) and tertile 2 (1.02 mU/L to <1.67 mU/L) and had increased in- hospital cardiogenic shock (p <0.001) and peri PCI bleeding (p- 0.005).**
19	**Ozcan KS *et al* [56]**	**2013**	**Prospective**	**STEMI**	**457**	**14 months**	**MACE such as recurrent MI, TVR mortality.**	**Among STEMI patients with thyroid dysfunction undergoing primary PCI showed significant difference in-hospital (p <0.01) and long term mortality (p <0.01) as compared with euthyroid.**

DCB-Drug coated balloon; RES-Ridaforolimus eluting stent; ZES-Zotarolimus eluting stent; ST-Stent thrombosis; TLR-Target lesion revascularization; TLF-Target lesion failure; HF-Heart failure; SYNTAX-Synergy between PCI with taxus and cardiac surgery; CTO-chronic total occlusion

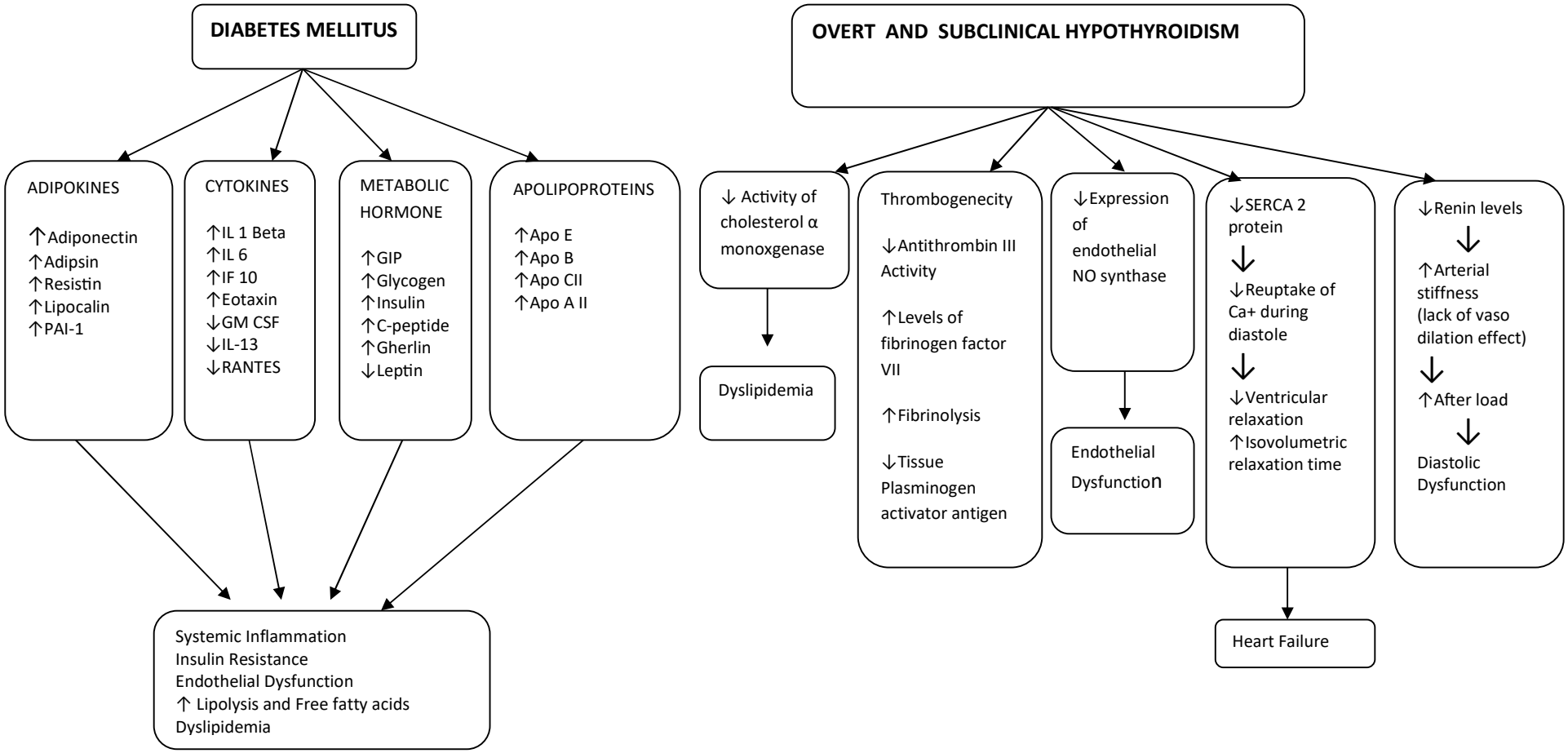

Figure 1: Shows the mechanism of diabetes mellitus and hypothyroidism causing cardiac complications. Protein markers that are responsible for the development and progression of diabetes , hypothyroidism and associated coronary artery disease complication. Different pathological protein markers may act as mediators in the initiation of insulin resistance, systemic inflammation, endothelial dysfunction, increase lipolysis and free fatty acids , dyslipidemia and diastolic dysfunction.(PAI-1-Plasmin activator Inhibitor-1, IL-Interleukin, IF- interferon, GM CSF-Granulocyte macrophage colony stimulating factor, RANTES-Regulated upon activation, normal T cell expressed and secreted, GIP- Gastric Inhibitory peptide,T_3- 3,5,3' triiodothyronine,T_4-3,5,3',5' tetraiodothyronine,Ca^+-Calcium, SERCA-Sarco endoplasmic reticulum Ca^{2+} ATPase, Apo-Apolipoprotein, NO -Nitric oxide)[2,57,58]

CONCLUSION:

CVD is a significant public health concern.T2DM and hypothyroidism are the two common endocrine disorders associated with CVD. There is a complex association between T2DM /hypothyroidism in patients with CVD attributed to insulin resistance and endothelium dysfunction. Both comorbidities have an increased risk for adverse outcomes among the patients undergoing PCI. On CV outcomes, it is essential to optimize the treatment of these conditions in patients undergoing PCI. Further large-scale evidence is needed to understand the combined effect of T2DM and hypothyroidism on CV outcomes in patients undergoing PCI.

Acknowledgement: I hereby acknowledge staff in cardiac catheterisation department and Indian cardiology research foundation, The Madras Medical Mission, Chennai

Conflict of interest: Nil

Financial disclosure: none

Data availability statement: Data sharing not applicable – no new data generated

REFERENCES:

[1] Sarfo-Kantanka, O., Sarfo, F.S., Ansah, E.O. and Kyei, I. (2018). The Effect of Thyroid Dysfunction on the Cardiovascular Risk of Type 2 Diabetes Mellitus Patients in Ghana. Journal of Diabetes Research

[2] Adela, R., Reddy, P.N.C., Ghosh, T.S., Aggarwal, S., Yadav, A.K., Das, B. and Banerjee, S.K. (2019). Serum protein signature of coronary artery disease in type 2 diabetes mellitus. Journal of Translational Medicine, 17(1).

[3] Mohan, V., Venkatraman, J.V. and Pradeepa, R. (2010). Epidemiology of Cardiovascular Disease in Type 2 Diabetes: The Indian Scenario. Journal of Diabetes Science and Technology, 4(1), pp.158–170.

[4] Regassa, L.D., Tola, A. and Ayele, Y. (2021). Prevalence of Cardiovascular Disease and Associated Factors Among Type 2 Diabetes Patients in Selected Hospitals of Harari Region, Eastern Ethiopia. Frontiers in Public Health, 8.

[5] Mooradian, A.D. (2003). Cardiovascular Disease in Type 2 Diabetes Mellitus. Archives of Internal Medicine, 163(1), p.33.

[6] Semple, R.K., Savage, D.B., Cochran, E.K., Gorden, P. and O'Rahilly, S. (2011). Genetic Syndromes of Severe Insulin

Resistance. Endocrine Reviews, 32(4), pp.498–514.

[7] King, R.J. and Grant, P.J. (2016). Diabetes and cardiovascular disease: pathophysiology of a life-threatening epidemic. Herz, 41(3), pp.184–192.

[8] Harjunpää, H., Llort Asens, M., Guenther, C. and Fagerholm, S.C. (2019). Cell Adhesion Molecules and Their Roles and Regulation in the Immune and Tumor Microenvironment. Frontiers in Immunology, 10.

[9] Gyongyosi, M., Yang, P., Hassan, A., Weidinger, F., Domanovits, H., Laggner, A. and Glogar, D. (1999). Coronary risk factors influence plaque morphology in patients with unstable angina. Coronary Artery Disease, 10(4), pp.211–220.

[10] Moreno, P.R., Murcia, A.M., Palacios, I.F., Leon, M.N., Bernardi, V.H., Fuster V. and Fallon, J.T. (2000). Coronary Composition and Macrophage Infiltration in Atherectomy Specimens From Patients With Diabetes Mellitus. Circulation, 102(18), pp.2180–2184.

[11] Matheus, A.S. de M., Tannus, L.R.M., Cobas, R.A., Palma, C.C.S., Negrato, C.A. and Gomes, M. de B. (2013). Impact of Diabetes on Cardiovascular Disease: An Update. International Journal of Hypertension, 2013, pp.1–15.

[12] Kasaoka, S., Okuda, F., Satoh, A., Miura, T., Kohno, M., Fujii, T., Katayama, K., Ogawa, H. and Matsuzaki, M. (1997). Effect of Coronary Risk Factors on Coronary Angiographic Morphology in Patients With Ischemic Heart Disease. Japanese Circulation Journal, 61(5), pp.390–395.

[13] Syvänne, M. and Taskinen, M.-R. (1997). Lipids and lipoproteins as coronary risk factors in non-insulin-dependent diabetes mellitus. The Lancet, 350, pp. S120–S123.

[14] TkáčI., Kimball, B.P., Lewis, G., Uffelman, K. and Steiner, G. (1997). The Severity of Coronary Atherosclerosis in Type 2 Diabetes Mellitus Is Related to the Number of Circulating Triglyceride-Rich Lipoprotein Particles. Arteriosclerosis, Thrombosis, and Vascular Biology, 17(12), pp.3633–3638.

[15] Cariou, B., Bonnevie, L., Mayaudon, H., Dupuy, O.,

Ceccaldi, B., & Bauduceau, B. (2000). Angiographic characteristics of coronary artery disease in diabetic patients compared with matched non-diabetic subjects. *Diabetes, nutrition & metabolism*, *13*(3), 134–141..

[16] Natali, A., Vichi, S., Landi, P., Severi, S., L'Abbate, A. and Ferrannini, E. (2000). Coronary atherosclerosis in Type II diabetes: angiographic findings and clinical outcome. Diabetologia, 43(5), pp.632–641.

[17] S, S. (2014). Comparitive Angiographic Profile in Diabetic and Non-Diabetic Patients with Acute Coronary Syndrome. Journal of Clinical And Diagnostic Research.

[18] Yang, Y., Park, G.-M., Han, S., Kim, Y.-G., Suh, J., Park, H.W., Won, K.-B., Ann, S.H., Kim, S.-J., Kim, D.-W., Park, M.-W., Her, S.H. and Lee, S.-G. (2018). Impact of diabetes mellitus in patients undergoing contemporary percutaneous coronary intervention: Results from a Korean nationwide study. PLOS ONE, 13(12), p.e0208746.

[19] Hwang, J.K., Lee, S.H., Song, Y.B., Ahn, J., Carriere, K., Jang, M.J., Park, T.K., Choi, S.-H., Yang, J.H., Choi, J.-H., Lee, S.H., Gwon, H.-C. and Hahn, J.-Y. (2017). Response by Hwang et al to Letter Regarding Article, "Glycemic Control Status After Percutaneous Coronary Intervention and Long-Term Clinical Outcomes in Patients With Type 2 Diabetes Mellitus." Circulation: Cardiovascular Interventions, 10(8).

[20] Nagendran, J., Bozso, S.J., Norris, C.M., McAlister, F.A., Appoo, J.J., Moon, M.C., Freed, D.H. and Nagendran, J. (2018). Coronary Artery Bypass Surgery Improves Outcomes in Patients With Diabetes and Left Ventricular Dysfunction. Journal of the American College of Cardiology, 71(8), pp.819–827.

[21] Farkouh, M.E., Dangas, G., Leon, M.B., Smith, C., Nesto, R., Buse, J.B., Cohen, D.J., Mahoney, E., Sleeper, L., King, S., Domanski, M., McKinlay, S. and Fuster, V. (2008). Design of the Future REvascularization Evaluation in patients with Diabetes mellitus: Optimal management of Multivessel disease (FREEDOM)

Trial. American Heart Journal, 155(2), pp.215–223.

[22] Jiang, Y.-J., Han, W.-X., Gao, C., Feng, J., Chen, Z.-F., Zhang, J., Luo, C.-M. and Pan, J.-Y. (2017). Comparison of clinical outcomes after drug-eluting stent implantation in diabetic versus nondiabetic patients in China. Medicine, 96(17), p.e6647.

[23] Wang, Q., Liu, H. and Ding, J. (2017). Outcomes of percutaneous coronary intervention in patients with coronary chronic total occlusions with versus without type 2 diabetes mellitus. Medicine, 96(45), p.e8499.

[24] Kappetein, A.P., Head, S.J., Morice, M.-C., Banning, A.P., Serruys, P.W., Mohr, F.-W., Dawkins, K.D. and Mack, M.J. (2013). Treatment of complex coronary artery disease in patients with diabetes: 5-year results comparing outcomes of bypass surgery and percutaneous coronary intervention in the SYNTAX trial†. European Journal of Cardio-Thoracic Surgery, 43(5), pp.1006–1013.

[25] Konigstein, M., Ben-Yehuda, O., Smits, P.C., Love, M.P., Banai, S., Perlman, G.Y., Golomb, M., Ozan, M.O., Liu, M., Leon, M.B., Stone, G.W. and Kandzari, D.E. (2018). Outcomes Among Diabetic Patients Undergoing Percutaneous Coronary Intervention With Contemporary Drug-Eluting Stents. JACC: Cardiovascular Interventions, 11(24), pp.2467–2476.

[26] Corpus, R.A., George, P.B., House, J.A., Dixon, S.R., Ajluni, S.C., Devlin, W.H., Timmis, G.C., Balasubramaniam, M. and O'Neill, W.W. (2004). Optimal glycemic control is associated with a lower rate of target vessel revascularization in treated type II diabetic patients undergoing elective percutaneous coronary intervention. Journal of the American College of Cardiology, 43(1), pp.8–14.

[27] Corpus, R.A., O'Neill, W.W., Dixon, S.R., Timmis, G.C. and Devlin, W.H. (2003). Relation of hemoglobin A1c to rate of major adverse cardiac events in nondiabetic patients undergoing percutaneous coronary revascularization. The American Journal of Cardiology, 92(11), pp.1282–1286.

[28] Vargas-Uricoechea, H., Bonelo-Perdomo, A. and Sierra-Torres, C.H. (2014). Effects of thyroid hormones on the heart. Clinica E Investigacion En Arteriosclerosis: Publicacion Oficial De La Sociedad Espanola De Arteriosclerosis, [online] 26(6), pp.296–309. Available at: https://pubmed.ncbi.nlm.nih.gov/25438971/ [Accessed 8 Dec. 2020].

[29] Udovcic, M., Pena, R.H., Patham, B., Tabatabai, L. and Kansara, A. (2017). Hypothyroidism and the Heart. Methodist DeBakey Cardiovascular Journal, 13(2), pp.55–59.

[30] Duntas, L.H. and Brenta, G. (2012). The Effect of Thyroid Disorders on Lipid Levels and Metabolism. Medical Clinics of North America, 96(2), pp.269–281.

[31] Tian, L., Zhang, L., Liu, J., Guo, T., Gao, C. and Ni, J. (2014). Effects of TSH on the function of human umbilical vein endothelial cells. Journal of Molecular Endocrinology, 52(2), pp.215–222.

[32] Cao, Q., Jiao, Y., Yu, T. and Sun, Z. (2020). Association between mild thyroid dysfunction and clinical outcome in acute coronary syndrome undergoing percutaneous coronary intervention. Cardiology Journal, 27(3), pp.262–271.

[33] Sun, J., Yao, L., Fang, Y., Yang, R., Chen, Y., Yang, K. and Tian, L. (2017). Relationship between Subclinical Thyroid Dysfunction and the Risk of Cardiovascular Outcomes: A Systematic Review and Meta-Analysis of Prospective Cohort Studies. International Journal of Endocrinology, [online] 2017, pp.1–15. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5610794/ [Accessed 25 Nov. 2019].

[34] Hayashi, T., Hasegawa, T., Kanzaki, H., Funada, A., Amaki, M., Takahama, H., Ohara, T., Sugano, Y., Yasuda, S., Ogawa, H. and Anzai, T. (2016). Subclinical hypothyroidism is an independent predictor of adverse cardiovascular outcomes in patients with acute decompensated heart failure. ESC Heart Failure, 3(3), pp.168–176.

[35] Sara, J.D., Zhang, M., Gharib, H., Lerman, L.O. and Lerman, A. (2015). Hypothyroidism Is Associated With Coronary Endothelial Dysfunction in

Women. Journal of the American Heart Association, 4(8).

[36] Iervasi, G., Pingitore, A., Landi, P., Raciti, M., Ripoli, A., Scarlattini, M., L'Abbate, A. and Donato, L. (2003). Low-T3 Syndrome. Circulation, 107(5), pp.708–713.

[37] Iervasi, G. (2007). Association Between Increased Mortality and Mild Thyroid Dysfunction in Cardiac Patients. Archives of Internal Medicine, 167(14), p.1526.

[38] Rodondi, N., den Elzen, W.P.J., Bauer, D.C., Cappola, A.R., Razvi, S., Walsh, J.P., Åsvold, B.O., Iervasi, G., Imaizumi, M., Collet, T.-H., Bremner, A., Maisonneuve, P., Sgarbi, J.A., Khaw, K.-T., Vanderpump, M.P.J., Newman, A.B., Cornuz, J., Franklyn, J.A., Westendorp, R.G.J. and Vittinghoff, E. (2010). Subclinical Hypothyroidism and the Risk of Coronary Heart Disease and Mortality. JAMA, 304(12), p.1365.

[39] P., U.K., V., S. and N., L.K. (2019). Role of Hypothyroidism in Dyslipidaemia and Blood Glucose Regulation. Perspectives in Medical Research, 7, pp.56–61.

[40] Zhang, M., Sara, J.D.S., Matsuzawa, Y., Gharib, H., Bell, M.R., Gulati, R., Lerman, L.O. and Lerman, A. (2016). Clinical outcomes of patients with hypothyroidism undergoing percutaneous coronary intervention. European Heart Journal, 37(26), pp.2055–2065.

[41] Ndrepepa, G., Braun, S., Mayer, K., Cassese, S., Fusaro, M., Byrne, R.A., Hoppmann, P., Schunkert, H., Laugwitz, K.-L. and Kastrati, A. (2015). Prognostic value of thyroid-stimulating hormone within reference range in patients with coronary artery disease. Metabolism, 64(10), pp.1308–1315.

[42] Izkhakov, E., Zahler, D., Rozenfeld, K.-L., Ravid, D., Banai, S., Topilsky, Y., Stern, N., Greenman, Y. and Shacham, Y. (2020). Unknown Subclinical Hypothyroidism and In-Hospital Outcomes and Short- and Long-Term All-Cause Mortality among ST Segment Elevation Myocardial Infarction Patients Undergoing Percutaneous Coronary Intervention. Journal of Clinical Medicine, 9(12), p.3829.

[43] Mayer, O., Šimon, J., Filipovský, J., Plášková, M. and Pikner, R. (2006). Hypothyroidism in coronary heart disease and its relation to selected risk factors. Vascular Health and Risk Management, 2(4), pp.499–506.

[44] Benjamin, B.K., Qiu, C., Han, Z., Lu, W., Sun, G., Qin, X., Wang, X., Wang, X., Li, R. and Pan, L. (2021). The Association between Type-2 Diabetes Duration and Major Adverse Cardiac Events after Percutaneous Coronary Intervention. Journal of Diabetes Research, 2021, pp.1–9.

[45] Koskinas, K.C., Siontis, G.C.M., Piccolo, R., Franzone, A., Haynes, A., Rat-Wirtzler, J., Silber, S., Serruys, P.W., Pilgrim, T., Räber, L., Heg, D., Jüni, P. and Windecker, S. (2016). Impact of Diabetic Status on Outcomes After Revascularization With Drug-Eluting Stents in Relation to Coronary Artery Disease Complexity. Circulation: Cardiovascular Interventions, 9(2).

[46] Sato, T., Ono, T., Morimoto, Y., Kawai, H., Fuke, S., Ikeda, T. and Saito, H. (2012). Differences in clinical and angiographic outcomes with different drug-eluting stents in Japanese patients with and without diabetes mellitus. Journal of Cardiology, 60(5), pp.361–366.

[47] Kassaian, S.E., Goodarzynejad, H., Boroumand, M.A., Salarifar, M., Masoudkabir, F., Mohajeri-Tehrani, M.R., Pourhoseini, H., Sadeghian, S., Ramezanpour, N., Alidoosti, M., Hakki, E., Saadat, S. and Nematipour, E. (2012). Glycosylated hemoglobin (HbA1c) levels and clinical outcomes in diabetic patients following coronary artery stenting. Cardiovascular Diabetology, 11(1).

[48] Sohrabi B, Ghaffari S, Habibzadeh A, Chaichi P. (2011). Outcome of Diabetic and Non Diabetic patients undergoing successful percutaneous coronary intervention of chronic total occlusion. Journal of cardiovascular and thoracic research, 3(2), 45–48.

[49] Ike, A., Nishikawa, H., Shirai, K., Mori, K., Kuwano, T., Fukuda, Y., Takamiya, Y., Yanagi, D., Kubota, K., Tsuchiya, Y., Zhang, B., Miura, S. and Saku, K. (2011). Impact of Glycemic Control on the Clinical Outcome in Diabetic Patients With Percutaneous Coronary Intervention - From the

FU-Registry -. Circulation Journal, 75(4), pp.791–799.

[50] Ruperto, C., Capodanno, D., Blundo, A., Capranzano, P., Sanfilippo, A., Caggegi, A., Bucalo, R., Giaimo, V. and Tamburino, C. (2011). Impact of diabetes mellitus on long-term follow-up of percutaneous coronary intervention based on clinical presentation of coronary artery disease. Journal of Cardiovascular Medicine, 12(6), pp.405–410.

[51] Liu, Y.-S., Wei, M., Wang, L., Liu, G., Ma, G.-P., Ono, K., Cao, Z.-L., Yang, M. and Zheng, M.-Q. (2021). The impact of subclinical hypothyroidism on long-term outcomes in older patients undergoing percutaneous coronary intervention. BMC Endocrine Disorders, 21(1).

[52] Singh, M., Mishra, A., Kamboj, M., Chaudhary, S., Kaluski, E. and Stapleton, D. (2014). Abstract 333: Hypothyroidism As a Predictor of Worse Clinical Outcomes After Percutaneous Coronary Interventions: 1 Year Follow Up Study. Circulation: Cardiovascular Quality and Outcomes, 7(suppl_1).

[53] Desai, R., Goyal, H., Kumar, G. and Sachdeva, R. (2018). Impact of Hypothyroidism on Outcomes of Percutaneous Coronary Intervention with Coronary Atherectomy for Calcified Coronary Lesions: A Propensity-matched Analysis. Cureus.

[54] Lee, Y., Lim, Y.-H., Shin, J.-H., Park, J. and Shin, J. (2018). Impact of subclinical hypothyroidism on clinical outcomes following percutaneous coronary intervention. International Journal of Cardiology, 253, pp.155–160.

[55] Xue, C., Bian, L., Xie, Y.S., Yin, Z.F., Xu, Z.J., Chen, Q.Z., Zhang, H.L., Fan, Y.Q., Du, R. and Wang, C.Q. (2017). Low fT3 is associated with diminished health-related quality of life in patients with acute coronary syndrome treated with drug-eluting stent: a longitudinal observational study. Oncotarget, 8(55), pp.94580–94590.

[56] Özcan, K.S., Osmonov, D., Toprak, E., Güngör, B., Tatlısu, A., Ekmekçi, A., Kaya, A., Tayyareci, G. and Erdinler, İ. (2014). Sick euthyroid syndrome is associated with poor prognosis

in patients with ST segment elevation myocardial infarction undergoing primary percutaneous intervention. Cardiology Journal, 21(3), pp.238–244..

[57] Jabbar, A., Pingitore, A., Pearce, S.H.S., Zaman, A., Iervasi, G. and Razvi, S. (2016). Thyroid hormones and cardiovascular disease. Nature Reviews Cardiology, [online]14(1),pp.39–55.

[58] Fazio, S., Palmieri, E.A., Lombardi, G. and Biondi, B. (2004). Effects of thyroid hormone on the cardiovascular system. Recent progress in hormone research, [online] 59, pp.31–50.