universität wien

DIPLOMARBEIT

Titel der Diplomarbeit

„Cardiovascular disease and Diabetes mellitus: analysis of mortality, morbidity and risk factors”

verfasst von

Rabab Hamid

angestrebter akademischer Grad

Magistra der Pharmazie (Mag.pharm.)

Wien, 2015

Studienkennzahl lt. Studienblatt:	A 449
Studienrichtung lt. Studienblatt:	Diplomstudium Pharmazie
Betreut von:	ao. Univ.-Prof. Mag. Dr. Rosa Lemmens-Gruber

Acknowledgment

I would like to extend my appreciations and deepest gratitude to my supervisor, Prof. Dr. Rosa Lemmens-Gruber for this Research paper for her time and effort in giving guidance and encouragement for me. I also would like to thank all the university staff and especially the library staff for their extended help in their assistance for using the library facilities for resources relevant to this research paper.

I would also like to thank my mother. She was always there cheering me up and encouraging me with her best wishes. Finally, I would like to thank my husband, Ali Qassim for his support.

Table of content

1. INTRODUCTION

Diabetes mellitus, especially type 2, is a metabolic disease which involves the coexistence of several cardiovascular risk factors. Affected patients are therefore at high cardiovascular risk (2-3 times higher than that of men in the general population and 2-6 times higher than that of women). Cardiovascular disease (CVD) is the main cause of death in the diabetic population (Nadal and Gutiérrez; 2013). There is growing interest to understand the prevalence of well-known risk factors such as hypertension, dyslipidaemia and obesity in these patients. Many of these risk factors could be common history for both diabetes mellitus (DM) and cardiovascular disease (Martin-Timon et al.; 2014).

It has been demonstrated that extensive strategies to control all the risk factors present in persons with type 2 diabetes mellitus associated with CVD and the possibility to reduce the progression of the DM disease can reduce the development of micro- and macro vascular complications and the incidence of CVD events in patients with diabetes (Stolar; 2010).

1.1 Aim of the research:

- To describe the risks for cardiovascular disease in association with diabetes mellitus.

Objective of the research:

- To highlight risk factors for cardiovascular disease in association with diabetes mellitus and discuss their role in the pathogenesis of the excess cardiovascular disease mortality and morbidity in these patients.

2. CARDIOVASCULAR DISEASES

2.1. Ischemic Heart Disease

Myocardial ischemia is prescribed as imbalance in the supply of oxygen to functioning heart cells relative to their demand for oxygen (Singh et al.; 1994) which is attributed to the alteration in the coronary arteries (Martins e Silva; 2006).

The factors which determine myocardial oxygen demand, are (1) heart rate, (2) tension developed in the left ventricular wall (which in turn is a function of systemic blood pressure (BP), left ventricular geometry, and other factors) and (3) myocardial contraction, while the important determinant of myocardial oxygen supply are (1) heart rate (duration of diastole), (2) oxygen carrying capacity of blood and (3) coronary arteries (Singh et al.; 1994).

According to Hawkins and Dunn (1990) ischemic heart disease is classified to stable angina and unstable syndromes (unstable angina and acute myocardial infarction). Variant angina and silent ischemia are considered separately (Singh et al.; 1994).

The diagnostic test for ischaemic heart disease (IHD), which is most commonly used, is the electrocardiodiagram during or immediately after efforts. Other methods for screening are electrocardiographic exercise testing which aids the diagnosis in patients who have normal resting ECGs, pharmacological stress testing for patients who are unable to exercise by using either intravenous dipyridamole or adenosine and stress perfusion imaging with thallium-201 or technetium. Also, there are other methods which are very specific, sensitive and invasive but also expensive and risky; these are coronary arteriography and cardiac catheterization (Shargel et al.; 2004).

2.1.2 Treatment

The aim of treatment is the way to change the relationship between the myocardial oxygen supply and demand. Nitrate is systemic as well as coronary arterial vasodilators. They decrease the left ventricular end diastolic pressure and subendocardial wall tension. The net effects of these actions are to increase coronary arterial flow and to shift the distribution of flow back toward subendocardial regions. β-adrenoceptor blocking agents decrease the myocardial and arterial responses to the circulating and neuronal released catecholamines.

They decrease myocardial contractility and oxygen demand (Singh et al.; 1994). Calcium channel antagonists decrease the influx of calcium into vascular smooth muscle and myocardial cells resulting in decrease in vascular resistance and increase in coronary blood flow and enhanced oxygen supply (Shargel et al.; 2004).

Other approaches in treatment are based on thrombolysis and related measures which involve inhibition of platelet aggregation and thromboxane A2 synthesis as well as tissue-type plasminogen activators (Hugenholtz and Goldman; 1985).

2.2 Heart failure

2.2.1 Definition

Heart failure (HF) is determined as an abnormality of cardiac function which is responsible for the failure of the heart to pump blood at rate adequate with the requirements of metabolizing tissue. It is frequently, but not always caused by a defect in myocardial muscle function. The congestive heart failure (CHF) develops with progressive worsening of myocardial function. The term CHF refers to vascular congestion in the pulmonary or systemic circulations, usually due to heart failure (Braunwald; 1980).

In case of the presence of a defect in myocardial function or an excessive hemodynamic burden placed on the ventricle, the heart depends on some compensatory mechanisms to maintain its pumping performance. These are the Frank Starling mechanism with an increased preload to maintain cardiac performance, increased release of catecholamines by adrenergic nerves and the adrenal medulla, which enhance cardiac contractility, and myocardial hypertrophy, in which the mass of contractile tissue is augmented. Each of these mechanisms has a limited potential and ultimately fails, as a consequence of this limitation, heart failure occurs (Braunwald; 1980).

I will focus on CHF due to systolic failure of the left ventricle (LV) due to loss of contractile tissue (e.g., recurrent myocardial infarction) or primary heart muscle disease as would occur in idiopathic dilated cardiomyopathy (Dzau; 1994).

The physiological parameters in HF are determined as (a) preload which is end–diastolic fiber length in intact circulation and is most closely correlated with left ventricular volume. Left ventricular end-diastolic pressure or pulmonary capillary wedge pressure are often used as substituent for measurement of preload. In congestive cadiomyopathy, preload is elevated as a

result of increased end-diastolic volume and altered function of LV. (b) Afterload which is defined as forces that appose emptying of the LV during systole as a result of systemic vascular resistance (Dzau; 1994).

2.2.2 Treatment

The renin-angiotensin-aldestrone system (RAAS) plays a central role in the hemodynamic and metabolic response to ventricular dysfunction and contributes directly to the pathophysiology of heart failure; so angiotensin-converting enzyme (ACE) inhibitors have a dramatic impact in all stages of heart failure from asymptomatic to severe. They reduce both pre- and afterload. Angiotensin II receptor antagonists may be useful in patients who are intolerant to ACE-inhibitors. Vasodilators are used to reduce heart's workload, by reducing the demand placed on the heart to generate pressure and/or to pump blood. Drugs such as diuretics are used to control excessive salt and water retention which is the cause of many manifestations of heart failure such as breathlessness and oedema. Stable patients initiated on low doses of a beta-blocker with upward dose titration may derive significant benefits. Potential mechanisms proposed to explain these beneficial effects include blockade of detrimental effects of sympathomimetic stimulation. They may also improve diastolic dysfunction by prolonging diastolic filling time. Positive inotropic acting drugs such as digitalis improve the heart's pumping capability to restore the contractility of the failing heart towards normal. There is controversy about the long term use of digitalis. Digoxin appears to reduce hospitalization and symptoms, but has no effect on all cause mortality. Thus, digoxin is only considered for patients with left ventricular systolic dysfunction and supraventricular tachyarrhythmias such as atrial fibrillation as well as for patients in sinus rhythm who remain symptomatic after optimization of therapies known to improve survival.

2.3 Peripheral vascular disease

2.3.1 Definition

The peripheral vascular disease (PVD) develops when arteries become narrowed or blocked. The disease mostly affects the arteries in the legs. The most important cause of PVD is atherosclerosis, in which fatty material called plaque deposit on the artery walls (O'Donnell et al.; 2011). Symptoms range from intermittent claudication during exercise to peripheral limb ischemia requiring limb amputation. Even asymptomatic peripheral artery disease (PAD)

warrants intensive treatment (Wilson et al.; 2007). Smoking, hypertension, diabetes, hyperlipidemia, and physical inactivity are the most important risk factors for the development of PAD (Bradberry; 2004).

2.3.2 Treatment

The goal of therapy is to improve the symptoms of PAD (especially intermittent claudication), avoiding onset of limb-threatening ischemia, and improve long-term survival. Alteration of risk factors is aimed, especially smoking cessation, initiation of regular exercise, control of hypertension, diabetes and hyperlipidemia, and use of antiplatelet agents to reduce the risk of atherothrombotic events, according to available data suggesting that aspirin reduces morbidity and mortality in PAD, while clopidogrel reduces the risk of atherothrombotic events such as MI and stroke in these patients (Bradberry; 2004).

2.4 Cardiac arrhythmia

2.4.1 Definition

Cardiac arrhythmias are considered the most important diseases contributing to morbidity and mortality. They can result in syncope, which is a transient loss of consciousness due to insufficient blood supply to the brain, and may lead to sudden cardiac death. According to cardiac frequency, cardiac arrhythmias are classified into tachyarrhythmias with excessively fast rate and bradyarrhythmias with excessively slow rate. Furthermore, cardiac arrhythmia can be subdivided into groups depending on their origin, atria or ventricles. Cardiac arrhythmias mostly occur as a result of an abnormal heart structure (e.g. post myocardial infarction or as a result of dilated or hypertrophic cardiomyopathy), but it has also been demonstrated that some people will develop lethal cardiac arrhythmias despite having a normal heart structure. There are also rare instances of unexplained sudden death with genetic basis such as Congenital Long QT Syndrome (LQTS), which is associated with prolongation of the QT interval. Moreover, it has been demonstrated that there are a number of monogenic disorders caused by mutations in non-ion channel genes that are associated with an increased risk of cardiac arrhythmias. These are mostly characterized as the inherited cardiomyopathies and in particular familial hypertrophic cardiomyopathy, in which the mutations occur in structural proteins that cause gross morphological changes in the heart and presumably interfere with the conduction of signals between cells**.** Another interesting disorder is

Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT), which is characterized by exercise-induced ventricular tachycardia and sudden death in the absence of gross myocardial disease or QT prolongation. This is due to the defects in proteins that regulate calcium homeostasis. Ventricular arrhythmias are an important cause of morbidity and sudden death in almost all forms of heart disease. The important causes of polymorphic ventricular tachycardia are acute myocardial ischaemia and genetic arrhythmia syndromes. This tachycardia, known as torsade de pointes, is associated with QT prolongation (prolonged repolarisation) and it is often characterized as waxing and waning QRS amplitude (Subbiah et al.; 2004).

If arrhythmia originates in the right ventricle or interventricular septum, syncope or cardiac arrest is the characterizing symptom. In structural heart disease, ventricular tachycardia is usually caused by re-entry, involving a region of ventricular scar which might be a result of previous myocardial infarction, cardiomyopathy, or ventricular surgery. Less frequent causes of ventricular tachycardia are reentry or automaticity in diseased Purkinje tissue. Ventricular tachycardia without structural heart changes is often defined as idiopathic tachycardia. The appearance of T waves often suggests LQT syndrome (John et al.; 2012).

Atrial fibrillation (AF) is characterized as sustained arrhythmia and is associated with older people, but it has been demonstrated that also other factors are implicated. Although hypertension poses the greatest risk, other metabolic factors also play a role such as obesity, which was associated with a 50% increase in risk of atrial fibrillation; some of the effects of obesity might be hemodynamic (e.g., through impaired ventricular relaxation or atrial stretch) and also has direct metabolic effects. DM is also independently associated with atrial fibrillation (Grace and Roden; 2012). Moreover**,** Shang-Hung Chang (2014) has suggested that inflammation is involved in the pathogenesis of AF associated with DM, and that AF leads to an increase in oxidative stress and induces structural remodeling in the atrial myocytes, such as degradation of myofibrils and glycogen deposition. During tachyarrhythmia, substantial oxidative damage and cellular (ionic and structural) remodeling occurs in atrial myocardium that can induce AF.

2.4.2 Treatment

Antiarrhythmic drugs are frequently used in the treatment of patients with arrhythmia. Amiodarone is the most effective antiarrhythmic drug and is well tolerated, but thyroid

dysfunction and dermatological abnormalities are common; and severe pulmonary toxicity is a rare side effect (Barbosa et al.; 2015).

Implantable cardioverter defibrillator (ICD) is recommended in the following situations: I) Resuscitation from cardiac arrest due to documented sustained ventricular tachycardia (VT) or ventricular fibrillation (VF) due to a non-reversible cause, with left ventricular ejection fraction (LVEF) less than or equal to 35% or structural heart disease; II) Spontaneous VT due to a non-reversible cause, with LVEF less than or equal to 35% or the presence of structural heart disease; and III) Syncope of unknown origin, with inducible, hemodynamically unstable or clinically relevant VT or VF, with LVEF less than or equal to 35% or the presence of structural heart disease (Barbosa et al.; 2013). The American College of Cardiology (ACC), American Heart Association (AHA) and Heart Rhythm Society (HRS) 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities also recommended ICD implantation in patients with arrhythmia in order to prevent sudden cardiac Death (Barbosa et al.; 2015). Although ICD is useful to some patients, it is associated with some risk effects such as inappropriate shock, pro-arrhythmia, and preoperative and postoperative complications. ICD implantation should be indicated only when it is cost-effective and should be restricted to patients who can benefit from the treatment (Barbosa et al.; 2013, 2015).

Ablation therapy is recommended for patients with VT due to structural heart disease in the for the control of symptomatic, sustained monomorphic VT, which recurs despite antiarrhythmic drug therapy or when antiarrhythmic drugs are not tolerated or desirable; and to control sustained monomorphic VT or a VT storm that is not due to a transient reversible cause. Furthermore, ablation is recommended for the control of bundle branch reentrant. For the control of recurrent, sustained polymorphic ventricular tachycardia VT or VF that is refractory to antiarrhythmic therapy. Ablation (surgical or catheter-based) is for many patients the only option to treat recurrent VT because of the toxicity of antiarrhythmic drugs and their failure in preventing recurrences. The electrophysiological mechanism of VT is reentry, and the main goal of ablation is to identify critical isthmuses that maintain tachycardia and to destroy small portions of the myocardium, so to prevent the electrical impulses that perpetuate arrhythmias (Barbosa et al.; 2013; 2015).

The site of origin of VT in cardiomyopathy is commonly in the LV; also it can be induced by large areas of fibrosis. Several morphologies of sustained VT can be induced, which require

extensive mapping and ablation. In approximately 30% of sustained VT episodes, the reentrant circuits are also located on the epicardial surface (Barbosa et al.; 2013; 2015).

3. DIABETES MELLITUS

3.1 Definition, classification and diagnosis

Diabetes mellitus is a metabolic disorder of multiple aetiology, which is characterized by chronic hyperglycemia with disturbance of carbohydrate, fat and protein metabolism that results from defects in insulin secretion, insulin action or both. The effects of DM include long-term damage, dysfunction and failure of various organs especially the eyes, kidneys, nerves, heart and blood vessels (American Diabetes Association; 2004). The most common symptoms of DM are thirst, polyuria, blurring of vision, and weight loss. In its most severe forms, ketoacidosis or a non-ketotic hyperosmolar state may develop and leads to stupor, coma and in absence of effective treatment to death. The long-term effects of DM include specific complications of retinopathy with potential blindness, nephropathy that may lead to renal failure, and/or neuropathy with risk of foot ulcers, amputation and sexual dysfunction. People with diabetes are at increased risk of cardiovascular, peripheral vascular and cerebrovascular diseases (World Health Organization; 1999).

The pathophysiology of DM is insulin deficiency as a result of destroying the beta cells of the pancreas, and others that result in resistance to insulin action. The abnormalities of carbohydrate, fat and protein metabolism are due to deficient action of insulin on target tissues resulting from insensitivity or lack of insulin (World Health Organization; 1999).

There are four clinical classes of T1DM, which is also described as insulin mellitus, juvenile, onset diabetes or ketosis prone diabetes caused from B cell destruction which may be from immune or non-immune factors leading to absolute deficiency of insulin secretion (Shargel et al.; 2004).

T2DM is a chronic metabolic disorder that results in progressive defects in both insulin secretion and insulin action. The increased rate of basal hepatic glucose production as a result of insulin insufficiency is the primary cause of fasting hyperglycemia. Impaired suppression

of hepatic glucose production by insulin and decreased insulin-mediated glucose uptake by muscle contribute almost equally to postprandial hyperglycemia (DeFronzo; 1999).

Gestational DM, defined as any degree of glucose intolerance which is first detected during pregnancy, during the second or third trimester. Other specific types (secondary diabetes) of DM occur in patients who have other causes of diabetes due to either diseases of pancreas, genetic defects and endocrinopathies or drugs. Pre-diabetes preserves as an intermediate metabolic stage between normal glucose homeostasis and diabetes which is a risk factor for future DM and the CV system (Shargel et al.; 2004).

Diabetes can be diagnosed by using blood glucose measurements such as fasting plasma glucose test if the level is 126 mg per dL (7.0 mmol per L) or greater on two separate occasions. This method has a slightly lower sensitivity for predicting microvascular complications than random blood glucose level of 200 mg per dL (11.1 mmol per L) or greater. The oral glucose tolerance test is considered a first-line diagnostic test. The test has poor reproducibility and is time-consuming, requires extensive patient preparation before the 75-g glucose load, which is followed two hours later by a blood draw. A1C measurement has been recently recognized by the ADA as a diagnostic test for diabetes. An A1C level of greater than 6.5 percent on two separate occasions is considered diagnostic of diabetes. It has advantages as it is more reproducible and requires no fasting and is less time consuming, however, blood disorders that effect glycosylation of hemoglobin such as anemia and the lack of standardization has deterred its use (Patel and Macerollo; 2010).

3.2 Treatment

One of the main goals of treatment DM is to produce near-normal glucose levels and to prevent the development of diabetic disease complications; controlling blood glucose will delay micro- and macrovascular complications. Treatment with diet, insulin, metformin or sulfonylurea is known to improve blood glucose level (Turner et al.; 1999) as well as acarbose, miglitol and a number of newly introduced compounds such as glinides, pioglitazone, inkretin mimetics and dipeptidyl-peptidas-4 inhibitors.

4. EPIDEMIOLOGY, PREVALENCE, INCIDENCE AND MORTALITY

4.1 Diabetes mellitus

DM is a major public health problem and emerging as a pandemic especially in developing countries. The Global Burden of Diabetes study estimates that the worldwide prevalence of adult diabetes was 4.0% in 1995 and is expected to rise to 5.4% by 2025. In figure 1 we can see a 42% increase in the number of affected adults in developed nations and a corresponding 170% increase in developing countries. It is anticipated that there will be approximately 300 million adult diabetics worldwide by 2025, of those 228 million will reside in developing countries (Patel et al. 2003).

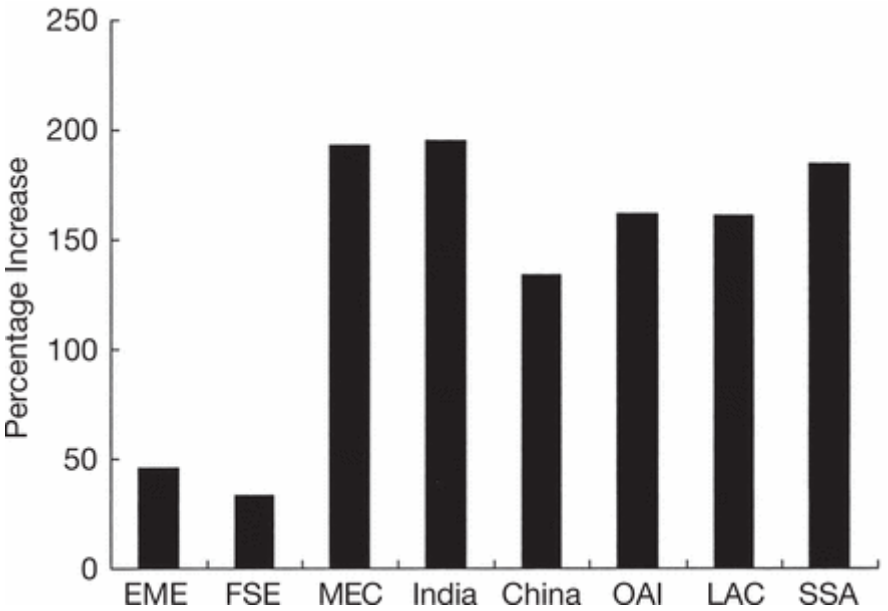

Figure (1)

Projected percentage increase in the number of adults with diabetes, 1995–2025.

(Patel et al.; 2003)

Abbreviations on Figure (1): EME = established market economies, FSE = former socialist economies of Europe, LAC = Latin America and the Caribbean, MEC = Middle Eastern crescent, OAI = other Asia and islands, SSA = sub-Saharan Africa.

This figure demonstrates that the disease is and will be continuing in the heavily populated and increasingly urbanized low- and middle-income countries of Asia Pacific, the Middle

East, and Latin America. India and China already have the largest number of adult diabetics and proportionate increases over the next couple of decades will also be greatest in these two countries. One of the most important factors in the epidemic of diabetes is the age structure of the adult diabetic populations as we see in figure 2, in developing countries compared with that in the developed countries. The prevalence of diabetes in developing countries peaks in the economically productive 45- to 64-year age group, compared with 65 years and above in developed regions (Patel et al.; 2003).

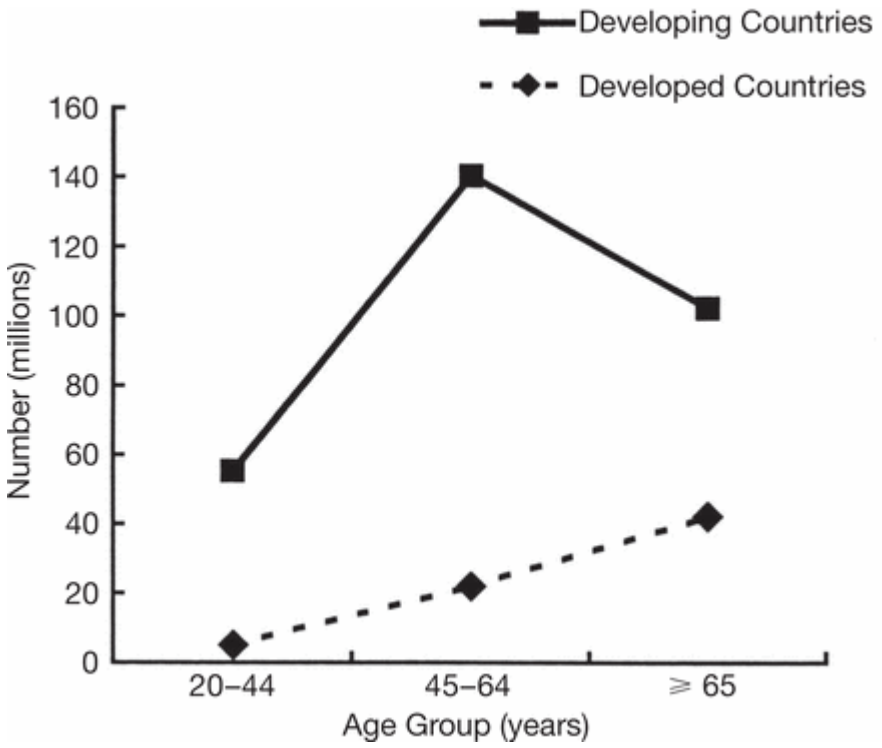

Figure (2)

Projected age distribution of adults with diabetes in developed and developing countries, 2025. (Patel et al.; 2003)

Another important factor which determines the prevalence of diabetics are genetic and environmental factors that influence both types of DM, type 1 (T1DM) and type 2 (T2DM). The prevalence of T2DM may vary widely between different ethnic groups living in the same country, suggesting that there is strong evidence for T2DM genotypes (Janka and Michaelis; 2002). The genetic factor appears to be a basic step for the development of non-insulin dependent DM (NIDDM), but the expression of the disease is influenced by exposure to different environmental factors. Some of these factors can be evaluated by comparing the incidence of diabetes in migrants with persons who stay in their home countries, taking into account that both groups have similar gene pools. The prevalence of diabetes increased over

10 years from 3 to 12%. This difference in the occurrence of diabetes in migrants provides evidence for the importance of environmental factors as determinant of NIDDM (Trevisan et al.; 1998).

The prevalence of T1DM is low or rare in certain ethnic groups, including Japanese, Indians, Chinese, Malays, Filipinos, American Indians, Eskimos, Maltese, Sri Lankans and Polynesians (Janka and Michaelis; 2002). According to a number of reports the highest frequency of onset occurs in fall and winter and lowest in summer, suggesting the association of T1DM with viral infections and that the infection is a precipitating factor in genetically susceptible individuals (Zimmet; 1983). Another possibility for the initiation of T1DM might be seasonal extrinsic factors which cause islet cell damage. Recent reports of environmental toxins, e.g. rodenticides and food preservatives are discussed as a possible cause of T1DM (Janka and Michaelis; 2002).

4.2 Cardiovascular disease in patients with diabetes mellitus

Cardiovascular disease is the major cause of death in patients with T2DM; more than 60% die of CVD, and a high percentage of people is suffering from serious CV-related complications. Diabetes is associated with a two- to fourfold increase in the risk of coronary heart disease and death (Hirshberg and Raz; 2011). The possibility that the patients with T2DM have myocardial infarction (MI) is similar to that of non diabetic patients who have had a prior MI. The Thrombolysis in Myocardial Infarction (TIMI) study group conducted clinical trials from 1997 to 2006 which suggest that, although modern treatments are used for acute coronary syndrome, diabetes still has significant adverse prognosis, with mortality rates of 7.2–8% during the first year after an event (Hirshberg and Raz; 2011). According to Hirshberg and Raz (2011) the microvascular complications in patients with DM can lead to significant morbidity and premature mortality. The prevalence rates of CVD in diabetic patients is different depending on duration of DM, age, sex, as well as possibly by race/ethnicity (De Ferranti et al.; 2014).

The International Diabetes Federation's global estimates for 2011 suggest that 52 million Europeans aged 20–79 years have DM and that this number will increase to over 64 million by 2030. In 2011, 63 million Europeans had impaired glucose tolerance (IGT). A total of 281 million men and 317 million women worldwide died with DM in 2011, most from CVD. The

healthcare expenditure for DM in Europe was about 75 billion Euros in 2011 and is projected to increase to 90 billion by 2030 (Rydén et al.; 2013).

There is a difference in the prevalence of CAD in patients with T1 or T2DM and also between different populations. A study of 10 centers of the WHO Multinational Study of Vascular Disease in Diabetes including about 4700 patients suffering from T1DM or T2DM, revealed that Japanese patients had a notably lower incidence of CAD than subjects from other parts of the world. Furthermore, their CAD incidence rates were lower than those in many non-diabetic western populations. CVD was the most common cause of mortality accounting for 44% of all deaths among patients with T1DM and 52% in patients with T2DM (Rydén et al.; 2013).

According to Patel et al. (2003) DM is associated with serious microvascular diseases such as retinopathy, nephropathy, and neuropathy as well as two- to threefold increase in the risk of developing macrovascular diseases, such as myocardial infarction and stroke. Also high incidence of hypertension is seen in patients with DM. The prevalence of hypertension in the general population is usually estimated to be in the order of 25%, the prevalence of hypertension in patients with DM ranges from 40% to 80% in various studies (Jeppesen; 2011). The older people with DM are at high risk to develop silent ischemia. They are also at higher risk of morbidity and mortality from cerebro-vascular disease. The prevalence of CVD in older population with diabetes was 10.6% and the prevalence of PVD is higher than in normal patients (Corriere et al.; 2013).

According to The Pittsburgh Epidemiology of Diabetes Complications (EDC) study, the incidence of CAD events in young adults (aged 28–38 years) with T1DM was 0.98% per year and increased to 3% per year after age 55 years (De Ferranti et al.; 2014). In contrast, incident first CVD in the non diabetic population ranges from 0.1% in 35- to 44-year-olds to 7.4% in adults aged 85–94 years (De Ferranti et al.; 2014).

5. DIABETES MELLITUS IMPACT ON CARDIO-VASCULAR SYSTEM

5.1 Coronary artery disease in patients with diabetes mellitus

5.1.1 Pathophysiology

5.1.1.1 Inflammation and vascular endothelial dysfunction

Both T1 and T2DM are independent risk factors for coronary heart disease (CHD). Myocardial infarction due to coronary atherosclerosis often occurs without symptoms in diabetic patients which indicates a multi vessel atherosclerosis that mostly occurs before manifestation of ischemic symptoms and before treatment is initiated. The delayed recognition of various forms of CHD worsens the prognosis for survival for many diabetic patients (Grundy et al.; 1999). Experimental studies have shown the involvement of inflammation in the pathogenesis of both diabetes and atherosclerosis and might be the factor linking diabetes to the development of atherosclerosis. Hyperglycemia and insulin resistance (IR) could accelerate the development of inflammation. Elevated glucose levels promote inflammation by increased oxidative stress, by the formation of advanced glycation end products (AGEs), and by increasing the transcription factor NFκB (Engström et al.; 2003).
Ceriello (2008) has also suggested that hyperglycaemia in the form of spikes is linked to immune activation via an oxidative mechanism and that both proteins and lipids are irreversibly glycated by a non-enzymatic mechanism. These AGEs accumulate in the cells and extracellular space of blood vessels, thereby accelerating atherogenic processes. A cell surface receptor for AGEs (RAGE) has been identified. Binding of AGEs and other pro-inflammatory ligands to this signal-transducing receptor leads to increased smooth muscle cell proliferation, migration and activation of mononuclear phagocytes, stimulation of cytokines such as TNF-α and in endothelial cells, increased vascular permeability, oxidative stress, vasoconstriction and increased expression of adhesion molecules (Engström et al.; 2003). Another concept is to demonstrate the relationship between the glucose level, vascular endothelial function and nitric oxide (NO) bioavailability. NO causes vasodilatation and platelet inhibition and thereby prevents vasoconstriction and thrombus formation. There is

evidence which supports the concept that hyperglycemia decreases endothelium-derived NO availability and affects vascular function.

These different steps of vascular endothelial dysfunction and inflammation under diabetes atherosclerotic plaque formation are initiated through uptake of LDL from blood by endothelial cells (Figure 3). Foam cells produce proinflammatory cytokines that are released into the lumen of blood vessel (far right). Both endothelial cells and vascular smooth muscle cells are capable of producing reactive oxygen species from a variety of enzymatic sources. In diabetes, reactive oxygen metabolites produced from vascular smooth muscle cells can increase substantially. Also increased production of the superoxide anion (O_2^-), ($ONOO^-$) can lead to decreased tissue bioavailability of nitric oxide (NO) or increase its degradation. Inducible nitric oxide synthase (iNOS) leads to increased reactive oxygen species (ROS) generation. Increased leukocyte adhesion and migration (bottom left), and also high glucose level leads to decreased L-arginine, which is a cofactor of endothelial nitric oxide synthase (eNOS). Tetrahydrobiopterin (BH4) leads to decrease in NO production in endothelial cells. All of these factors are proinflammatory and contribute to atherogenesis (Kolluru et al.; 2012).

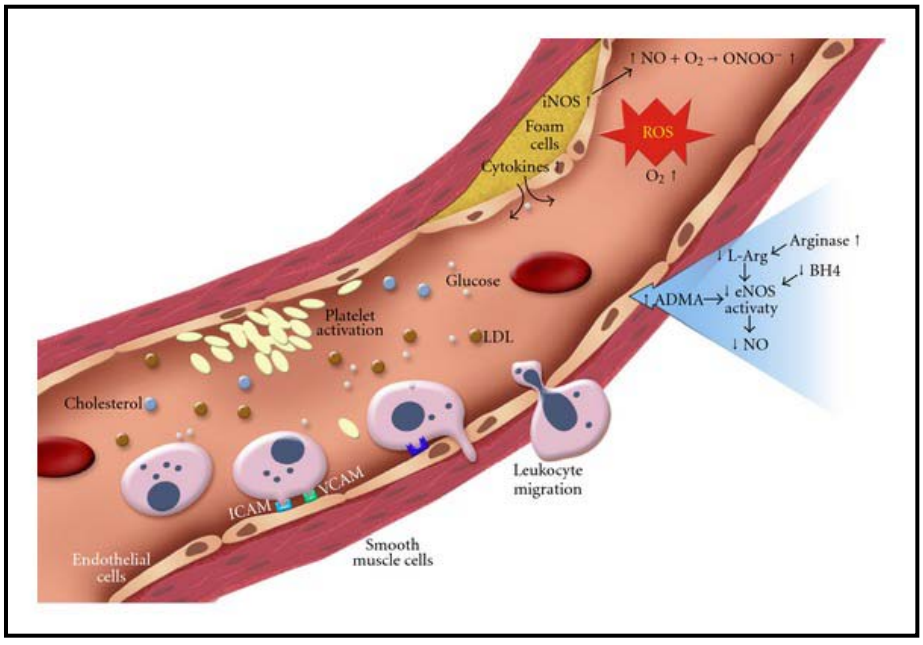

Figure (3)

Inflammation and vascular endothelial dysfunction

(Kolluru et al.; 2012).

Endothelial dysfunction may potentiate reduced nitric oxide production, increased platelet aggregation, increased expression of adhesion molecules, increased expression of chemokines and cytokines, and increased reactive oxygen species production from the endothelium, which play prominent roles in endothelial dysfunction and development of diabetic vascular complications. Notably, endothelial dysfunction is important for the prognosis in the detection of cardiovascular diseases such as MI, peripheral vascular disease and ischemic stroke (Kolluru et al.; 2012).

5.1.1.2 Platelet function and coagulation disorder

Platelet function also plays an important role in determining the natural history of atherosclerosis and consequences of plaque rupture, so that there is a link between cardiovascular risks and platelet function abnormalities and coagulation disorders in the diabetic patient. Hyperglycemia affects platelet function by impairing calcium homeostasis, altering platelet conformation, secretion and aggregation, and thromboxane formation. Other abnormalities affecting platelet function include impaired endothelial production of nitric oxide and prostacyclin, and increased production of fibrinogen, thrombin, and von Willebrand factor. It also enhances expression of glycoprotein Ib and IIb/IIIa which increase both platelet-von Willebrand factor and platelet-fibrin interaction. Moreover, plasma coagulation factors (e.g. factor VII and thrombin), lesion-based coagulants (e.g. tissue factor), and plasminogen activator inhibitor-1 (PAI-1) (a fibrinolysis inhibitor) are increased, and endogenous anticoagulants (e.g. thrombomodulin and protein C) are decreased. That means platelet function and plasma coagulation factors are altered in diabetes, favoring platelet aggregation, increase blood coagulability and thrombosis (Rydén et al.; 2014).

5.1.2 Potential therapeutic strategy

The pathophysiology of diabetes-related atherogenesis is broad and it is important that the patients get the comprehensive medical therapy to prevent its progress. Improvements in dyslipidaemia, IR, hypertension, and platelet activation are the main objectives in the treatment of patients with diabetes to minimize the complications of atherosclerosis. Statin therapy provides important risk reduction to diabetic patients with and without diagnosed atherosclerosis. Reduction in blood glucose level reduces the incidence of myocardial infarction and improvements in insulin sensitivity due to metformin treatment results in long-

term reductions in cardiovascular death. Antiplatelet therapy with for example aspirin plays a major role in patients with atheroscelerosis. Treatment of hypertension is important to reduce stroke and death (Beckman et al.; 2013). Renin-angiotensin system inhibitors exert additional beneficial effects on microvasculature and atherosclerosis, and thus should be included in initial therapy (Beckman et al. 2013). The beneficial effects of statins are described later with risk factors.

5.1.2.1 β-Adrenergic Blockers

Care should be taken regarding the use of β-blockers in diabetic patients because of the risk of masking hypoglycemia and decrease insulin production (Beckman et al.; 2002). However, β-blockers decrease the risk of re-infarction and cardiac mortality in patients with diabetes (McDonald et al.; 2005). In a retrospective study of more than 45.000 patients, β-blockers reduced the risk of MI by 23% in patients with T2DM without increasing diabetes-related complications. It is advocated to use β-blockers in DM after MI and emphasized on patient education to decrease the frequency of diabetes-related events (Beckman et al.; 2003). Overall, the positive effects of β-blockade on prognosis far outweigh the negative glucometabolic effects (Rydén et al.; 2014)

5.1.2.2 Antiplatelet Therapy

Because of the potential increase in thrombosis danger in diabetic patients, it should be taken in consideration the use of antiplatelet therapy to decrease the incidence of myocardial infarction and death in patients with diabetes (Beckman et al.; 2002). Treatment with platelet inhibitors and anticoagulans is of particular importance in diabetic patients with coronary artery disease (CAD), as platelet antagonists lower the combined risk of vascular death, MI, and stroke by 19% in diabetic patients.

Platelet GpIIb/IIIa inhibitors are also useful in unstable coronary syndromes according to a study which has suggested that the addition of tirofiban to heparin reduces the incidence of mortality and MI in diabetic patients more than in non diabetics. In a meta-analysis of more than 43.000 patients, including 4529 patients with diabetes, demonstrated that the reduction in absolute mortality in those with diabetes exceeded that of patients without diabetes (Haffner et al.; 2002). Regardless of the diabetes status, addition of clopidogrel to aspirin led to a reduction in death, MI or stroke in patients with unstable angina/non–ST-segment-elevation MI. These findings emphasize the importance of antiplatelet therapy in the short-term and long-term management of diabetic patients with atherosclerosis. Antiplatelet therapy has also

to be considered in diabetic patients who have not had clinical manifestations of atherosclerosis because platelet function is abnormal in patients with diabetes (Lüscher et al.; 2003; Beckman et al; 2013). The “Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance” (CHARISMA) trial of patients with established atherosclerosis or multiple risk factors for atherosclerosis, showed that the addition of clopidogrel to aspirin was not more effective than aspirin alone in the prevention of the composite endpoint of cardiovascular death, MI, and stroke (Bhatt et al.; 2006), but Beckman et al. (2013) demonstrated the benefit of clopidogrel in “Unstable Angina to Prevent Recurrent Events” (CURE) trial and in reducing the composite of cardiovascular death, non-fatal MI, and stroke with the addition of clopidogrel to aspirin in both non-diabetic and diabetic patients with acute coronary syndrome.

5.1.2.3 Revascularation in Diabetes

Patients with diabetes often have severe atherosclerosis and an increased risk of organ ischemia which requires revascularization. The higher risk for restenosis and graft occlusion should be taken in consideration in case of revascularization strategies, as well as the comorbid sequelae that complicate interventions in diabetic patients (Lüscher et al.; 2003; Beckman et al.; 2013). Most patients with stable coronary artery disease, normal left-ventricular function and no severe myocardial ischaemia on a stress test, may be treated with optimal medical therapy alone to reduce death and MI, except an acute coronary syndrome develops (Lüscher et al.; 2003; Beckman et al.; 2013).

5.1.2.4 Hyperglycemia and Insulin Resistance

Hyperglycemia and IR which are the main features of T2DM are important goals of treatment. The degree of IR relates directly to increasing rates of MI, stroke, and PAD. The “United Kingdom Prospective Diabetes Study” shows that intensive treatment of hyperglycemia reduces the risks of microvascular complications such as nephropathy and retinopathy, and improving IR with metformin decreased macrovascular complications. This result caused some controversy because the addition of sulfonylurea to metformin therapy seemed to increase cardiovascular risk.

The thiazolidinediones (TZDs) provide a novel approach to glycemic control. Thiazolidinediones improve glycemia by decreasing IR (Beckman et al.; 2002). Thiazolidinediones can also reduce the expression of markers of systemic inflammation such

as C-reactive protein (CRP) and interleukin-6 (IL-6) which have been considered to be risk factors for CV disease in patients with T2DM, and also matrix metalloproteinase-9 (MMP-9) which has been implicated in the pathogenesis of atherosclerotic plaque rupture. This might lead to the possibility of the use of MMP-9 levels as a marker for future myocardial infarction or unstable angina (Haffner et al.; 2002).

Peroxisome proliferator-activated receptor-γ (PPAR-γ) is a member of the nuclear receptor superfamily that, when activated by insulin sensitizers of the TZD class, including pioglitazone, and rosiglitazone, regulates a host of target genes. PPAR-γ is expressed in all major cell types which are involved in vascular injury, such as endothelial cells, vascular smooth muscle cells (VSMCs) and macrophages. It regulates the recruitment of monocytes to endothelial cells, modulates the inflammatory response in monocytes/macrophages and inhibits macrophage foam cell formation and VSMCs proliferation and migration. In experimental models of atherosclerosis, ligand-activated PPAR-γ prevents the progression of atherosclerotic lesions, with a concomitant reduction in macrophage accumulation in the atheromatous plaque. It is possible that the antiatherogenic effect of TZDs is mediated primarily through their direct action on these receptors. Apart from its antidiabetic effect, pioglitazone also exerts an antiatherogenic effect, which is probably mediated via mechanisms distinct from its antidiabetic effect (Satoh et al.; 2003).

Several other hypoglycaemic medications are commonly employed for diabetes such as glinides, inkretin mimetics and dipeptidyl-peptidase-4 inhibitors, which are used in combination therapy. But so far there is not enough data to recommend their use as treatments to reduce cardiovascular events. Acarbose, an alpha glucosidase inhibitor, reduced the rate of myocardial infarction by 91% and a composite of cardiovascular events (myocardial infarction, new angina, revascularization, cardiovascular death, CHF, cerebrovascular events and PVD) by 49% in subjects with impaired glucose tolerance, however, cardiovascular risk reduction with acarbose has not been reported in patients with diabetes (Beckman et al.; 2013).

5.2 Heart failure in patient with Diabetes mellitus

5.2.1 Pathophysiology

5.2.1.1 The mechanism by which interaction of diabetes and ischemia cause heart failure

The impact of diabetes on HF progression according to the etiology of HF suggests that diabetes and IHD interact to accelerate the progression of myocardial dysfunction, a hypothesis which suggests that there may be additional mechanisms for a synergy between these two disease processes. Ischemic cardiomyopathy is characterized by a shift in myocardial cell substrate utilization from free fatty acids (FFA) to increased reliance on glucose and glycolysis. In the presence of the greater dependence on glycolysis and decreased reliance of FFA metabolism in chronic CAD, adding the impaired myocardial glucose uptake in diabetes may be particularly dangerous. Moreover, the additive effects of both cumulative oxidative stress of chronic ischemia and the oxidative stress caused by diabetes, might lead to myocardial subcellular remodeling and result in abnormal intracellular calcium homeostasis (Dries et al.; 2001). Although diabetic cardiomyopathy is a part of the diabetic atherosclerosis process, it also could be independent of the coexistence of IHD, hypertension, or other macrovascular complications. The pathological substrate is characterized by the presence of myocardial damage, reactive hypertrophy, fibrosis, structural and functional changes of the small coronary vessels, disturbance of the management of the metabolic cardiovascular load, and cardiac autonomic neuropathy. All these alterations make the diabetic heart more susceptible to ischemia and difficult to recover from an ischemic attack (Voulgari et al.; 2010).

Arterial hypertension is a frequent co-morbidity in diabetic patients. Atrial hypertension aggravates dysfunction of the heart, and leads to premature appearance of HF. However, postmortem, experimental, and observational studies also provide evidence for a specific cardiomyopathy in diabetes, which may contribute to myocardial dysfunction in the absence of coronary artery atheroscelerosis. According to the molecular theory of diabetes cardiomyopathy, hyperglycemia is the main pathogenetic factor, which causes structural and functiona abnormalities in the cardiac myocyte. Moreover, atheromatous plaques in diabetic patients are intensive, more diffuse, and involve distal vessels in both the coronary and peripheral circulation. So the pathologic anatomical changes of the small coronary vessels and the myocardial blood vessels endothelium occur which include increased cell adhesiveness,

impaired relaxation, impaired fibrinolysis, and increased permability. All these alterations lead to impaired myocardial cell contraction. As the disease progresses, the hypertrophy of the myocardial cells, the interstitial and perivascular fibrosis, the increase in thickening of the capillary basement membrane, and the formation of microaneurysms in small capillary vessels could lead to the appearance of LV hypertrophy. This may be the actual pathophysiological connection between diabetic microvascular and macrovascular disease. It is difficult to prove a relationship between the loss of cardiac function and the histological damage in the diabetic blood vessels. However, it is reasonable that the structural changes and loss of elasticity contribute to hypertension and in this way, probably to a significant increase in risk for macrovascular diseases in diabetic patients (Voulgari et al.; 2010).

Characteristic changes in the heart during DM are abnormal diastolic function, ultimate loss of systolic function and overt clinical symptoms. The pathogenesis of diabetic cardiomayopathy involves hyperglycemia, lipotoxicity, and IR which contribute to reactive oxygen species generation, mitochondrial dysfunction, and impaired calcium metabolism. Moreover, renin angiotensin system activation, altered substrate metabolism, and endothelial dysfunction ultimately lead to diastolic dysfunction and heart failure (Joshi et al.; 2014).

5.2.1.2 Elevated aldosterone level and its role in diabetic cardiac remodeling

According to Rao et al. (2013) aldosterone and the mineralocorticoid receptor have been implicated in the pathogenesis of vascular injury and cardiac fibrosis demonstrating that aldosterone is associated with myocardial extracellular matrix expansion. These results show that aldosterone has a role in early myocardial remodeling in T2DM. Patients with T2DM have changes in cardiac structure and function with impairment of myocardial blood flow and expansion of the cardiac extracellular matrix and increased aldosterone levels. There is evidence that aldosterone blockade reduces biomarkers of collagen turnover and cardiovascular mortality in patients with heart failure. These data confirm the role of extracellular matrix expansion as an early disease marker in patients with T2DM and suggest implication of aldosterone in this early phase of diabetic cardiac remodeling.

5.2.1.3 Accumulation of advanced glycated end products

AGE accumulation could also play an important role with the development of diabetic adverse outcome. One of these diabetic complications associated with AGE accumulation is the development of cardiac dysfunction. The first manifestation is asymptomatic diastolic dysfunction, which later progresses to systolic dysfunction. AGEs can covalently bind other AGEs and form additional cross-links between matrix proteins like collagen, laminin, and elastin. Excessive cross-linking caused by AGE accumulation weakens the flexibility of matrix proteins. This increased rigidity may induce diastolic dysfunction in the heart. Another pathway by which AGEs may contribute to the development of diastolic dysfunction is via the activation of AGE receptors, which have been identified on several cell types. One of the receptors which mediate effects of AGEs is the induction of fibrosis via the up regulation of transforming growth factor-β (TGF-β). AGE-receptor activation also seems to influence calcium metabolism in cardiac myocytes and over expression of AGE receptor was found to reduce the systolic and diastolic intra-cellular calcium concentration. Exposure to AGE caused a significant delay in calcium re-uptake. As a consequence, the duration of the repolarisation phase of the cardiac contraction may increase, causing diastolic dysfunction. Also the reduced levels of intra-cellular calcium induced by AGEs may induce systolic dysfunction due to decreased myocardial contractility. AGE accumulation may be involved in the development of systolic dysfunction by enhancing the progression of CAD (Hartog et al.; 2007).

5.2.1.4 Activation of the neurohormonal compensatory systems

Activation of neurohormonal pathways in the setting of kidney or heart failure contributes to the further development and progression of dysfunction. One of the most important of these neurohormonal pathways is the sympathetic nervous system (SNS). There is a strong relationship between SNS over activity and the evidence that blockade of SNS reduces morbidity and mortality in patients with diabetes (Iyngkaran et al.; 2013). Due to impaired myocardial performance the neurohormonal compensatory systems (RAAS and SNS) are activated to avoid systemic hypoperfusion. Activation of these and other autocrine and paracrine systems leads to the progressive loss of cardiac myocytes because of enhanced apoptosis and necrosis, which cause further myocardial dysfunction and cardiac failure. As a result of the activation of RAAS and SNS, compensatory changes in the shape and size of the cardiac chambers via cellular hypertrophy or remodeling are induced. This includes increase in cardiac muscle mass, modification in cellular and non cellular composition, energy and

geometry. These changes cause further decrease of ventricular function and generate an increase in neurohormonal activation (Bell; 2003). In addition, activation of the RAS and SNS leads to abnormalities in β-adrenergic receptor signal transduction and induction of the fetal gene program. Stimulation of β-adrenergic receptor signaling increases the activity of carnitine palmityl transferase 1 (CPT-1). This mitochondrial enzyme plays a prominent role in the transport of long-chain acyl-CoA compounds into the mitochondria, thereby promoting myocardial fatty acid rather than glucose utilization. Increased myocardial use of FFAs results in the uncoupling of oxidative phosphorylation, inhibition of membrane ATPase activity, increased myocardial oxygen consumption, myocardial ischemia, impaired myocardial function, and finally cardiac arrhythmias. So, it is suggested that CPT-1 inhibition is one of the mechanisms which are responsible for the cardioprotective effect of β-receptor blockade (Bell; 2003).

5.2.1.5 Insulin-resistance and diabetic cardiomyopathy

Signs of diabetic cardiomyopathy are reduced mechanical function, electrophysiological abnormalities, defects in subcellular organelles, and receptor down regulation due to long-lasting high levels of catecholamines. In animal models it could be demonstrated that under diabetic conditions changes in cellular calcium transport in the myocard and changes in contractile proteins occur, resulting in subclinical systolic and diastolic dysfunction. Furthermore, the increased myocardial collagen content in diabetic cardiomyopathy further deteriorates diastolic dysfunction. In the insulin-resistant or diabetic patient, endothelial dysfunction could lead to repeated episodes of vasoconstriction, with subsequent reperfusion injury and myocardial dysfunction. Also the increased permeability of small vessels related with endothelial dysfunction could lead to interstitial edema, fibrosis, and myocardial dysfunction (Bell; 2003). Sotoye et al. (2013) reported that increased apoptosis in cardiac muscle of diabetic patients caused increased collagen deposition, and as a result of fibrosis and connective tissue proliferation decreased ventricular compliance occurred. All these structural abnormalities may cause increased wall stress, increased oxygen demand, ischemia, and the development of left ventricular diastolic dysfunction, which has been proposed to be the first stage of the putative diabetic cardiomyopathy (DCM) (Sotoye et al.; 2013).

There is strong evidence suggesting that the biological effects of higher fasting insulin levels and IR could initiate or lead to the development or worsening of heart failure. During periods of myocardial stress in advanced stages of heart failure, the heart switches to a fetal gene program, leading to a relative increase in the utilization of glucose as a fuel rather than FFAs.

In case of IR, however, this switch is impaired, since glucose utilization is ineffective, and the heart enters an ‘energy starved state’.

IR may also contribute to the development of heart failure either through direct effects of higher fasting insulin levels upon the myocardium and its vasculature, including chronic adrenergic stimulation, cellular apoptosis and endothelial dysfunction, or indirect effects, such as impairment of myocardial energy metabolism, hypertension and dyslipidemia. Further evidence of the link between IR and heart failure lies in the association IR with structural abnormalities that predispose to diastolic heart failure such as increased left ventricular mass and left ventricular hypertrophy (Banerjee et al.; 2013**).**

IR and hyperinsulinemia have been determined as risk factors for DCM. An imbalance in the direct effects of insulin action occurs, accompanied by other cardiovascular risk factors associated with the IR syndrome such as obesity, hyperglycemia, hypertriglyceridemia, low high-density lipoprotein (HDL), and hypertension. These CV and atherothrombotic risk factors go along with IR and provide a starting point for DCM. Furthermore, they are often accompanied with adverse CV effects, such as elevated levels of PAI-1, factor VII, factor XII, and fibrinogen. Increased levels of factor VII and XII may also occur through activation by triglyceride-rich particles. Moreover, IR is often associated with a combination of established and emerging risk factors, including hypertension and CRP. These are acute-phase inflammation marker and are associated with an increased risk for DCM. Recent studies have confirmed the association between increased levels of CRP and worsening of LV myocardial performance. Furthermore, it has been established as a risk factor for atherosclerosis and CVD (Voulgari et al.; 2010).

LV hypertrophy is also associated with an enhancement in systemic inflammation markers, such as fibrinogen, and microalbuminuria. In a study with 1,299 patients suffering from T2DM, it could be demonstrated that microalbuminuria is a marker of endothelial dysfunction and increased risk of atherosclerosis, and in addition a positive association with LV mass was described (Voulgari et al.; 2010).

5.2.2. Treatment

There is different therapeutic management which aims to prevent, to delay progression and eventually treat emerging heart failure. Because hyperglycemia increases the FFA levels, stimulates the oxidative stress, activates the growth factors and disturbs the calcium homeostasis and lipid metabolism it is important to regulate blood glucose level (Mytas et al.; 2009).

5.2.2.1 Decrease insulin resistance

IR and hyperinsulinemia can be managed first with a change in lifestyle, physical activity, body weight control and certain medication which increase insulin sensitivity (Mytas et al.; 2009). Treatment with metformin significantly improved IR and resulted in significant weight loss in CHF patients identified to have IR. Although metformin use in patients with CHF had been discouraged due to concerns over the risk of lactic acidosis, clinical experience suggests that the risk of metformin associated lactic acidosis is low (Wong et al.; 2012). Recent studies demonstrated that metformin may be associated with improved survival in patients with DM and HF. Also recent animal studies in HF models have demonstrated cardioprotective effects of metformin therapy on progression of HF through activation of protein kinase pathways, inhibition of cardiac fibrosis, and modulation of cardiomyocyte autophagy (Nasir and Aguilar; 2012). Also according to Eurich et al. (2013) metformin improves cardiac function through attenuation of oxidative stress–induced cardiomyocyte apoptosis, improved IR, and left ventricular end diastolic pressure, and thus prevents the progression of HF. Metformin also appears to enhance cardiac structure, function, and to improve survival rate in patients with IHD through activation of adenosine monophosphate-activated protein kinase. Metformin is contraindicated in patients with advanced renal insufficiency and should be used cautiously or avoided in patients at risk for worsening renal dysfunction such as acute decompensated HF. Sulfonylureas are frequently used in diabetic patients with HF. Sulfonylureas cause hypoglycemia and weight gain, and these adverse effects need to be monitored in patients with DM and HF. Thiazolidinediones are also insulin-sensitizing agents that have been used for treatment of T2DM. For TZDs fluid retention and increased rates of HF have been reported. Prospective randomized controlled studies in patients with HF have demonstrated more often edema, more intense treatment of HF medications and a higher frequency for hospitalization in patients treated with TZDs compared with placebo or sulfonylurea. Therefore, the use of TZDs in all patients with signs and symptoms suggestive

of HF has to be concerned. TZDs are contraindicated in patients with New York Heart Association (NYHA) class III/IV HF (Nasir and Aguilar; 2012).

5.2.2.2 Blockade of the renin-angiotensin-aldosterone axis

As mentioned earlier, activation of the RAS leads to myocardial remodeling. Early prevention is very important or to stop the progression of HF, as a lot of patients with left ventricular dysfunction remain undiagnosed and untreated until advanced disease causes disability. This delay mainly occurs because of the asymptomatic nature of early HF, which necessitates more aggressive assessment of HF risk factors (Bell; 2003). Blockade of the RAAS axis is the basis of treatment for all patients with HF – including those with DM. In a large, randomized clinical trial, ACE inhibitor therapy clearly decreased mortality and HF readmission, and may also help to prevent progression from asymptomatic to symptomatic HF in DM (Peterson et al., 2012). Therefore, prevention is indicated in diabetics even without frank HF. Blockade of the RAS with ARBs also decreases the development of symptomatic HF in patients with DM, and in addition, ARBs are commonly better tolerated than ACE-I. Treatment with an ARB is recommended in patients who cannot tolerate ACE-I therapy due to side effects such as ACE-I-induced cough. However, similar to ACE-I therapy, ARBs are generally not appropriate for patients who are at risk for hyperkalemia or who have type 4 renal tubular acidosis (Peterson et al.; 2012). Randomized clinical trials have clearly established improved survival with the use of ACI inhibitors in diabetic patients with HF; also some studies have demonstrated associations between ACE inhibitors or ARBs and the reduced incidence of new DM in HF patients. Data from the Studies of Left Ventricular Dysfunction (SOLVD) showed a low incidence of new diabetes in patients treated with enalapril and candesartan, respectively, when compared with placebo. The mechanisms for the reduced incidence of DM in patients with ACE inhibitors or ARBs is not fully understood, but include improved insulin sensitivity by increasing of peripheral blood flow to skeletal muscle through suppression of angiotensin II or by elevating bradykinin levels (Nasir and Aguilar; 2012). According to American Diabetes Association guidelines ACI inhibitor enalapril was excellent in glycemic, BP, and lipid management (Rao et al.; 2013)**.** In a study, with unknown myocardial dysfunction (low ejection fraction) or HF ramipril has achieved a significant reduction in the new cases with DM in the high-risk population included in the study. A double-masked, randomized, parallel-controlled group trial determined the effectiveness of losartan, a selective angiotensin II type 1 (AT1) receptor antagonist in comparison with the β-blocker atenolol in reducing cardiovascular morbidity and mortality in diabetic patients with hypertension and LV

hypertrophy. Losartan was more effective than atenolol in reducing cardiovascular morbidity and mortality (76% reduction of the relative risk of a primary cardiovascular end point) (Voulgari et al.; 2010).

5.2.2.3 Aldosterone receptor antagonists

Aldosterone receptor antagonists are active against interstitial fibrosis and cardiovascular remodeling, improve the endothelial dysfunction and promote the balance of the autonomous nerve system (Mytas et al.; 2009), and are effective in improving survival in patients with severe HF and in those with HF after a MI. Subgroup analysis in the Eplerenone Post-Acute Myocardial Infarction and Heart Failure Efficacy and Survival Study (EPHESUS) demonstrated that patients with DM had the same survival benefit as non-diabetics. Aldosterone antagonism could be used in treatment of HF in diabetic patients, who do not have a tendency to hyperkalemia or have severe renal dysfunction or other contraindications (Peterson et al.; 2012).

5.2.2.4 Beta-blockers

Although beta-blockers may worsen glycemic control and mask symptoms of hypoglycemia, multiple studies have demonstrated that beta-blockers are associated with improved survival in individuals with DM and HF. In a meta-analysis of randomized controlled trials, beta-blocker therapy compared with placebo was associated with a 16% reduction in mortality (RR 0.84, 95% CI 0.73–0.96). In addition, beta-blockers have been shown to reduce HF hospitalization in patients with and without DM (Nasir et al.; 2012). Beta-blockers not only prevent, but may also reverse cardiac remodeling. The metabolic side effects that have been associated with β-adrenergic inhibitors in the diabetic patient may be prevented by the use of a third-generation β-blocker. Prophylactic use of ACE inhibitors and β-blockers should be considered in high-risk diabetic patients (Bell; 2003).

Some studies have demonstrated that beta-blockers with potential vasodilator properties (non-selective beta-blockers) may be associated with improved measures of glycemia compared to beta-blockers without these properties. In a study of 1235 patients with DM and hypertension but without HF, carvedilol modestly improved glycemia compared to metoprolol tartrate. Furthermore, in a retrospective analysis of the Carvedilol Or Metoprolol European Trial (COMET), the use of carvedilol in HF patients was related to a reduced incidence of new-

onset diabetes when compared with metoprolol tartrate. These modest benefits in glycemia and reduction in new diabetes with specific beta-blockers has not been determined (Nasir and Aguilar; 2012). Carvedilol might be the beta-blocker of choice for diabetic patients, because it has a beneficial effect on insulin tolerance and does not change the lipid profile, exerts a peripheral vasodilatatory effect. Moreover, it has an anti-oxidative and anti-apoptotic activity, promoting the reverse cardiovascular remodeling. Other beta-blockers that are indicated in CHF are bisoprolol, metoprolol and nebivolol. Diabetic patients need a more aggressive management. Thus, it is to be concluded that the use of beta-blockers have to be recommended in DM except, of course, in cases where it is contraindicated (Mytas et al.; 2009).

5.2.2.5 Incretin peptides

Inkretins are a group of gastrointestinal proteins, which regulate glucose metabolism. Incretin-based therapies have been developed to treat T2DM. These agents include the glucagon-like peptide-1 (GLP-1) agonists exenatide and liraglutide, and dipeptidyl peptidase-IV (DPP-IV) inhibitors such as sitagliptin, saxagliptin, and linagliptin. These agents have less risk of hypoglycemia when used as a monotherapy and cause modest weight loss, and thus represent potential benefits in patients with HF (Nasir and Aguilar; 2012). According to Sokos et al. (2006) chronic infusion of GLP-1 significantly improves left ventricular function, functional status, and quality of life in patients with severe HF. In addition to its antihyperglycaemic effect GLP-1 also has a beneficial role in CV function, because it improves left ventricular haemodynamics with advanced dilated cardiomyopathy. These effects were combined with an increase in myocardial uptake of glucose, without any change in levels of insulin, suggesting that GLP-1 exerts insulin mimetic effects in the myocardium. Furthermore, also a clinical trial reported about beneficial effects of GLP-1 on the heart. The study showed that chronic treatment with exenatide in mice with dilated cardiomyopathy and rats with CHF delays the progression of HF and prolongs the animals' survival, probably as a result of changes in glucose metabolism (Nathanson et al.; 2012).

Connelly et al. (2013) demonstrated that endothelial integrity and restitution are mediated partially through stromal cell derived factor-1a (SDF-1a), a chemokine that is elaborated by ischemic tissue but rapidly degraded by DPP-4. Accordingly, inhibition of this enzyme may lead to beneficial effects following MI in the diabetic setting. DPP-4 inhibition ameliorates several, but not all, aspects of cardiac dysfunction and adverses remodeling in the post-MI

setting. To improve oxygen delivery and mitigate the effects of ischemia on cardiomyocytes, the heart initiates a series of homeostatic responses that include neoangiogenesis. The response to SDF-1 is, however, reduced in diabetes, due at least in part to the increased activity of the enzyme DPP-4 which is responsible for its degradation. Thus, inhibition of this enzyme may be advantageous on the angiogenic response and adverse remodeling that follow MI (Connelly et al.; 2013). Cardiovascular safety of DPP-4 inhibitors such as saxagliptin and alogliptin, demonstrate that these drugs do not increase the incidence of ischemic events and have acceptable cardiovascular safety profile. Furthermore, it has been demonstrated that these drugs can provide effective glycemic control. But this needs to be combined with management of standard risk factors to reduce cardiovascular risk in patients with DM (Lim; 2013).

Preclinical work for GLP-1 has demonstrated a potential role for GLP-1 based therapies in HF and potential benefits on left ventricular structure and function, but more studies are needed to assess the safety and efficacy of these agents in patients with DM and HF (Nasir and Aguilar; 2012). Moreover, incretin-based therapy may represent a novel therapeutic strategy in the treatment of HF patients with DM, because of their cardioprotective effects independent of tight glycemic control (Khan et al.; 2013).

5.2.2.6 The pharmacological manipulation of myocardial FA metabolism

The direct approach to manipulate cardiac energy metabolism consists in modification in the use of the metabolic substrate of the diabetic heart, and seems to be very attractive. Special metabolically active medication that shifts energy substrate preference away from the use of fatty acids towards glucose as an oxidative fuel is a therapeutic goal to preserve or to improve the mechanical function and limit the progression of HF. To date, the most effective metabolic modulation of β-oxidation in myocardium is seen with trimetazidine and perhexiline, which directly inhibit fatty acid oxidation (FAO) and improve myocardial function (Lionetti et al.; 2011). According to first results trimetazidine, a stimulator of the lactate dehydrogenase, seems to improve the ventricular function of the diabetic heart, while its action appears to be in favor of the endothelial function by promoting the expression of cGMP and reducing the levels of endothelin-1 (Mytas et al.; 2009). The best-known pharmacological agents utilized for modulation of FAO in HF and reduction of the circulating levels of FA are nicotinic acid and its derivatives, which can decrease myocardial FAO through a progressive decrease in plasma levels of FA. Acute treatment with acipimox, a nicotinic acid derivative with profound antilipolytic effects, caused a decrease in myocardial

FAO and enhanced glucose uptake in patients with dilated cardiomyopathy (Lionetti et al.; 2011).

Studies have shown that kinins, the vasoactive peptides and part of the kallikrein–kinin system (KKS) are involved in remodeling, inflammation, and angiogenesis. It has been demonstrated that the KKS is involved in the inflammatory processes of the heart and shows that the KKS has beneficial effects in myocardial diseases by protecting from inflammation, fibrosis, and apoptosis. KKS also appears to have a proinflammatory effect by increasing the production of cytokines and stimulating the migration of immune cells and also contributes to neovascularization and recruitment of endothelial progenitor cells in ischemic areas and endothelial dysfunction. All these effects suggest that the KKS may consider a potential therapeutic target in the treatment of myocardial ischemia and diabetic cardiomyopathy (Voulgari et al.; 2010). ROS play an important role in the development of DCM and its activation of MMP-2 contributes to the acute loss of myocardial contractile function by targeting and cleaving susceptible proteins such as troponin I and α-actinin. In a study which evaluated the 4-week administration effect on heart function of a daily *in vivo* administration of sodium selenate (0.3 mg/kg) or pure ω-3 fish oil with antioxidant vitamin E (ω-3E, 50 mg/kg), both treatments prevented the diabetes-induced functional changes. However, the improvement in myocardial function was greater with sodium selenate compared with omega-3/vitamin E. These treatments reduced the diabetes-induced increase in myocardial oxidized protein sulfhydryl and nitrite concentrations. The diabetes-induced changes in myocardial levels of MMP-2 were associated with a significant reduction in troponin I and α-actinin protein levels in both treatment groups, suggesting that diabetes-induced alterations in MMP-2 could lead to myocardial contractile dysfunction by targeting troponin I and α-actinin and that sodium selenate or omega-3E might have a therapeutic effect in DCM (Voulgari et al.; 2010).

5.2.2.7 Cell-based myocardial regenerative therapy

Cell-based myocardial regenerative therapy can be applied in the treatment of DCM in order to limit the consequences of decreased contractile dysfunction and ventricles damage due to ischemic and non ischemic myocardial areas. A different variety of myogenic and angiogenic cell types have been suggested, such as skeletal myoblasts, mononuclear and mesenchymal bone marrow cells, circulating blood-derived progenitors, adipose-derived stromal cells, induced pluripotent stem cells, umbilical cord cells, endometrial mesenchymal stem cells, adult testis pluripotent stem cells, and embryonic cells. Selected patients should be in an early

stage of HF, because the aim of this regenerative approach is to avoid or to delay organ transplantation (Voulgari et al.; 2010).

5.3 Arrythmia in patients with Diabetes Mellitus

5.3.1 Pathophysiology

The most common form of cardiac arrhythmia is AF and is associated with severe morbidity and mortality. Several epidemiologic studies have reported that DM is considered as an independent risk factor for AF. Although the causal relationship between DM and AF remains to be elucidated, one likely explanation is that DM affects cardiac electrophysiology directly or indirectly by means of autonomic, electrical, and structural changes (Huang et al.; 2015).

5.3.1.1 Inflammation

The mechanisms, which might cause AF, are complex. Inflammation is involved with the pathogenesis of AF in association with DM and there is a link between oxidative stress and AF. So during tachyarrhythmia, substantial oxidative damage and cellular remodeling occurs in myocardial atria that can induce AF (Wang et al.; 2012). Diabetes might lead to elevated CRP level which is a marker of chronic inflammation. High level of CRP may promote myocardial fibrosis and diastolic dysfunction, and dilated cardiomyopathy may propagate development of AF. Moreover, increase left atrial size induced from DM could lead to HF (Stratmann and Tschöpe; 2012).

5.3.1.2 Activation of AGE–RAGE axis

According to Raposeiras-Roubín et al. (2012), several evidences have suggested that the activation of AGE – receptor of advanced glycation end products (RAGE) axis, has an important role in the initiation and propagation of inflammatory and oxidative stress responses. They are also implicated in proteins alteration, resulting in fibrosis, tissue stiffening and loss of elasticity. This have led to an indication that there is a specific link between AGE and connective tissue growth factor (CTGF) and that CTGF was up-regulated by AGE. Also CTGF is a mediator of the induction of the extracellular matrix protein fibronectin.

Diabetes promoted atrial structural remodeling through activation of the AGE–RAGE system and the upregulation of CTGF, so that the diabetic hearts had a significant increase in the

production of AGE and expression of the AGE receptors. AGE can also accelerate the protein cross-linking which leads to alteration of protein structure and function. For example, this is the case type I collagen and elastin in the extracellular matrix, which results in atrial fibrosis. Furthermore, activation of the AGE–RAGE axis has been shown to stimulate the production of MMPs, where some enzymes such as MMP-9 are associated with the appearance of AF, which could have contributed to structural remodeling and dilatation of atria. In addition, AGE–RAGE interaction leads to increase in production of proinflammatory mediators by the activation of nuclear factor NF-κB and generation of ROS, which contributes to atrial remodeling (Zhang et al.; 2013).

5.3.1.3 Prolongation of QTc interval during hyperglycemia

Another study has demonstrated that acute hyperglycemia has lead to increased QT interval in type 2 diabetic patients, and postprandial glucose level was also demonstrated to be an independent risk factor for prolongation of the QT corrected for heart rate (QTc) interval. The mechanisms underlying the prolongation of QTc interval during hyperglycemia were increase in intracellular calcium concentration and impairment of the sympathovagal balance. Free radical production increases and NO production is reduced under hyperglycemic conditions. Reduced NO could cause inhibition of Ca^{2+}-ATPase and K^{+}/Na^{+}-ATPase activity, which leads to an increase in cytosolic free calcium and prolongation of myocardial repolarization. Moreover, hyperglycemia has been demonstrated to produce an increase in sympathetic activity, which gets obvious by increased concentrations of plasma catecholamines. Sympathetic stimulation unopposed by vagal activity may also induce ventricular electrical instability. QTc interval represents an index of myocardial refractoriness and electrical stability. Its prolongation is associated with ventricular fibrillation and cardiac sudden death. Prevalence of prolonged QT interval is higher in patients with T1 or T2DM as compared to patients without DM. Several risk factors have been demonstrated to contribute to the prolongation of QTc interval among patients with diabetes such as gender, IR, hypertension, insulin concentration, hyperglycemia, diabetic microvascular complications such as diabetic retinopathy, neuropathy, microalbminuria, and preexisting CHD (Li et al.; 2012). QT dispersion (QTd), microvascular diseases and nephropathy are indicators of an increased risk of sudden cardiac death in diabetic patients (Nakou et al.; 2012).

5.3.2 Treatment

Treatment of arrhythmia in diabetic patients is multifactorial and effective, in particular treatment with statins and anti-hypertensive drugs with evidence of a positive effect on diabetic patients. The reduction in mortality associated with statins is pronounced. Statins have been shown to have antiarrhythmic properties, which could be relevant for patients with AF. Beta-blockers have been associated with the low mortality, considering their effect in reducing mortality in myocardial infarction with AF (Wändell et al.; 2014).

Anticoagulation is an important component in the management of AF, because arrhythmia is associated with an increased risk for stroke. More than half of the patients with or without diabetes were prescribed aspirin or clopidogrel, although they were confirmed to be ineffective in preventing thrombus. The fear of bleeding, the inconvenience of frequent INR monitoring, and excessive interaction between warfarin and other medications or foods may result in hesitating to select warfarin (Huang et al.; 2015).

In addition, administration of ARBs and TZDs to patients suffering from DM and AF may show beneficial effects. A study suggests that use of ARBs was associated with a decreased risk of all-cause mortality. Moreover, use of lipid-lowering agents was associated with a decreased risk of stroke (Huang et al.; 2015).

Thiazolidinediones, which act by activating PPARγ, have been shown to decrease new onset of AF in patients with T2DM who are not treated with insulin. The implication of oxidative stress in tachycardia-induced cellular remodeling demonstrates the protective effect of anti-inflammatory and antioxidant mechanisms. Metformin has been shown to have anti-inflammatory and antioxidant properties. *In vitro* experiment provides the first evidence that metformin may be able to ameliorate tachycardia-induced oxidative stress generation and subsequent atria remodeling. Further animal and clinical studies are necessary to validate these findings and to clarify the mechanisms (Chang et al.; 2014). Currently, catheter ablation may be beneficial in the treatment of AF-associated DM (Huang et al.; 2015**).**

6. DIABETES AND CARDIOVASCULAR AUTONOMIC NEUROPATHY

Cardiovascular autonomic neuropathy (CAN) is a common complication of diabetes and it is associated with an increased risk of cardiovascular morbidity and mortality**.** Risk factors for CAN in T1DM are insufficient blood glucose level control, and in T2DM a combination of hypertension, dyslipidaemia, obesity, and blood glucose control. In clinical trials risk markers for CAN are correlated with age, diabetes duration, blood glucose level and microvascular complications (peripheral polyneuropathy, retinopathy, and nephropathy). CAN could be a progression promoter of diabetic nephropathy (Spallone et al.; 2011). Major clinical manifestations of CAN are resting tachycardia, orthostatic hypotension, silent myocardial ischemia, impaired neurovascular function and hypoglycemic autonomic failure (Vinik et al.; 2003).

Dimitropoulos et al. (2014) and Vinik et al. (2003) have shown that CAN results from damage to autonomic nerve fibers which innervate the heart and blood vessels, resulting in abnormalities in the heart rate control and vascular dynamics. Reduced heart rate variation (HRV) considers the earliest indicator of CAN. For a better prevention and treatment, both HRV and scintigraphy have assisted in diagnosis at a subclinical stage (Dimitropoulos et al.; 2014). Up today, there is no definite therapeutic approach.

6.1. Pathophysiology

CAN is caused by injury to the autonomic nerve fibers that innervate the heart and blood vessels, and autoimmune damage also due to the abnormalities in nerve conduction. DM affects the autonomic and the peripheral nervous system. The vagus nerve, which is the longest autonomic nerve, mediates 75% of the overall parasympathetic activity, and is involved early in the course of CAN development. Reduction of the parasympathetic activity resulting from the early deterioration of the vagus nerve in the course of disease development, leads to sympathetic predominance and remains until sympathetic denervation arises, which is the latest stage of CAN (Dimitropoulos et al.; 2014). Moreover, the relationship between vascular stiffness and dysfunction of the baroreflex response has also been noted. Furthermore, some studies have suggested that the primary dysfunction may be the defective activation of central parasympathetic pathways. There is evidence that abnormalities of the

autonomic nervous system, reflected by increased heart rate and reduced HRV, are associated with cardiovascular mortality and morbidity (Nakou et al.; 2012). According to Vinik (2003) hyperglycemic activation of the polyol pathway leads to accumulation of sorbitol and potential changes in the NAD:NADH ratio. This may generate direct neuronal damage and/or decreased nerve blood flow. Furthermore, activation of protein kinase C induces vasoconstriction and reduces neuronal blood flow. Increased oxidative stress, with increased free radical production causes vascular endothelium damage and reduces NO bioavailability. Also reduction in neurotrophic growth factors, deficiency of essential fatty acids, and formation of AGEs (localized in endoneurial blood vessels) could lead to reduced endoneurial blood flow and nerve hypoxia with nerve function alteration. The result of this multifactorial process may be activation of poly-ADP-ribosylation depletion of ATP, resulting in cell necrosis. Also there is a possible activation of genes involved in neuronal damage. Diabetes leads to diffuse and widespread damage of peripheral nerves and small vessels (Vinik et al.; 2003).

The role of autoimmunity has also been discovered especially in patients with T1DM. The presence of antibodies against sympathetic and parasympathetic tissues in T1DM patients and their association with CAN was described in the early 90s. The prevalence of phospholipid autoantibodies (PLA) in the serum of T1DM patients was significantly higher in those persons tested positive for autonomic neuropathy. Patients with T1DM, who had a positive test for complement-fixing antibodies to the sympathetic ganglion, vagus nerve and adrenal medulla, had a significantly higher risk to develop cardiac autonomic dysfunction (Dimitropoulos et al.; 2014).

Cardiovascular autonomic neuropathy may induce ischaemic episodes by disturbing the balance between myocardial supply and demand. Moreover, there is evidence that a prolonged QT interval, which is a common risk factor for ventricular arrhythmias and sudden cardiac death in patients with DM, is associated with the extent of cardiovascular autonomic neuropathy. In an animal model of diabetes, the presence of AF was enhanced by the activation of adrenergic system in the diabetic heart, in which the sympathetic innervation was evident. Moreover, the delay in intra-atrial conduction and fibrotic deposition in the atria were found to play a major role in producing atrial tachyarrhythmias. Diabetes is also associated with microvascular disease and autonomic neuropathy (Nakou et al.; 2012).

6.2 CAN and resting tachycardia

A common characteristic of CAN is resting tachycardia which can already occur at an early stage of the disease. A heart rate of 90-130 beats per minute (bpm) can be determined which represents a reduction in parasympathetic tone followed by an increased sympathetic tone as CAN develops. A fixed heart rate which remains constant and does not change during exercise, sleep or stress is a sign of complete cardiac denervation (Dimitropoulos et al.; 2014).

6.3 CAN and orthostatic hypotension

Orthostatic hypotension is characteristic for advanced CAN, which occurs as a result of the impairment of the sympathetic response to postural change secondary to poor norepinephrine response and abnormalities in the baro-receptor sensitivity. This impaired response results in inadequate heart rate response and peripheral vasoconstriction (Dimitropoulos et al.; 2014). In patients with diabetes, orthostatic hypotension is usually due to damage to the efferent sympathetic vasomotor fibers, particularly in the splanchnic vasculature, also due to the decrease in cutaneous, splanchnic, and total vascular resistance (Vinik et al.; 2003). The presence of orthostatic hypotension after exclusion of other causes suggests advanced CAN. For the prognostic value, orthostatic hypotension should be controlled regularly in diabetic patients even without symptoms, in particular after the age of 50 (Spallone et al.; 2011).

6.4 CAN and exercise intolerance

Autonomic dysfunction can impair exercise tolerance, according to a study which has demonstrated a reduced response in heart rate and BP during exercise in individuals with CAN, and a decreased cardiac output in response to exercise in individuals with CAN. It should also be noted that decreased ejection fraction, systolic dysfunction, and diastolic filling limit exercise tolerance (Vinik et al.; 2003).

6.5 CAN and silent ischemia

CAN is associated with a prolonged subjective angina threshold (which is defined as the time between the observation of 1 mm ST depression on the electrocardiogram and the development of symptoms of angina pectoris), so that the patients with CAN are more

susceptible to experiencing silent myocardial ischaemia and cardiac infarction, although they remain asymptomatic. CAN is associated with silent ischaemia in patients with DM. Although several mechanisms have been proposed including altered pain threshold and impaired afferent myocardial autonomic pathway, the mechanisms underlying the relationship between CAN and silent ischaemia are still unknown. Both CAN and silent ischaemia can also occur in patients with CAD and DM (Dimitropoulos et al.; 2014). The neuropathic damage to the myocardial sensory afferent fibers in the autonomic nerve supply reduced the diabetic individual's sensitivity to regional ischemia by interrupting pain transmission. Symptoms such as unexplained fatigue, confusion, tiredness, edema, hemoptysis, nausea and vomiting, diaphoresis, arrhythmias, cough, or dyspnea are the alert notifications to the possibility of silent MI (Vinik et al.; 2003).

6.6 CAN and cardiomyopathy

Diabetic cardiomyopathy is characterized with left ventricular hypertrophy and remodeling, and is a result of sympathetic-vagal imbalance. Diabetic cardiomyopathy results in variable degrees of systolic and mainly diastolic dysfunction in the absence of structural or valvular cardiac disease, coronary vessel disease, or hypertension. Very often the only detectable abnormality in the early stages of CAN is an isolated diastolic dysfunction with a normal LV ejection fraction associated with high CVD morbidity, demonstrating that CAN is associated with significant reduction in the peak diastolic filling and an increase in the atrial component of diastole. In T2DM patients with T2DM both torsion and maximal torsion rate are increased, independently of energetic deficits but related to microvascular perfusion deficits and changes in sympathetic denervation. Myocardial Perfusion Reserve is a diagnostic tool for the detection of microvascular abnormalities. With this method in asymptomatic patients early stages of CAN could be detected. There are several mechanisms discussed for the development of diabetic cardiomyopathy. The parasympathetic denervation observed in the early stages of the disease leads to a dominant sympathetic tone, which promotes a cascade of intrinsic metabolic changes, including the release of high myocardial catecholamine levels. This catecholamine rise induces mitochondrial uncoupling, and shifts cardiac energy generation from myocardial glucose to FFAs. However, this is considered an inefficient energy source and increases the oxygen demand. These effects lead to cell death, fibrosis and finally hypertrophy and remodeling of the LV. The most implicated mediators in this process are the mitochondrial ROS and IR. Moreover, diastolic dysfunction in CAN is associated with

delayed relaxation, impaired filling and increased stiffness of the LV. Sympathetic predominance is a stimulator of the RAAS axis, resulting in increased heart rate, cardiac output and peripheral vasoconstriction. All these alterations can lead to reduction of coronary blood perfusion and diastolic dysfunction (Dimitropoulos et al.; 2014).

6.7 CAN and arrhythmia

The prolongation of the QT interval is the result from many factors, including imbalance in cardiac sympathetic innervation, intrinsic metabolic and electrolytic myocardial changes, left ventricular hypertrophy, CAD, and genetic factors. Reversible QT interval prolongation may be induced by hyperinsulinaemia in healthy subjects and by hyperglycaemia or by acute hypoglycaemia in both healthy and diabetic subjects. In T1DM patients, prolonged QTc was shown to occur frequently during overnight hypoglycaemia and to be associated with cardiac rate/rhythm disturbances. These findings may explain sudden death during sleep and a possible role in cardiovascular events of hypoglycaemia-induced sympathetic activation (Spallone et al.; 2011).

6.8 CAN as a promoter of nephropathy progression

Several studies have shown that CAN could lead to development of diabetic nephropathy. It was suggested that this could be mediated by CAN-induced changes in glomerular haemodynamics, in the circadian rhythms of BP and albuminuria. Moreover, erythropoietin-deficiency anaemia and early dysregulation of erythropoietin production have been described in patients with CAN and are a predictor of nephropathy progression, as erythropoietin is considered to have direct renoprotective effects. Thus, both anaemia and erythropoietin deficit may contribute to kidney damage in diabetes. Resting heart rate was reported to be associated with nephropathy development in T1DM patients. In the Atherosclerosis Risk in Communities (ARIC) study it has been shown that higher resting heart rate and lower HRV indices were associated with the highest risk of developing end-stage renal disease (Spallone et al.; 2011).

Studies suggested that sympathetic over-activity could cause glomerular and tubular dysfunction in diabetic animal models indirectly (hypertension and angiotensin II) and directly (vascular smooth muscle proliferation, vasoconstriction). Furthermore, it has been

demonstrated that CAN is associated with haemodynamic changes such as lack of nocturnal BP dipping (causing increased intra-glomerular pressure, resulting in albuminuria), diurnal, postural falls in BP (resulting in lower intra-glomerular pressure) and endothelial dysfunction in humans (Dimitropoulos et al.; 2014).

6.9 Treatment

CAN treatment can either be symptomatic or is aimed at slowing or reversing CAN progression. However, effective therapies to slow or reverse CAN progression are limited as the complete underlying pathogenesis remains unclear (Dimitropoulos et al.; 2014).

6.9.1 Glycemic control

Intensive insulin treatment in T1DM patients reduced the incidence of CAN by 53% compared to conventional therapy and should be initiated as early as possible. However, the beneficial effect of intensive glycaemic control on CAN in T2DM has not been specifically proven (Spallone et al.; 2011).

6.9.2 Lifestyle modification

An intensive management of cardiovascular risk factors reduced the progression or the development of CAN among type 2 diabetic patients. Lifestyle changes such as weight reduction, especially in obese, physical activity and metabolic control might prevent or slow the progression of cardiac autonomic neuropathy (Spallone et al.; 2011). A recent review study, summarizing the evidence for the impact of life style interventions on CAN, demonstrated that moderate endurance and aerobic exercise in both T1DM and T2DM, improve HRV and cardiac autonomic function significantly, in favour of parasympathetic dominance, and independent of body mass index (BMI), glycaemic or BP control and duration of DM (Dimitropoulos et al.; 2014).

6.9.3 Therapies based on CAN pathogenesis

There is increasing focus on the use of pharmacotherapy to target specific pathogenic pathways, according to some randomized controlled trials which have shown favorable effects of using the anti-oxidant α-lipoic acid, vitamin E, and C-peptide. However, more studies are

required to confirm these findings (Spallone et al.; 2011). There is some data, which support the use of certain pharmacological agents to improve the LV dysfunction associated with autonomic neuropathy in diabetes. In patients with HF, the use of bisoprolol or the addition of spironolactone to enalapril, furosemide and digoxin, demonstrated a beneficial effect on autonomic function. It is well documented that the use of ACE inhibitors potentially improves the parasympathetic/sympathetic balance and improves prognosis in HF. There is diverse discussion whether the addition of ARBs to ACE inhibitors may be superior to monotherapy, due to the enhanced blockade on RAAS. The use of ACE inhibitors or ARBs shows beneficial effects on diabetic autonomic neuropathy and LV diastolic dysfunction (Dimitropoulos et al.; 2014). Also treatment of symptomatic orthostatic hypotension is required in symptomatic patients with autonomic neuropathy. A risk-benefit consideration should be taken for each individual before starting a medication. Midodrine is a peripheral selective α_1-adrenergic agonist, which is considered a first line agent that acts through peripheral vasoconstriction of arterioles and veins. It remains to date the only drug approved by the Food and Drug Administration (FDA) for the treatment of orthostatic hypotension. 9-α-fluorohydrocortisone, which is a synthetic mineralocorticoid, is another first line option that acts through sodium retention and plasma expansion. It treats successfully the orthostatic hypotension of patients with diabetes and autonomic neuropathy, but special care should be taken when prescribed in patients with HF, because it can cause fluid overload. There is usually a period of 10-14 d before its effects become clinically evident. Somatostatin and somatostatin analogues (octreotide) inhibit the release of vasoactive peptides from the gastro-intestinal tract and thus increase splanchnic vasoconstriction, leading to increase in mean BP. Other treatment options are the administration of erythropoietin which can increase the erect BP through the increase of red cell mass and circulating volume. Erythropoietin improves anaemia and its regulatory effect on vascular tone. Desmopressin acetate mainly has a positive effect on morning time hypotension. Caffeine and acarbose can be used in the management of post-prandial hypotension. In a case report of a 58 years old patient with DM and severe postprandial hypotension refractory to the use of midodrine and octreotide, the alpha-glucosidase inhibitor acarbose reduced the postural drop from 50 mmHg to 18 mmHg, improving the patients symptoms dramatically (Dimitropoulos et al.; 2014).

7. ASSOCIATED RISK FACTORS BETWEEN CVD AND DM

DM is associated with risk factors for CVD. Adults with diabetes have a 77%–87% prevalence of hypertension, a 74%–81% prevalence of elevated low-density lipoprotein cholesterol (LDL-C), and a 62%–67% prevalence of obesity. There is association between the high risk of CVD in patients with diabetes and the prevalence of other CVD risk factors. Therefore, it is imperative to manage the CVD risk factors to decrease the risk of both microvascular and macrovascular complications of diabetes. These factors include hyperglycemia, hypertension, dyslipidemia, obesity, cigarette smoking, and physical inactivity (Lorber; 2014).

7.1 Obesity

Obesity is an independent risk factor for CVD in non diabetic populations. Although the impact of obesity in T1DM has not been fully established, but according to Pittsburgh EDC study the prevalence of overweight and obesity in T1DM has increased significantly. The effect of obesity was largely accounted for by waist circumference, which is a measure of central obesity. Central obesity in T1DM can be accompanied by increased CVD risk factors, including visceral adiposity, higher BP, adverse lipoprotein changes, and IR (De Ferranti et al.; 2014). Abdominal obesity, as detected by increased waist circumference, is recognized as one of the most important factors contributing to metabolic syndrome: obesity contributes to hypertension, high serum cholesterol, low HDL cholesterol and hyperglycaemia, and it associates with higher CVD risk. Excess visceral adipose tissue releases several products that apparently exacerbate these risk factors including FFAs, which overload muscular and liver tissues with lipids, thus enhancing IR, PAI-1, which contributes to a prothrombotic state, CRP, which may signify cytokine excess and a pro-inflammatory state (Martín-Timón et al.; 2014). So, obesity is a complex disorder leading to alterations in lipid metabolism, deregulation of hormonal axes, oxidative stress, systemic inflammation, and ectopic fat distribution. FFAs bind to toll-like receptor (TLR) and trigger through different mechanisms tissue inflammation due to up-regulation of inflammatory genes IL-6 and TNF-α. TNF-α also stimulates the expression of CRP which down-regulates eNOS and increases the production of adhesion molecules and endothelin1 (Paneni; 2013). Moreover Hayashino et al. (2013) have demonstrated that CRP, inflammatory cytokines, and adipokines contribute to

atherosclerosis, IR, and development of late-onset complication in patients with T2DM. The strong connection between abdominal obesity and risk factors led to define the metabolic syndrome as a cluster of metabolic complications of obesity (Martín-Timón et al.; 2014).

Studies have demonstrated an independent association between obesity and AF. Weight gain and obesity are associated with structural and functional changes of the CV system including left atrial and ventricular remodeling, haemodynamic alterations, autonomic dysfunction, and diastolic dysfunction. Obesity was also associated with an increase in left atrial diameter, a recognized precursor of AF and its risk in obese subjects is mediated through left atrial enlargement. Left atrial enlargement is observed in most obese adolescents and adults. Weight reduction may attenuate left atrial enlargement. The mechanism for the relationship between obesity, left atrial enlargement and AF is not completely understood, however, it is suggested to be multifactorial including haemodynamic disturbances, autonomic dysfunction and induction of RAAS, which results in mechanical and electrical remodeling of the left atrium (Asghar et al.; 2012).

Generalized obesity, which is detected by the BMI, and abdominal obesity is measured by the waist circumference WC, both are related with a variety of CVD risk factors. Clinical guidelines do not indicate whether BMI or the WC measurements have identical utility in predicting cardiovascular risk in individuals with T2DM compared to non-diabetic patients (Martín-Timón et al.; 2014).

7.1.1 Recommendation

Caloric restriction and increased physical activity are the most important lifestyle changes to decrease excessive weight gain in T1DM. In addition, these lifestyle changes have to be accompanied by patient education about frequent blood glucose monitoring and appropriate modifications in bolus or basal insulin administration with food intake and exercise in order to minimize the risk of hypoglycemia (De Ferranti et al.; 2014).

7.1.1.1 Physical activity

Regular physical exercise is associated with a lower risk of cardiovascular morbidity and mortality, both in primary and in secondary prevention. However, it should be taken into account that very often patients also stop smoking or start eating healthy food, so that this can

contribute to the positive effect of sportive activities. A Finnish study with 3316 diabetic patients showed that physical activity at work and during leisure time was linked with a decrease in cardiovascular mortality and total mortality. But it is important to mention that patients with T2DM have a reduced capacity for exercise due to age, the high BMI and the frequent presence of left ventricular dysfunction. Exercise improves insulin sensitivity in diabetic patients as well as in non-diabetic patients. Patients with diabetes have greater IR which can be mediated by different defects in the glucose metabolism, and this could be improved with physical exercise. Increased physical activity achieves higher mitochondrial enzyme activity and increases insulin sensitivity. It is well proven in a number of studies that physical exercise is able to improve cardiovascular risk factors such as dyslipidaemia, hypertension and body composition in patients with T2DM. However, not all kinds of physical activities have the same influence on CV risk. For example, aerobic exercise only or combined with resistance exercise improves glycaemic control, BP and the amount of triglycerides. But resistance exercise alone does not have an impact on CV risk factors. Prospective cohort studies suggested that exercise is associated with improved CVD and reduced cardiovascular mortality and total mortality in patients with T2DM. Moreover, results from the Nurses' Health Study reported that 5125 women with T2DM who exercised for at least 4 h per week had a 40% lower risk of developing CVD compared to those who did not. This improvement in lowering risk of CVD remained after adjustments for smoking, BMI, and other cardiovascular risk factors (Martín-Timón et al.; 2014).

Physical activity might influence CVD risk via mechanisms not related to weight loss. These mechanisms include decreased systemic inflammation, improved early diastolic filling, improved endothelial vasodilator function, and decreased abdominal visceral fat (Lorber; 2014). Although there is considerable variation in the range of benefits reported, the recommendation to incorporate at least 150 minutes per week of moderate (to vigorous) aerobic physical activity, in addition to resistance training at least twice a week, remains a cornerstone of T2DM management and prevention of CVD in T2DM (Lorber; 2014).

According to Hayashino et al. (2013) exercise decreases inflammatory cytokine (CRP and IL-6) in patients with T2DM, and it could be a therapeutic option for improving inflammation abnormalities in patients with diabetes.

7.1.1.2. Weight loss

Weight reduction in obese persons will reduce all of the CVD risk factors associated with T2DM and will improve hyperglycemia. Moderate weight loss (e.g., 7–10% of body weight in 1 year) could be achieved (Buse et al.; 2007). Even if no weight reduction can be achieved, it is important to maintain weight rather than to increase weight. A diet with low carbohydrate and high in fat may cause greater weight loss within a short period of time but this has not been demonstrated to result in greater weight loss after 1 year. On contrary, diets with more balanced proportions of fats and carbohydrates might be more successful in permanent weight reduction **(**Buse et al.; 2007).

Weight reduction is advised for all overweight patients with T2DM. Recommended strategies to reduce weight include regular physical activity and to maintain a healthy eating pattern. Weight loss has been clearly demonstrated to improve quality of life, IR, and other CVD risk factors. Therefore, clinical guidelines continue to recommend weight loss for obese individuals with T2DM (Lorber; 2014)**.**

7.1.1.3 Diet

Dietary intervention is highly recommended. The EASD Diabetes and Nutrition Study stress the importance of a diet rich in fruits, vegetables, wholegrain cereals, and low-fat protein sources. It has been suggested that there is no benefit in a high protein over a high carbohydrate diet in T2DM, also specific dietary recommendations including limited saturated and trans-fats and alcohol intake, monitoring carbohydrate consumption, and increasing dietary fiber. However, supplementation with anti-oxidants like vitamins E and C and carotene, is not proven to be of benefit, and thus regular use is not recommended. For those who prefer a higher intake of fat, a Mediterranean-type diet is acceptable, provided that fat is composed of mainly monounsaturated fatty acids, using oils such as virgin olive oil (Rydén et al.; 2013, 2014).

7.2. Insulin resistance

Most patients with T2DM have IR. IR is a multisystem disorder that predisposes to both CVD and DM, and it induces several metabolic alterations. Factors that contribute to IR are genetics, obesity, physical inactivity, and advanced age. Patients with IR often have

abdominal obesity. Metabolic risk factors that occur commonly in patients with IR are atherogenesis, hypertension, glucose intolerance, and a prothrombotic state (Grundy et al.; 1999). Moreover, in hyperinsulinemia and IR, an imbalance in the direct effects of insulin action occurs, which is accompanied by the effects of other cardiovascular risk factors associated with the IR syndrome. Hyperinsulinemia and IR are also associated with a cluster of thrombotic risk factors, such as elevated levels of PAI-1, factor VII, factor XII, and fibrinogen, and is also associated with increases level of CRP, which is an acute-phase inflammation marker that has been associated with an increased risk for DCM. Recent studies have confirmed the association between increased levels of CRP protein and worsened LV myocardial performance (Voulgari et al.; 2010).

The fuel-sensing enzyme AMP-activated protein kinase (AMPK) was first described as an enzyme activated by changes in the AMP/ATP ratio that could both increase cellular ATP generation (e.g., fatty acid oxidation) and diminish ATP use for less critical processes (e.g., fatty acid, triglyceride, and protein synthesis) (Ruderman et al.; 2013). AMPK regulates a lot of physiological events, including cellular growth and proliferation, mitochondrial function and biogenesis, glucose transport, lipid and protein synthesis, and fuel metabolism and factors that have been linked to IR, including inflammation, oxidative stress. So, dysregulation of AMPK plays an important role in the pathogenesis of IR. As AMPK has a central role in regulating insulin sensitivity, many strategies that activate AMPK could be used for the prevention and treatment of these abnormalities. Some studies also demonstrated the possibility that pharmacological AMPK activators as well as exercise could be used for preventing IR in T2DM. Three known AMPK regulators concurrently activate endothelial eNOS, an enzyme, which generally protects against atherogenesis in experimental animals (Ruderman et al.; 2013).

7.2.1 Recommendation

AMPK activation is used as a target therapy for prevention and treatment of IR.

7.2.1.1 Metformin

Metformin, which is widely used as antidiabetic drug acts by modestly increases in insulin sensitivity. It was reported to act as an AMPK activator by moderately inhibiting complex 1 of the mitochondrial electron transport chain and in this way decreasing the cellular energy

state. In the liver, this decrease in energy state is sufficient to reduce glucose production. Metformin has been shown to activate AMPK in many tissues, including adipose, skeletal muscle and heart (Ruderman et al.; 2013).

7.2.1.2 Adiponectin

AMPK is also activated by the adipokine adiponectin. Notably, diminished serum adiponectin levels are associated with IR and appear to be a strong predictor of T2DM and CVD in obese patients. On the other hand, elevated adiponectin levels are associated with increased insulin sensitivity, a lower incidence of T2DM that is independent of obesity, and a decreased risk of CHD (Ruderman et al.; 2013).

7.2.1.3 Thiazolidinediones and other AMPK activators

The thiazolidinediones (TZDs) were found to be AMPK activators. TZDs can activate AMPK in some tissues by lowering their energy state; moreover studies strongly suggested the TZDs' ability to increase hepatic insulin sensitivity *in vivo* is mediated predominantly via adiponectin. TZDs are also well-established activators of the PPARs. So, the adiponectin-independent mechanism of TZD-induced changes could be PPAR mediated (Ruderman et al.; 2013).

Other pharmacological AMPK activators have been found or are in development. These include several compounds which directly activate AMPK. Some therapeutically used antidiabetic drugs such as GLP-1 receptor activators and DPP IV inhibitors, or others in clinical trials have been shown to increase AMPK activity in a number of tissues in addition to their other actions (Ruderman et al.; 2013).

It is well known that exercise can lead to activation of AMPK. These observations, in addition to epidemiological observations which give evidence that diseases associated with the metabolic syndrome (e.g., T2DM, hypertension, atherosclerotic cardiovascular disease, and even certain cancers) occur less frequently in physically active people and that regular exercise improves whole-body insulin action, suggest a central role for AMPK in regulating insulin sensitivity. Pharmacological AMPK activators as well as exercise could be used for ameliorating IR in T2DM. Exercise acutely increases AMPK activity in adipose tissue and aortic endothelium, as well as in liver and muscle (Ruderman et al.; 2013).

According to Romeo et al. (2012) targeting inflammation is an important therapeutic approach in IR and T2DM. Chronic inflammation is a promising target for the prevention and therapy of IR, T2DM, and cardiovascular disease. The well-established role of TNF-α in inflammation and IR in animal models, could be a rational target for new therapeutic intervention. However, several approaches to antagonize TNF-α have had no effect on glucose levels in patients with T2DM and only marginal impact on insulin sensitivity in non-diabetic, insulin-resistant patients. When IL-1R1 is blocked by a specific binding protein (IL-1RA) insulin sensitivity and β-cell secretory profile are improved while reducing markers of systemic inflammation (Romeo et al.; 2012).

7.3 Dysglycemia

Studies on endothelial function, autonomic neuropathy, arterial stiffness and LV function in T1DM have demonstrated the correlation between abnormal blood glucose level and atherosclerosis. Elevation in resting heart rate, which is a characteristic of patients with T1DM and autonomic function, was prevented and better controlled in patients with intensive DM management, and also LV mass and function improved with better blood glucose control (De Ferranti et al.; 2014). It has been demonstrated that lowering post-prandial glucose may lead to a reduction in CVD in subjects receiving acarbose compared with placebo, since acarbose specifically reduces post-prandial glucose excursions. The risk for MI was significantly lower in patients receiving acarbose compared with those on placebo. Diabetic microangiopathy and neuropathy can be reduced by tight glycaemic control. This will also exert a favorable influence on CVD. Intensified treatment options, aimed at lowering haemoglobin HbA_{1c} close to the normal range, have been associated with a markedly decreased frequency and extent of microvascular and neuropathic complications in people with T1 and T2DM. Microvascular complications such as at the kidney and the eye level, need further therapeutic measures, including adequate control of BP with the use of ACE-inhibitors and/or angiotensin receptor-II-blockers and the cessation of smoking. The relation between macrovascular disease and hyperglycaemia is less clear than the relation to microangiopathy, glycaemic control (mean HbA_{1c} close to 7% over the first 7–10 years), effectively reduced cardiac and other macrovascular disease manifestations (Rydén et al.; 2013).

7.3.1 Obtain and maintain euglycaemic control

Lowering blood glucose level toward the normal range, in the long term, should be considered. This might need special targeting of post-prandial hyperglycaemia (Rydén et al. 2014). Postprandial hyperglycaemia appears to be related with an increased risk of cardiovascular events in patients with and without T2DM. Therefore, it is important to discuss the role of postprandial glycemia as a predictor of cardiovascular events, and its importance as a treatment target (Martín-Timón et al.; 2014). An HbA_{1c} target of <7.0% (<53 mmol/mol) to reduce microvascular disease is generally recommended. The evidence for an HbA_{1c} target in relation to macrovascular risk is less compelling, due to the complexities surrounding the chronic, progressive nature of DM (Rydén et al.; 2014**).** In T1DM, the standard therapy is intensified insulin therapy, depending on appropriate nutrition and blood glucose self-monitoring, aiming at HbA_{1c} below 7%. In T2DM a common pharmacologic treatment approach is less well-accepted. Various diabetes associations have advocated HbA_{1c} targets below 7.0 or 6.5%, respectively. BMI and the risks of hypoglycaemia, renal insufficiency, and HF are the major determinants for the choice of treatment. According to Grundy et al. (1999) weight loss and increased exercise are first-line therapy for reducing hyperglycemia. If hyperglycemia persists, metformin can be prescribed. Metformin proved efficacious, but the combination of metformin and sulfonylureas apparently increases death rates, which is attributed to sulfonureas. This calls for more study on the safety of this combination. Metformin is recommended as first line drug in overweight T2DM (Rydén et al. 2014). Another group of agents for treatment of T2DM are the thiazolidenediones. These agents lower glucose levels by reducing IR. The first drug in this class to be approved for clinical use was troglitazone. This agent was approved for use in combination with insulin therapy to improve glycemic control. However, troglitazone had to be withdrawn from market due to its rare, but severe liver toxicity. New drugs of the same class, rosiglitazone and pioglitazone, may have less potential hepatotoxicity, but rosiglitazone was reported to induce cardiovascular complications, and thus its approval is at rest. Another drug for glucose control is acarbose, which acts by partial blockade of glucose absorption. In patients who fail to achieve glucose control by life style changes and oral hypoglycemic agents, insulin should be initiated (Grundy et al.; 1999). Meal-time short-acting insulin is recommended (Rydén et al. 2014).

7.4 Hypertension

Epidemiological analyses and randomized clinical trials have demonstrated the impact of elevated BP as a risk factor for both microvascular and macrovascular diseases in diabetes. For patients with diabetes, it is recommended that the appropriate diastolic BP target is ≤80 mmHg. Although it is unclear exactly how much systolic BP should be lowered below 140 mmHg, various groups have recommended systolic BP targets of <135 mmHg and <130 mmHg (Buse et al.; 2007). Hyperglycemia also contributes to hypertension. Long term and intensive DM therapy reduced the long-term risk of hypertension by 24%. Hypertension correlated with disease duration and severity, particularly nephropathy (De Ferranti et al.; 2014).

Hyperinsulinemia is associated to increased renal reabsorption of sodium and to increased sympathetic tone (Martín-Timón et al.; 2014). So the anti-natriuretic effect of insulin, together with its ability to activate the sympathetic nervous system and the abnormal vascular function leads to the development of hypertension. Moreover, both hyperglycaemia and insulin activate the RAAS by enhancing the expression of angiotensinogen, angiotensin II, and AT1 receptor, which contributes to an increase in BP in patients with IR (Rydén et al. 2014). Aging, obesity, and the onset of renal disease also promote hypertension (Martín-Timón et al.; 2014).

7.4.1 Reduce hypertension

BP must be routinely measured. Patients with diabetes should be treated to a systolic BP <130 mmHg and a diastolic BP <80 mmHg. Weight control, increased physical activity, moderate alcohol consumption, reduction in sodium intake, and emphasis on increased consumption of fresh fruits, vegetables, and low-fat dairy products for a maximum of 3 months could be the only management for patient with systolic BP of 130–139 mmHg or diastolic BP of 80–89 mmHg. If, after these efforts, targets are not achieved, treatment with pharmacological agents should be initiated (Buse et al.; 2007).

Patients with diabetes and hypertension (systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg) should be treated with drug therapy in addition to lifestyle, with a regimen that includes either an ACE inhibitor or an ARB. If one class is not tolerated, the other should be substituted. Other drug classes demonstrated to reduce CVD events in patients with diabetes (β-blockers,

thiazide diuretics, and calcium channel blockers) should be added as needed to achieve BP targets (Buse et al.; 2007). According to Beckman et al. (2013) there is no difference in the primary outcome among chlorthalidone, amlodipine, and lisinopril in patients with diabetes. If the primary goal of treatment is to reduce BP, then a thiazide diuretics, dihydropyridine calcium-channel blockers, or ACE inhibitors are acceptable first choices. β-adrenergic antagonists should not be considered as first-line agents for treating hypertension in most patients, as β-adrenergic blocker therapy was associated with an increased risk for new-onset diabetes, and an increased risk of stroke. In contrast, β-adrenergic blocker therapy is recommended for three years after MI and in the setting of LV dysfunction, with or without HF. Moreover, β-adrenergic blocker therapy, titrated to full dose, is recommended for the treatment of stable angina. If the goal of treatment is secondary prevention of atherosclerosis, antagonists of the RAAS take the first choice because of the benefit effects beyond BP lowering effect. In a trial of secondary prevention after a cardiovascular event, ACE inhibition has shown to reduce recurrent stroke in diabetic patients with previous stroke and reduce mortality in diabetic patients after MI. ARBs have similar efficacy to ACE inhibitors after MI. In the Acute Myocardial Infarction Trial valsartan was as effective as captopril for the primary endpoint of total mortality in the subgroup of diabetic patients with MI complicated by LV systolic dysfunction. In the Losartan Intervention For Endpoint Reduction in Hypertension Study, losartan was found to be superior to atenolol in diabetic patients with end-organ damage for the primary composite endpoint of cardiovascular death, MI, and stroke. In the Valsartan Antihypertensive Long Term Use Evaluation (VALUE) study, valsartan was equivalent to amlodipine for the endpoint of cardiovascular morbidity and mortality in hypertensive diabetic patients (Beckman et al.; 2013).

Furthermore, many recent studies with ACE inhibitors and ARBs suggest benefits, which cannot be fully attributed to BP lowering in preventing or delaying the progression of advanced diabetic kidney disease. For these reasons, current guidelines suggest that ACE inhibitors are the drugs of choice in the initial management of hypertension in people with diabetes or kidney. If ACE inhibitors, ARBs or diuretics are used, renal function and serum potassium levels should be monitored within the first three months. If levels are stable, follow-up could occur every 6 months thereafter. Multiple-drug therapy generally is required to achieve BP targets in diabetic patients (Buse et al.; 2007).

7.5 Dyslipidaemia

Lipid abnormalities usually occur in accompany with T2DM. These abnormalities include moderate elevation of fasting and non-fasting triglycerides and low HDL-C. Other features comprise elevations of triglyceride-rich lipoprotein, including very low-density lipoprotein (VLDL) remnants and small dense low-density lipoprotein (LDL) particles. The imbalance between the hepatic import and export of lipids results in non-alcoholic fatty liver disease (Rydén et al.; 2014). Bad glycemic control, higher weight and IR are associated with a more atherogenic cholesterol distribution in men and women with T1DM. The HDL-C fraction is of special interest because the metabolism of HDL-C in T1DM may be altered due to abnormal lipoprotein lipase and hepatic lipase activities associated with exogenously administered insulin (De Ferranti et al.; 2014). Data from statin trials demonstrate that lower levels of HDL is an independent CVD risk marker, even when LDL-C level is not elevated (Rydén et al.; 2014). A LDL-C value of more than 100 mg/dL is associated with increased CVD risk, and a meta-analysis of data which included T1DM patients suggested that lowering LDL level reduces CVD events (de Ferranti et al.; 2014). Buse et al. (2007) suggested that in patients with T2DM, triglycerides are often elevated, HDL cholesterol is generally decreased, and LDL cholesterol may be elevated, on borderline, or normal. Although an elevated LDL cholesterol level generally is not recognized as the major lipid abnormality in patients with T2DM, clinical trials demonstrate that lowering LDL cholesterol level with drugs will reduce risk for major coronary events regardless of diabetes status. Elevated LDL cholesterol is identified as the primary target of lipid-lowering therapy by both the ADA and the AHA. The focus on LDL cholesterol is supported by results of controlled clinical trials that have shown that LDL cholesterol lowered with statins will reduce the risk of major CVD events in patients with diabetes, moreover triglyceride-rich lipoproteins, especially VLDLs, are often elevated in patients with diabetes, which appear to be atherogenic and represent a secondary target of lipid-lowering therapy (after the goal for LDL cholesterol is attained). The ADA recognizes serum triglycerides as a surrogate for atherogenic triglyceride-rich lipoproteins and suggests a target of <150 mg/dl. The AHA suggests an alternative approach, for patients with diabetes and no clinical CVD whose triglyceride level is >200 mg/dl, and the AHA recommends a non-HDL target of <130 mg/dl (Buse et al.; 2007).

7.5.1 Correct Dyslipidaemia

In addition to lifestyle modification with reduction of saturated fat and cholesterol intake, weight loss whenever necessary, increased consumption of dietary fiber and regular physical activity, adult patients should measure lipid level at least annually (Buse et al.; 2007).

The primary goal of therapy is to reduce LDL-cholesterol levels to≤100 mg/dL. This goal should be achieved by addition of drug therapy to dietary interventions. Statins are first-line therapy to achieve LDL cholesterol of ≤100 mg/dL (Grundy et al.; 1999). Statin drugs proved to be well-tolerated and highly effective. These drugs are specific, competitive inhibitors of the enzyme 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG CoA reductase), which catalyzes the major rate determining step in cholesterol synthesis. This enzyme inhibition causes an increase in hepatic LDL receptor activity, and consequently an increased uptake of LDL cholesterol, which results in decreased plasma LDL-cholesterol. The statins are the most potent drugs for lowering plasma LDL-cholesterol (Rydén et al.; 2014). When triglycerides remain >200 mg/dL in patients receiving statin therapy, fibrates could be added to achieve the secondary goal of lipid management, which means triglyceride <200 mg/dL (Grundy et al.; 1999). If triglycerides are≥500 mg/dl, treatment options includ e fibrates or niacin before LDL-lowering therapy. A non-HDL cholesterol level≤130 mg/dl should be achieved if possible (Buse et al.; 2007). Although nicotinic acid effectively lowers triglycerides and raises HDL levels in patients with T2DM, its tendency to worsen hyperglycemia causes relative contraindication (Grundy et al.; 1999). Adults T1DM patients with an abnormal lipid profile and other risk factors for CVD such as hypertension, obesity or smoking, and who have not developed CVD or who have other additional risk factors should be treated with statins (De Ferranti et al.; 2014). Combination therapy of LDL-lowering drugs (e.g., statins with fibrates or niacin) may be necessary to achieve lipid targets, but attention should be considered to the risk for myositis and rhabdomyolysis.

Both the ADA and the AHA support efforts to increase HDL cholesterol level in high-risk patients when these levels are reduced. The most effective available drug for raising HDL cholesterol levels is nicotinic acid. Clinical trials suggest CVD risk reduction with nicotinic acid, although no trials of this drug that specifically targets patients with diabetes have been performed. Furthermore, at higher doses, nicotinic acid can worsen hyperglycemia (Buse et al.; 2007). The combination of statin with nicotinic acid has proved to be successful in

atheroma regression trials; so it is likely to be considered giving nicotinic acid at doses less likely to impair IR (Rydén et al. 2014).

According to Goldfine and Beckman (2008), evidence from clinical trials emphazises the importance of lipid-lowering therapy for patients with DM. Statins are the drugs of choice for effective primary and secondary prevention of CV diseases. The Heart Protection Study (HPS) with around 6000 DM patients demonstrated that cholesterol lowering with simvastatin reduced the rate of first major vascular events by >25%, even in patients without established coronary disease or markedly elevated baseline cholesterol levels. The Landmark Collaborative Atorvastatin Diabetes (CARDS) Study suggested that treatment with atorvastatin, 10 mg daily, compared with placebo resulted in a 37% reduction in major CV events in T2DM patients with low-density lipoprotein cholesterol levels of 4.14 mmol/L (160 mg/dL) or lower over a mean follow-up of 4 years (Goldfine and Beckman; 2008).

7.6 Diabetic kidney disease

Diabetic kidney disease (DKD) is a complication of DM and is associated with CVD. DKD appears as microalbuminuria or macroalbuminuria, impaired glomerular filtration rate (GFR), or both. The earliest manifestation of DKD is microalbuminuria with an albumin excretion rate of 30 to 299 mg/24 h, while macroalbuminuria correlates with progressive loss of GFR, and is defined as an albumin excretion rate≥300 mg/24 h . Macroalbuminuria is also used to define diabetic nephropathy. Impaired GFR is usually defined in T1DM as an estimated GFR (eGFR) <60 mL min^{-1} 1.73 m^{-2}. It can occur in any stage of DM, but seems to occur less frequently than in the past. The risk of all-cause mortality increased with the severity of DKD. The presence of microalbuminuria account for all the excess mortality, in which CAD was the leading cause of death after 20 years suffering from DM. Microalbuminuria reflects a diffuse vascular injury and is highly correlated with CVD. Microalbuminuria is highly associated with increased CVD and mortality risks and can be mediated by other CV risk factors, such as hypertension, dyslipidemia, and IR. Improvement in blood glucose level has reduced the incidence of microalbuminuria. Macroalbuminuria indicates significant kidney damage and is also associated with CVD. Mechanisms may include functional consequences of kidney disease, such as higher LDL-C and lower HDL-C. These data suggest that the processes through which T1DM increases CVD risk are largely reflected by albuminuria (microalbuminuria and macroalbuminuria) (De Ferranti et al.; 2014). Diabetic nephropathy

could also be accelerated by high BP leading to a vicious cycle once hypertension and nephropathy are present. It should be noted that renal artery stenosis may be responsible for both renal insufficiency and hypertension in the diabetic patient. Screening for this condition is warranted in patients with refractory hypertension and/or renal insufficiency (Rydén et al.; 2014).

Impaired GFR is a risk factor for CVD, independent of albuminuria. In the CACTI study, lower GFR in T1DM was associated with increased risk of coronary artery calcification progression (Schauer et al; 2011). In T2DM, low eGFR without albuminuria is becoming highly common over time and is associated with substantially increased risks of CVD and death. A number of potential explanations have shown that increased CVD risk is associated with DKD in patients with T1DM. Many risk factors for developing DKD and CVD are overlapping, including hyperglycemia, hypertension, dyslipidemia, obesity, and IR. Therefore, DKD may simply mark the severity and duration of these CVD risk factors. Secondly, DKD could also contribute to the worsening of CVD risk factors, for example, volume retention and RAAS activation, which lead to increased BP, dyslipidemia (low HDL-C, high triglycerides, and a shift in LDL-C distribution to small, dense particles), and IR. DKD may also lead to CVD through novel disease pathways, for example, an accumulation of asymmetric dimethylarginine, disruption of mineral metabolism, and anemia caused by erythropoietin deficiency, which contributes to LV hypertrophy (De Ferranti et al; 2014).

7.6.1 Preventing and slowing DKD

Although microalbuminuria and macroalbuminuria are interesting therapeutic targets for CVD prevention, there are no specific interventions directed at the kidney that prevent DKD. Inhibition of RAAS would be a promising option but has not been proved to prevent DKD before it is clinically apparent. Some therapeutic interventions targeting risk factors are more likely to prevent DKD, including maintenance of euglycemia. In the Diabetes Control and Complications Trial (DCCT), intensive DM therapy reduced the incidence of microalbuminuria and macroalbuminuria by 39% and 54%, respectively, and reduced impaired GFR by 50%. Effects of intensive DM therapy on impaired GFR were fully explained by treatment group differences in HbA_{1c} or albuminuria, which suggests that hyperglycemia, drives both albuminuria and GFR loss in T1DM. Treatment of DKD with agents that inhibit the RAAS is effective. The Collaborative Study Group's captopril trial

demonstrated that ACE inhibitors reduce the progression of DKD and death in T1DM. So, the treatment with ACE inhibitors is advisable to prevent further progression of DKD once the kidney disease has developed, and also to inhibit other CVD risk factors (De Ferranti et al.; 2014).

All patients with T1DM and hypertension or albuminuria should be treated with an ACE inhibitor. If an ACE inhibitor is not tolerated, an ARB could be used as they have similar efficacy, although this has not been studied specifically in patients with T1DM. Optimal dosing for ACE inhibitors or ARBs in the setting of DKD is not well defined; titration may be guided by BP, albuminuria, serum potassium, and creatinine. Combination therapy of ACE and ARB blockade is not recommended at this time (De Ferranti et al.; 2014). It is also important to restrict sodium and dietary protein. Treatment of hypertension with ACE inhibitors can retard the progression of diabetic nephropathy. Although there are reports about a beneficial effect of ACE inhibitors in nephropathy even in the absence of hypertension, there is still discussion whether normotensive patients should use them for prevention of nephropathy (Grundy et al.; 1999).

7.6.2 Simultaneous glucose lowering and reno-protective effect of sodium–glucose linked transporter-2 inhibitors

Kidneys have a major role in glucose homeostasis and are recognized as a contributor to both gluconeogenesis and glucose reabsorption. Sodium glucose cotransporter-2 (SGLT-2) inhibitors are new antihyperglycaemic agents with multiple effects such as a decrease of glucose reabsorption by the kidneys via an increase in urinary glucose excretion. So these agents improve blood glucose control independently of insulin secretion and with a low risk of hypoglycaemia. There are currently three drugs of this class that have been approved by FDA and European Medicines Agency (EMA): canagliflozin, dapagliflozin and empagliflozin. These agents can be used either as a monotherapy or in combination with other glucose-lowering drugs.

Although a lot of risk factors can be modulated positively with SGLT-2 inhibitors such as BP, weight, visceral obesity, hyperinsulinaemia, arterial stiffness, albuminuria, hyperuricemia and oxidative stress, an increase in LDL cholesterol levels have also been demonstrated for these class of drugs, which theoretically might affect some of these benefits (Inzucchi et al.; 2015).

According to Rosenwasser et al. (2013), canagliflozin 300 mg daily had positive effects on the lipid profile with increases in HDL by 7.1% to 10.6%, decreases in triglyceride by−2.3%, and increases in LDL by 7.1%. These changes in lipid profiles were not established with dapagliflozin use. After 24 weeks of therapy with dapagliflozin, no significant changes in the lipid profile were noted besides small increases in HDL (Rosenwasser et al.; 2013).

In clinical trials, SGLT-2 inhibitors have led to weight reductions of up to 4.7 kg when administered as a monotherapy or as add-on therapy to metformin, sulfonylurea, or insulin over study periods ranging from 4 to 104 weeks. Canagliflozin and dapagliflozin caused a decrease in body weight, which was mainly due to loss of fat mass, and this was slightly more from visceral abdominal tissue than from subcutaneous abdominal tissue. Waist circumference was reduced approximately −1.6% to −3.5% or around −1.52 cm (Rosenwasser et al.; 2013). In studies of SGLT-2 inhibitors in patients with T2DM, a lower systolic BP of ~ 2–10 mmHg was demonstrated; declines in diastolic BP were smaller and less consistent across clinical trials (Chao; 2014)**.** The initial inhibition of BP seen with SGLT2 inhibitor use is due to the osmotic diuresis effects as a result of inhibition of renal glucose and sodium reabsorption. Over time, this prolonged reduction in BP might be attributed to local inhibition of the RAAS which can lead to reductions in BP and also to nephroprotection owing to the decrease in intraglomerular pressure and hyperfiltration (Rosenwasser et al.; 2013). This new class of drugs has other contributions which provide a theoretical basis for kidney protection above their anti-hyperglycemic effects. Besides its BP lowering effect, SGLT2 inhibitors also reduce single-nephron glomerular filtration rate in chronic kidney disease, though by quite different mechanisms from RAAS blockers. Cell culture studies demonstrated that reabsorption of glucose from the tubular lumen as well as from the basolateral compartment might contribute to the production of proximal tubular extracellular matrix proteins. Whether this could attribute to reducing the progression of chronic kidney disease will require further dedicated studies (Gilbert; 2014).

7.6.3 Dipeptidyl peptidase inhibitor and its role to attenuate kidney injury

DPP IV inhibitors or incretin based agents delay the degradation of GLP-1 and its binding affinity to the GLP-1 receptor, suggesting that DPP IV inhibitors, partly by increasing GLP-1 level, can exert reno-protective effects in the hyperglycemic state, because diabetic nephropathy has a close relationship with other diabetic microvascular complications (Liu et

al.; 2012). DPP IV inhibitors can decrease proteinuria, albuminuria, urinary albumin/creatinine ratio, and serum creatinine, improve creatinine clearance, and delay glomerular and tubulointerstitial fibrosis in diabetic rats (Liu et al.; 2012).

Treatment with the DPP IV inhibitor up-regulate GLP-1 receptor expression in both the glomerulus and tubules. In addition to the inhibition of DPP IV activity, it enhanced the level of active GLP-1 by binding to GLP-1 receptor causing several pathological processes to ameliorate renal lesions. In insulin-resistant obese men, intravenous infusions of GLP-1 reduced glomerular hyperfiltration and enhanced sodium excretion, suggesting an action mediated by GLP-1 receptors in the kidneys (Gutzwiller et al., 2004). Moreover, GLP-1 receptor agonists offer antihypertensive and renoprotective properties, at least partly, through their binding affinity for GLP-1 receptors in mice. The specific mechanism remains unclear, but antioxidation and antiapoptosis through GLP-1receptor activation are probably the main pathways for tissue protection. Another mechanism for renal protection is that activation of GLP-1 receptors leads to protection of renal and retinal cells through amelioration of oxidative DNA damage and apoptosis in diabetic microvascular complications (Liu et al.; 2012).

7.7 Smoking

Smoking is a strong risk factor for CVD. The risk of smoking on CVD is particularly important in patients with DM, as smoking increased the risk of DM nephropathy, retinopathy, and neuropathy in patients with T1DM, because of adverse effects on inflammation and endothelial function. Smoking increases CVD risk factors in T1DM due to impairment of glucose metabolism, lipids, and endothelial function. Smoking cessation can lead to weight gain, which often prevents smokers with DM from quitting. The efficacy and safety of smoking cessation pharmacotherapy in patients with T1DM has not been confirmed (De Ferranti et al.; 2014), and needs further research.

Smoking cessation should be recommended to all patients with T1DM as part of an overall strategy to lower CVD, in particular PAD (De Ferranti et al.; 2014). All patients with diabetes should be asked and assisted by counseling and by initiation of a cessation plan, or pharmacotherapy (including nicotine replacement and Bupropion) should be incorporated as needed (Buse et al.; 2007).

7.8 Genetics and epigenetics

T2DM is an independent risk factor for developing CVD with the relative risk of CVD mortality of 4.9 in women and 2.1 in men, relative to non-diabetics subjects. Genetic and environmental factors could be contributing to this risk. Genome-wide association studies had suggested the number of common single-nucleotide polymorphisms, which demonstrate the relationship between T2DM and CVD (Martín-Timón et al.; 2014).

7.8.1 Haptoglobin polymorphism

Haptoglobin is a serum protein for which there are two common alleles in humans, denoted 1 and 2. The genotype of an individual may therefore be described as being Hp 1-1 (homozygous for the 1 allele), Hp 2-2 (homozygous for the 2 allele), or Hp 2-1 (the heterozygote). The two alleles are in a balanced polymorphism with approximately 30% of the alleles being T1DM and 70% T2DM. The distribution of these two alleles in individuals with diabetes is not different to that in the general population. Haptoglobin is an antioxidant as a direct result of its ability to prevent hemoglobin-driven oxidation. Haptoglobin acts as an antioxidant through stabilization of the heme moiety within the hemoglobin protein. This ability of haptoglobin to protect against hemoglobin-driven oxidative stress is lost when hemoglobin becomes heavily glycosylated, as in the diabetic condition. It has been demonstrated that diabetic individuals with Hp 1-1 are exposed to less hemoglobin-driven oxidative stress than diabetic Hp 2-2 individuals because the Hp1-1-glycosylated hemoglobin complex is more rapidly scavenged by the macrophage as compared to the Hp 2-2-glycosylated hemoglobin complex (Levy; 2003, 2004). According to Martín-Timón et al. (2014), haptoglobin has been involved in both T2DM, and T2DM related CVD and binds to ApoA1 in the same location as lecithin-cholesterol acyltransferase (LCAT). This leads to a decrease in LCAT activity and consequently limited HDL maturation. This inhibits reverse cholesterol transport causing HDL to become proatherogenic. According to several studies investigating haptoglobin polymorphisms and CVD risk in T2DM, in a study with 206 CVD patients and 206 CVD controls also Levy (2003, 2004) suggested, that CVD events in diabetes is five times greater with the HP 2-2 phenotype than with HP 1-1. A multivariate analysis for conventional CVD risk factors and DM characteristics, haptoglobin phenotype was a statistically significant predictor of CVD in diabetes. The ratio of having CVD in diabetes with the haptoglobin phenotype 2-2 was 5.0 times greater than that in diabetes with

the haptoglobin 1-1 phenotype. An intermediate risk of CVD was associated with the haptoglobin 2-1 phenotype. No significant association between haptoglobin type and CVD risk was found in non-diabetic individuals. Based on two small studies which showed a relationship between angioplasty and haptoglobin type regarding the necessity for repetition of angioplasty in individuals with diabetes, a study was initiated to determine if the haptoglobin genotype was predictive of major adverse cardiac events after coronary artery stenting in individuals with diabetes. A consecutive series of 935 with oral agents and/or insulin treated diabetic patients were followed for one year after stenting for major adverse cardiac events defined as target vessel revascularization, MI, and death. In multivariate analysis controlling for all known determinants of outcome after stent placement, it has been demonstrated that haptoglobin genotype was a significantly independent predictor of major adverse cardiac events in the one year period following stent placement in diabetic patients. There were also significant differences in the risk of MI development and in the need for target vessel revascularization in the one year period following stent placement (Roguin et al.; 2003).

7.8.2 Apolipoprotein E gene polymorphism and risk of CVD in T2DM

ApoE is important in lipid metabolism as a ligand for many cell-surface receptors including the LDL receptor, LDL-receptor related protein and VLDL receptor. Human ApoE is genetically controlled by three alleles (e2, e3, and e4) at a single gene locus in chromosome 19; these code for three isoforms (E2, E3, and E4) and thus determine the six genotypes (e2/2, e4/2, e3/2, e3/3, e4/3, and e4/4). ApoE ε2 allele has been associated with higher plasma levels of ApoE, reduced plasma levels of LDL-C and lower risk of CAD. ApoE ε4 is related with lower plasma level of ApoE, elevated plasma levels of total cholesterol, LDL-C, VLDL-C, and greater risk of CAD when compared to ApoE3 homozygotes. In diabetic population, Apoe4 allele is related with the risk of CAD, occurrence of exercise-induced silent myocardial ischemia, impairment of endothelium-dependent artery dilation, and CAD death (Martín-Timón et al.; 2014).

7.8.3 Epigenetics and the risk of CVD in T2DM

There is evidence linking epigenetic factors to diseases such as DM and CVD. Epigenetic factors could be an important mediator between DM, CVD and chronic inflammatory

response, and, by different types of reactions such as acetylation and methylation, could mediate the interaction between genes and environment resulting in activation, depression or silencing the genetic transcription. Methylation of DNA has been associated to several cardiovascular-related biomarkers. Hyperglycaemia might lead to epigenetic changes of genes involved in vascular inflammation. Poor glycemic control increases nuclear transcription factor-κB (NF-κB), which regulates the expression of genes involved in inflammatory diseases, including atherosclerosis and diabetic complications, activity in monocytes and gene expression of inflammatory cytokines. Moreover, epigenetic changes in the NF-κB p65 promoter induced by transient hyperglycaemia, which persist for 6 d during culture at normal glucose levels, can be regulated by two histones, histone methylase and histone demethylase. The epigenetic changes induced by transient hyperglycemia could explain the hyperglycaemic memory. Epidemiological studies demonstrate that hyperglycemia may induce epigenetic changes of proinflammatory genes, which subsequently regulate gene expression and thereby the development of vascular inflammation (Martín-Timón et al.; 2014).

8. METABOLIC SYNDROME

Metabolic syndrome (MetS) is a complex disorder with high socioeconomic cost that is considered a worldwide epidemic. MetS is defined by a cluster of interconnected factors that directly increase the risk of CHD, other forms of cardiovascular atherosclerotic diseases, and T2DM. Its main components are dyslipidemia (elevated triglycerides and apolipoprotein B - containing lipoproteins, and low HDL), elevation of arterial BP and dysregulated glucose homeostasis, abdominal obesity and/or IR **(**Kassi et al.; 2011**).** Any three or more of these components confer a diagnosis of the syndrome and represent a two- to threefold increased risk for the development of cardiovascular morbidity and mortality (Bello-Rodriguez et al.; 2013). Recently, other abnormalities such as chronic proinflammatory and prothrombotic states, non-alcoholic fatty liver disease and sleep apnea have been added to the entity of the syndrome (Kassi et al.; 2011**).** IR represents as a major characteristic of MetS and increases the risk of diabetes development. Diabetes significantly influences the development of CAD, and most diabetic subjects have MetS, which represents a major phenotype of IR (Won et al.; 2014). IR and obesity play a central role in causing hypertension and dyslipidemia, and further predisposes to MetS (Yadav et al.; 2014). MetS is also linked to the development of

fatty liver, hyperuricemia/gout, polycystic ovarian syndrome, gallstones, and sleep disorders (Nashar and Egan; 2014).

8.1 Pathophysiology

The pathogenesis of MetS is still not completely elucidated. However, genetic predisposition induced by multiple genes is a prerequisite for the initiation of MetS, together with a sedentary lifestyle and a high-calorie diet (Rask-Madsen and Kahn; 2012**).**

IR and inflammatory markers (IL-6, TNF-α, hsCRP) were higher and insulin sensitivity was significantly lower in subjects with MetS compared to subjects without MetS (Mahalle et al.; 2014), although the mechanism of the link between MetS and increased CAD risk remains uncertain. Obesity and IR remain at the core of the pathophysiology of MetS, but also a number of other factors such as chronic stress and dysregulation of the hypothalamic-pituitary-adrenal axis and autonomic nervous system, increases in cellular oxidative stress, RAAS activity, and intrinsic tissue glucocorticoid actions, as well as currently discovered molecules such as micro RNAs can also be involved in its pathogenesis. Central obesity is thought to be an early step, as visceral adipose tissue secretes a variety of bioactive substances termed adipocytokines, such as leptin, resistin, TNFα, IL-6, and angiotensin II which induce IR, along with plasminogen activator inhibitor 1 (PAI-1), which is related to thrombogenic vascular diseases. Adiponectin is an adipocytokine that protects against the development of T2DM, hypertension, inflammation, and atherosclerotic vascular diseases. It is decreased in persons with visceral fat accumulation, which is a known risk factor for MetS. Moreover, adipocytokines such as visfatin, as well as enzymes expressed in adipose tissue, such as neprilysin, and growth factors, like fibroblast growth factor 21, an important regulator of glucose and lipid metabolism, play a role in the pathogenesis of MetS. In particular, visfatin has been suggested to exert insulin-mimicking/sensitizing effects but can also contribute to the inflammatory processes by triggering cytokine production and NF-κB activation. Other compounds produced by adipose tissue possibly implicated in the pathogenesis of MetS, are the non-esterified FFAs. IR leads to acceleration of the process of FFAs mobilization from stored adipose tissue triglycerides. Due to hepatic IR FFAs lead to increased production of glucose and triglycerides and secretion of VLDL in the liver. FFAs also reduce insulin sensitivity in muscle by inhibiting insulin-mediated glucose uptake and increase fibrinogen and PAI-1 production **(**Kassi; 2011**)**. MetS may further predispose to beta cell dysfunction

through lipotoxicity. Thus, it should not be surprising that the MetS associates with a high risk for diabetes (Grundy; 2012).

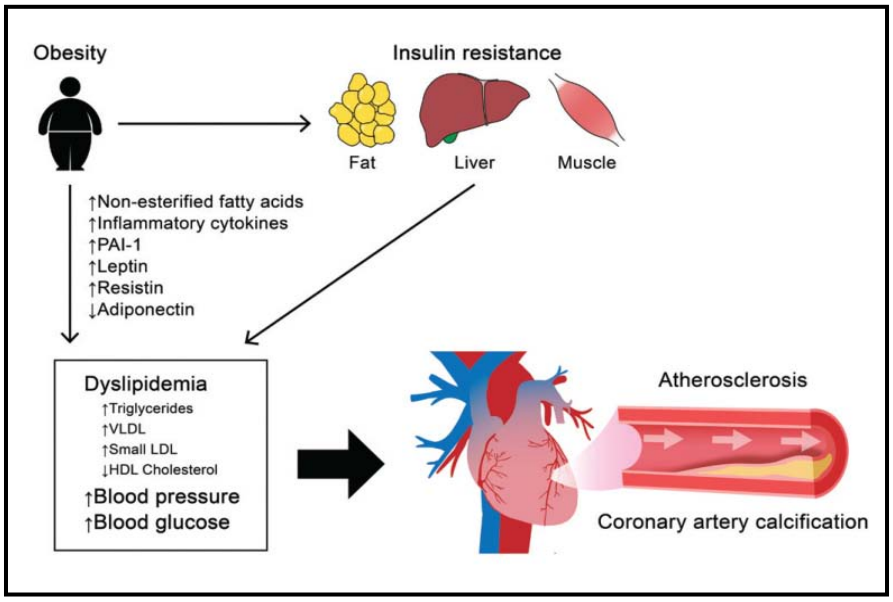

Figure (4) (Ha and Kim; 2015)

Figure 4 shows the proposed mechanism for the link between MetS and coronary arterial calcification.

MetS, obesity and IR, are significantly associated with the development of subclinical atherosclerosis (Ha and Kim; 2015). Other evidence suggests that NO, inflammatory and oxidative stress also play important roles in the pathophysiology of MetS hypertension and T2DM. Increased production of ROS in numerous tissues, including skeletal muscle and cardiovascular tissues leads to activation of the RAAS and elevation of angiotensin II, which are also implicated in the development of IR. Furthermore, either use of angiotensin II type 1 receptor antagonists or genetic knockout of angiotensin II type 1 receptor are known to effectively attenuate lipid accumulation in the liver (Kassi et al.; 2011).

8.2 Diagnosis

The diagnosis of the MetS is based on measurements of plasma glucose (less than 100 mg/dl) and other parameters such as triglycerides, HDL cholesterol, BP, and waist circumference. Abnormalities in three of the five risk factors are required for a MetS diagnosis. The International Diabetes Federation (IDF) introduced abdominal obesity as a prerequisite of the diagnosis of MetS, with particular emphasis on waist measurement as a simple screening tool

(Kassi et al.; 2011). Individuals with the MetS typically have a decreased capacity for exercise and show evidence of low-grade inflammation (Ruderman et al.; 2013).

8.3 Treatment

Therapeutic lifestyle changes, including exercise, are recommended as first line strategy in the treatment of cardiovascular risk factors, in patients with the MetS. It has been demonstrated that continuous training is associated with favorable effects on most cardiovascular risk factors related to the MetS. Also further results showed that in these patients dynamic endurance training also favorably affects other important cardiovascular risk factors including LDL-C, total cholesterol, BMI, so that exercise is a key component in the treatment of patients with the MetS and in the prevention of CVD morbidity and mortality (Pattyn et al.; 2012), and also weight reduction in obese subjects, reduced intakes of dietary saturated and trans-fatty acids, cholesterol, and sodium. The main targets of drug therapy include dyslipidemia, hypertension, and prothrombotic factors. In patients with CVD plus MetS, LDL cholesterol levels should be reduced to <70 mg/dl, and LDL + VLDL cholesterol (non-HDL cholesterol) to <100 mg/dl. Statins are first-line drugs. If treatment with a statin is not sufficient to achieve these levels, a second-line LDL-lowering drug can be used such as nicotinic acid, bile acid sequestrant, or ezetimibe. If CVD is not present, goals are an LDL cholesterol <100 mg/dl and a non-HDL cholesterol <130 mg/dl. In most patients, monotherapy with a statin is sufficient to achieve this goal (Grundy; 2012).

BP should be lowered to <130/<85 mm Hg, and preferably to <120/<80 mm Hg. Any of the standard BP–lowering drugs (e.g., ACE inhibitors/ARBs, calcium blockers, diuretics, and beta-blockers) can be employed. Beta-blockers and higher doses of thiazide diuretics raise glucose levels and predispose patients to conversion to diabetes, so care should be taken when prescribing these drugs, in order to reduce IR, which is best achieved by lifestyle intervention - weight reduction and increased physical activity. All persons with pre-diabetes should be encouraged to participate in a lifestyle intervention program. Metformin therapy also could delay progression of pre-diabetes to diabetes in about 40% of subjects. This has led to a recommendation on the part of some diabetologists for the use of metformin in persons with impaired fasting glucose (IFG) plus impaired glucose tolerance (IGT) and other MetS risk factors (Grundy; 2012).

9. EFFECTS OF DIABETES TREATMENT ON CARDIOVASCULAR SAFETY

9.1 Saxagliptin and Cardiovascular Outcomes in Patients with T2DM

Although improvement of blood glucose level has been shown to reduce microvascular diabetic complications, there is uncertainty regarding whether any particular glucose-lowering strategy, or specific therapeutic agent, is safe from a cardiovascular standpoint or can actually lower cardiovascular risk. So far, most studies which evaluate the effects on CV outcomes of specific glucose-lowering therapies have shown no significant CV benefit or an increased risk of death or HF. In a placebo-controlled trial, the DPP-4 inhibitor saxagliptin showed no effect on the primary composite end point of cardiovascular death, MI, or ischemic stroke, when added to therapy in patients at high risk for CV events. Moreover, saxagliptin was associated with significantly improved glycemic control and reduced the development and progression of microalbuminuria; however, it increased the risk of hospitalization for HF and the risk of hypoglycemic events. The observation of a higher incidence of hospitalization for HF among patients treated with saxagliptin was unexpected. Therefore, this finding needs to be evaluated in other ongoing CV outcome studies with DPP-4 inhibitors (Scirica et al.; 2013).

The Saxagliptin Assessment of Vascular Outcomes Recorded in patients with DM (SAVOR) study reported an increased risk for hospitalization for HF; this led to increase the awareness and monitoring of this adverse event. Two meta-analyses recently showed a significant increase in hospitalization for HF in patients treated with DPP-4 inhibitors, raising further concern for this adverse event. Further analyses of the studies many DPP-4 inhibitor revealed that the risk for CHF is high in persons with the greatest underlying CV risk. This suggests that health-care providers should be more cautious in using DPP-4 inhibitors in patients prone to HF. The mechanisms, which are responsible for the increased risk of HF and use of DPP-4 inhibitors still has to be elucidated. Increased level of substance P, which stimulates sympathetic activity, is one possibility. Moreover, there it is speculated that this effect may be particularly relevant in patients taking ACE inhibitors, as this combination may further increase substance P levels. Although supported by experimental data, this hypothesis requires further examination (Koska et al.; 2015).

9.2 The effect of weight gain and hypoglycemia associated with diabetes mellitus therapy and its outcome on cardiovascular system

Hypoglycemia is a common problem in patients with DM who need to be treated with insulin or sulfonylureas. Hypoglycemia, especially when severe, is a powerful stimulant of the sympathetic nervous system, which may trigger adverse CV events, such as cardiac arrhythmias, sudden cardiac arrest, and acute MI. Prolongation of the QT interval, ventricular arrhythmias, and impaired autonomic function are also associated with hypoglycemic episodes (O'Keefe et al.; 2011). Joseph and Donner (2015) suggested that catecholamine elevations and hypokalemia potentiate the arrhythmogenic effect of QT prolongation and also demonstrated that hypokalemia occurred in patients with severe hypoglycemia and in T2DM patients placed on hyperinsulinemic glucose clamp in emergency room. Moreover, in 25 T1DM patients who were monitored by 24 hour electrocardiogram and continuous glucose measurements, bradycardia and rhythm disturbances including ventricular ectopics, atrial ectopics and P wave abnormalities were discovered in 62% of nocturnal hypoglycemia episodes. Other studies have examined the relationship between hypoglycemia and CV risk in patients with T2DM. An evaluation of the 11,140 patients in the ADVANCE trial found that a prior episode of severe hypoglycemia was associated with a 2.88-fold increased risk of macrovascular event and a 2.68-fold increased risk of cardiovascular death (Joseph and Donner; 2015).

Hypoglycemia is also pro-inflammatory and can increase the risk of plaque inflammation, rupture, and CV events. Severe hypoglycemia in the course of an aggressive glycemic control strategy may prevent the CV benefits of improved glycemic control. This may occur in patients who are predisposed to adverse CV events, such as persons with significant atherosclerosis and/or structural heart disease, LV hypertrophy or systolic and/or diastolic dysfunction. For this reason, patients with long-lasting T2DM and/or existing CV disease may be more susceptible to the cardiotoxicity induced by hypoglycemia (O'Keefe et al.; 2011).

9.3 Sulphonylurea treatment and its assocation with all-cause and cardiovascular mortality

Sulphonylureas (SUs) are a well proved oral therapy for the reduction of blood glucose levels in patients with T2DM. SUs are used not only in combination with metformin, but also as

monotherapy. After the initiation of treatment, SUs effectively lower haemoglobin A_{1c} (HbA_{1c}) levels by approximately 1%–1.5%, similar to metformin. SUs are cheap medicines, which is one of the reasons for their widespread use despite newer treatment options that have no risk of causing hypoglycaemia and the advantage of absence of weight gain. Several studies provide evidence for an increased risk for CV mortality in SU-treated T2DM patients. According to the results of the University Group Diabetes Program (UGDP) study the SU tolbutamide is associated with increased CV mortality. Although the 'United Kingdom Prospective Diabetes Study' (UKPDS) did not identify an effect of SU monotherapy on CV mortality, but patients treated with SUs in combination with metformin were found to have a significantly increased risk of diabetes-related mortality compared to metformin mono-therapy. A recent cohort study from Italy also reported an increased risk of macrovascular disease, which progressively increased as the compliance with SU therapy increased, indicating a direct effect of these agents on patient outcome. The pathophysiological effects of SUs on patients' CV risk and mortality have not been fully elucidated, but there are at least four different pathways that could explain these findings. One possibility could be weight gain during SU therapy, especially an increase of the visceral fat, and this has been shown to increase IR and to deteriorate several CV risk markers such as lipid profile and high-sensitivity CRP. Moreover, this may cause high BP and a significant increase in CV morbidity and mortality. A further possibility is that SU treatment not only stimulates insulin but also proinsulin release. While the insulin/proinsulin ratio was introduced as a marker for beta cell functionality and the capability of the beta cell to convert intact proinsulin into insulin and C-peptide, the absolute plasma levels of intact proinsulin were shown to be predictive of CV risk in patients with and without diabetes. Third, SUs have been shown to block the process of ischaemic preconditioning, an endogenous mechanism that protects the heart from ischaemic injury. Moreover, some SUs like tolbutamide, chlorpropamide, gliclazide and glipizide have a high selectivity for the pancreatic SU receptors, while others like glibenclamide (glyburide) and glimepiride also bind to SU receptors on myocardial muscle cells. The latter group of SUs would be expected to affect myocardial function and this has suggested that different types of SUs may differ in their association with CV mortality. Gliclazide, for example, showed no association with CV mortality, whereas glimepiride was associated with an increased risk. However, a smaller cohort analysis found no differences in mortality between users of pancreatic-specific and non-pancreatic-specific SUs. In a retrospective analysis of electronic health-care records derived from a clinical data repository at the Cleveland Clinic, treatment with glipizide, glyburide and glimepiride all

resulted in a significantly increased mortality rate compared with metformin treatment. However, in this study, the glimepiride arm had a slightly lower mortality rate than the other SUs in the subgroup of patients with a history of CAD. Also hypoglycaemia is a common side effect of SU therapy. According to the recent large-scale studies (ACCORD, ADVANCE and VADT) T2DM patients who experience severe hypoglycaemic episodes are at an increased risk of all-cause and CV mortality. During acute hypoglycaemia, electrocardiogram (ECG) abnormalities and symptoms of ischaemia may occur; in particular, prolonged QTc intervals have been reported. These pathophysiological pathways – accumulation of visceral fat, rise in proinsulin levels, and inhibition of ischaemic preconditioning and higher frequency of hypoglycaemia – may contribute to the increased mortality risk during SU treatment. According to a new common position statement of the European Association for the Study of Diabetes (EASD) and the American Diabetes Association (ADA), glucose lowering treatments in T2DM patients should be done within risks reduction strategy, especially in older patients (>65 years) or patients with an unfavorable CV risk profile. Treatments associated with weight gain or increased risk of hypoglycaemia should be considered with caution. Based on these considerations, the risks and benefits of SU treatment should be carefully evaluated for each individual patient (Forst et al.; 2013).

9.4 Insulin and cardiovascular outcomes

Exogenous insulin therapy is the most effective treatment for hyperglycemia in T1DM and also in poorly controlled T2DM patients; its use is mostly associated with excessive weight gain. The Diabetes Control and Complications Trial (DCCT) showed that weight gain related to insulin therapy was greater in patients receiving intensified intervention than in those receiving conventional intervention, and that not all types of insulin treatment are equally prone to cause weight gain. Home et al. (2014) showed that the weight gain, which was associated with insulin therapy despite the intensive glycemic control, was modest with 2.1 kg more than on the oral regimen, and the rate of hypoglycemia requiring assistance was modest (1% per year; <10% per year for non severe confirmed hypoglycemia). There was no evidence of increased risk of malignancy or other serious adverse events. Insulin detemir treatment, a basal insulin analog, has been shown to cause no weight gain in patients with T1DM, comparing with NPH insulin, and lower weight gain in T2DM patients. A myristic fatty-acid chain which is attached to the B-terminal of the insulin molecule results in reversible albumin binding and prolongation time in the subcutaneous depot and also in the

circulation. The underlying mechanism that shows advantage of insulin detemir has not been fully identified, but it could mediate its weight-sparing effects by changing the energy intake rather than energy expenditure, which may be mediated by a direct or indirect effect of insulin detemir on the hormones that control satiety. Moreover, it reduced blood glucose variability and reduced the risk of hypoglycemia compared with treatment with NPH insulin; so patients are avoiding weight gain by reducing snacking (Zachariah et al.; 2011).

9.5 Thiazolidinediones and Cardiovascular outcome

TZDs or glitazones are PPARγ modulators; they increase the sensitivity of muscle, fat, and liver to endogenous and exogenous insulin and thus are called insulin sensitizers. The TZDs have a more durable effect on glycemic control. The most common adverse effects associated with TZDs are weight gain and fluid retention leading to peripheral edema and a twofold increased risk for CHF (Nathan; 2009). Some studies have shown that there is an increase in adiposity, especially subcutaneous, with some reduction in visceral fat. The TZDs may either improve (pioglitazone) or have a neutral (rosiglitazone) effect on blood lipid profiles. According to Schernthaner et al. (2013) TZDs attenuate the blood levels of proinflammatory mediators in patients with T2DM, including CRP, IL-6, CD40L, monocyte chemoattractant Protein-1, and metalloproteinase-9. They also increase levels of the vascular-protective adipokine adiponectin and improve the circulating levels and functional activity of angiogenic endothelial progenitor cells. These findings are approved clinically by evidence of improved endothelial function, reduced carotid intima-media thickness, and improvements in stenosis after coronary artery stent implantation in patients treated with TZDs (Schernthaner et al.; 2013).

Several meta-analyses have suggested a 30–40% relative increase in risk for MI with rosiglitazone**.** However, compared with placebo the Prospective Pioglitazone Clinical Trial in macrovascular events (PROactive) did not show significant effects of pioglitazone on the primary CVD outcome (Nathan; 2009)**.** Although meta-analyses have suggested a possible beneficial effect of pioglitazone on CVD risk**,** caution in using either TZD is required, as they are both associated with increased risks of fluid retention and CHF. Currently, in the U.S., the TZDs are approved for use in combination with metformin, sulfonylureas, glinides, and insulin (Nathan; 2009)**.** Edema occurs in ~5% of patients treated with pioglitazone in monotherapy or in oral combination therapy and in ~10% of patients treated with TZDs in combination with insulin. Edema rate may be the cause of contraindication to pioglitazone,

but a recent large observational study demonstrated that edema was rarely the cause (0.9% of 12,772 patients) of withdrawal of pioglitazone therapy. The underlying mechanism of edema and CHF exacerbation might be due to fluid retention and plasma volume expansion and that pioglitazone activation of PPARγ receptors in the distal nephron increases sodium reabsorption through the epithelial Na^+ channel. In humans, pioglitazone treatment has led to decreased urine sodium excretion and also to increased plasma renin and aldosterone levels. Increased vasodilation and increased vascular permeability may also contribute to edema (Schernthaner et al.; 2013).

FDA restricted prescription of rosiglitazone to healthcare providers and patients, whereas the drug was withdrawn from the European market due to deterioration of MI. Cardiac morbidity and mortality in association with pioglitazone is not affected or even slightly reduced**.** Several studies demonstrated that pioglitazone led to increased risk of bladder cancer. So, it should not be prescribed to newly diagnosed diabetic patients anymore and only retained in patients who benefit from PPAR*γ*-activating drugs (Düfer et al.; 2013)**.**

10. CONCLUSION

A number of studies on CVD in T1DM demonstrated that better glycemic control reduces the incidence of atherosclerosis in T1DM. The management of CVD risk factors and blood glucose control has a positive effect on CVD event rates. Understanding the cellular and molecular pathophysiology is a challenging area of research. More insight is needed into the development of atherosclerotic lesions, and knowledge of the clinical role of inflammatory markers in DM and CVD prediction and management. Moreover, it is important to distinguish contributors to macrovascular disease from those that promote microvascular disease. Studies on inflammation process and genetically based pathways are hot topics of research along with tests for preclinical disease. Acceleration of understanding the underlying mechanisms will facilitate discovery of beneficial treatments for diabetic patients to reduce the risks of morbidity and mortality. Much work needs to be done to improve our understanding of DM and to help ameliorate the CVD effects of diabetes. People with either T1 or T2DM are at increased risk for CVD and have worse outcomes after surviving a CVD event. In recent years there have been major advances of the influence of risk factors for CVD in DM. The major risk factors for CHD in patients with diabetes are duration of disease, smoking,

hypertension, renal disease (macroalbuminuria and renal insufficiency) and dyslipidemia. This knowledge should lead to the development of more effective therapeutic strategies to prevent cardiovascular events. Lifestyle modifications and medical interventions will delay or prevent the development of CVD in people with diabetes and allow them to live healthier and longer lives. Optimal targets for glycemic management need to be better understood, and safe and effective therapeutics developed in order to control this disease.

Intense research is required to elucidate the impact of genetic changes in DM. This could lead to the development of new therapeutic strategies for patients suffering from DM. Research should concentrate on the genetic factors that lead to dysfunction and failure of islet, particularly those acquired at an early age. Epigenetic regulation of metabolic genes may be one of the fields of research.

A lot of clinical trials are ongoing to evaluate CV outcomes with promising new antidiabetic drugs. A large number of patients participate in trials testing DPP-4 inhibitors, GLP-1 agonists, SGLT-2 agents, and a GPR40 agonist.

Success in reducing the CV risks in addition to glucose-lowering remains the main focus in the development of new diabetes drugs. But also aggressive control of other modifiable risk factors such as hypertension, smoking, and hyperlipidemia remains critical to reduce CV risk in diabetic patients.

11. ABSTRACT

The global incidence and prevalence of type 2 diabetes mellitus (T2DM) is increasing and is primarily associated with age, ethnicity, genetics, smoking, obesity, and physical inactivity. Diabetes-related complications, such as cardiovascular disease, kidney disease, neuropathy, retinopathy, and peripheral vascular disease consider significant cause of increased morbidity and mortality among people with diabetes.

This review highlights the available data on cardiovascular diseases (CVD) in DM; although the increased rate of CVD in DM is well documented, understanding the cellular and molecular pathophysiology is a hot topic in research. Care should be taken to distinguish contributors to macrovascular diseases from those that promote microvascular diseases. More insight is needed into the development of atherosclerotic lesions, knowing the clinical role of inflammatory markers in DM and CVD prediction. It has been attempted to summarize the evidence supporting lifestyle and medical interventions that will delay or prevent the development of CVD in people with diabetes.

Available data on the control of the main risk factors show that adjustment of blood sugar with therapy that includes an agent that improves insulin sensitivity, such as metformin is more effective in counteracting microvascular damage than in preventing major cardiovascular events, which requires a more comprehensive approach to the whole constellation of risk factors. These include lipid-lowering therapy with statins, blood pressure control, and antiplatelet therapy in patients with increased cardiovascular risk scores.

This review will also evaluate the effects on cardiovascular outcomes of specific glucose-lowering strategies or drugs which have shown no significant cardiovascular benefit or even an increased risk of death or heart failure, and which also have shown a reno-protective effect besides the anti-hyperglycemic effects of SGLT2 inhibitors, DPP IV inhibitors or incretin based agents.

Further work is needed to understand the impact of epigenetic changes of complications of DM, which can lead to the development of new therapeutic strategies and much work remains to be done to improve our understanding of DM and to help ameliorate the CVD effects of this widespread disease.

12. ZUSAMMENFASSUNG

Die Wahrscheinlichkeit an Diabetes mellitus Typ 2 (T2DM) zu erkranken ist weltweit im Ansteigen begriffen und ist global von zunehmender Bedeutung. T2DM steht in Zusammenhang mit Alter, Ethnizität, genetischen Faktoren, Rauchen, Fettleibigkeit und körperlicher Inaktivität. Diabetiker erleiden häufiger kardiovaskuläre Erkrankungen (CVD), Nierenschäden, Neuropathie, Retinopathie und periphere Gefäßerkrankungen, die zu erhöhter Morbidität und auch Mortalität führen.

In dieser Übersichtsarbeit werden die Gründe und Ursachen für CVD aufgezeigt. Obwohl das vermehrte Auftreten von CVD bei Diabetikern gut dokumentiert ist, ist der zugrunde liegende zelluläre und molekulare Mechanismus noch nicht vollständig aufgeklärt und wird deshalb intensiv beforscht. Es muss zwischen den Mechanismen, die makrovaskuläre oder mikrovaskuläre Erkrankungen auslösen oder fördern, unterschieden werden. Insbesondere die Entwicklung von atherosklerotischen Läsionen und die Rolle von Biomarkern bei Entzündungen als Indikatoren für die Entstehung von DM und/oder CVD sind von Interesse. In der Arbeit wird auch die Rolle von Lebensstilfaktoren und medizinischen Interventionen beschrieben, um CVD bei Diabetikern zu verhindern bzw. zumindest hinauszuzögern.

Verfügbare Daten über die wichtigsten Risikofaktoren zeigen, dass die Kontrolle des Blutzuckerspiegels vorallem in der Prävention von mikrovaskulären Komplikationen von Bedeutung ist, jedoch weniger Auswirkungen auf makrovaskuläre Erkrankungen hat. Letztere benötigen eine umfassendere Therapie mit Korrektur der Lipidstoffwechselstörung, Senkung des Blutdrucks und Thrombozytenaggregationshemmung.

Weiters wird die Wirkung von spezifischen Blutglucose senkenden Maßnahmen sowie Arzneistoffen und deren Effekt auf die Morbiditäts- und Mortalitätsrate beschrieben. Insbesondere wird auf die renoprotektive Wirkung und die Wirksamkeit neuerer Arzneistoffklassen wie SGLT2 Inhibitoren, DPP IV Inhibitoren oder Inkretin-Mimetika eingegangen.

Weitere Forschung ist notwendig, um epigenetische Faktoren bei der Entstehung von CVD-Komplikationen bei Diabetikern zu eruieren. Diese Erkenntnisse könnten möglicherweise zur Entwicklung neuer therapeutischer Ansätze führen.

13. ABBREVIATIONS

ACE	angiotensin-converting enzyme
AF	atrial fibrillation
AGEs	advanced glycation end products
AMPK	adenosine monophosphate-activated protein kinase
ARB	angiotensin-receptor blocker
BMI	Body mass index
BP	blood pressure
CAD	coronary artery disease
CAN	cardiovascular autonomic neuropathy
CHD	coronary heart disease
CHF	congestive heart failure
CPT-1	carnitine palmityl transferase 1
CPVT	catecholaminergic polymorphic ventricular tachycardia
CRP	C-reactive protein
CTGF	connective tissue growth factor
CV	cardiovascular
CVD	cardiovascular disease
DCM	diabetic cardiomyopathy
DKD	diabetic kidney disease
DM	diabetes mellitus
DPP-IV	dipeptidyl peptidase-IV
eNOS	endothelial nitric oxide synthase
FAO	fatty acid oxidation
FFAs	free fatty acids
GLP-1	glucagon-like peptide-1
GFR	glomerular filtration rate
HDL	high-density lipoprotein
HF	heart failure
HRV	reduced heart rate variation
ICD	implantable cardioverter defibrillator
IGT	impaired glucose tolerance
IHD	ischaemic heart disease

IL-6	interleukin-6
iNOS	inducible nitric oxide synthase
IR	insulin resistance
KKS	kallikrein–kinin system
LCAT	lecithin-cholesterol acyltransferase
LDL	low-density lipoprotein
LQTS	ong QT syndrome
LV	left ventricle
LVEF	left ventricular ejection fraction
MetS	metabolic syndrome
MI	myocardial infarction
MMP-9	matrix metalloproteinase-9
NF-κB	nuclear transcription factor-κB
NIDDM	non-insulin dependent DM
NO	nitric oxide
PAD	peripheral artery disease
PAI-1	plasminogen activator inhibitor 1
PPAR-γ	peroxisome proliferator-activated receptor-γ
PVD	peripheral vascular disease
QTc	corrected QT for heart rate
RAGE	receptor for advanced glycated end products
RAAS	renin-angiotensin-aldosteron system
ROS	reactive oxygen species
SDF-1a	stromal cell derived factor-1a
SGLT-2	sodium glucose cotransporter-2
SNS	sympathetic nervous system
SUs	sulphonylureas
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
TZDs	thiazolidinediones
VF	ventricular fibrillation
VLDL	very low-density lipoprotein
VSMCs	vascular smooth muscle cells
VT	ventricular tachycardia

14. REFERENCES

American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care (2004) 1:S5-S10.

Asghar O, Alam U, Hayat SA, Aghamohammadzadeh R, Heagerty AM, Malik RA. Obesity, diabetes and atrial fibrillation; epidemiology, mechanisms and interventions. Curr Cardiol Rev (2012);8(4):253-264.

Banerjee D, Biggs ML, Mercer L, Mukamal K, Kaplan R, Barzilay J, Kuller L, Kizer JR, Djousse L, Tracy R, Zieman S, Lloyd-Jones D, Siscovick D, Carnethon M. Insulin Resistance and Risk of Incident Heart Failure: Cardiovascular Health Study. Circ Heart Fail (2013);6(3): 364–370.

Barbosa MPT, Rocha MOdC, Barbosa de Oliveira A, Lombardi F, Ribeiro ALP. Efficacy and safety of implantable cardioverter-defibrillators in patients with Chagas disease. Europace (2013);15(7):957-962.

Barbosa MPT, Carmo AALd, Rocha MOdC, Ribeiro ALP. Ventricular arrhythmias in Chagas disease. Rev Soc Bras Med Trop (2015);48(1):4-10.

Beckman J, Paneni F, Cosentino F, Creager MA. Diabetes and vascular disease: pathophysiology, clinical consequences, and medical therapy: part II. Eur Heart J (2013);34(31):2444-2452**.**

Beckman JA, Creager MA, Libby P. Diabetes and Atherosclerosis, Epidemiology, Pathophysiology, and Management, JAMA (2002);287(19):2570-2581.

Bell DSH. Heart Failure: The frequent, forgotten, and often fatal complication of diabetes, Diabetes Care (2003);26(8):2433-2441.

Bello-Rodriguez BM, Sanchez-Cruz G, Delgado-Bustillo F, Asiama G. The relationship between metabolic syndrome and target organ damage in Ghanaian with stage-2 hypertension. Ghana Med J (2013);47(4):189-96.

Bhatt DL, Fox KAA, Hacke W, Berger PB, Black HR, Boden WE, Cacoub P, Cohen EA, Creager MA, Easton JD, Flather MD, Haffner SM, Hamm CW, Hankey GJ, Johnston SC, Mak KH, Mas JL, Montalescot G, Pearson TA, Steg PG, Steinhubl SR, Weber MA, Brennan DM, Fabry-Ribaudo L, Booth J, Topol EJ, for the CHARISMA Investigators. Clopidogrel and Aspirin versus Aspirin Alone for the Prevention of Atherothrombotic Events. N Engl J Med (2006);354:1706-1717.

Bradberry JC Peripheral arterial disease: pathophysiology, risk factors, and role of antithrombotic therapy. J Am Pharm Assoc (2004);44(2 Suppl 1):S37-44.

Braunwald E (1980), Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine. Bonow RO, Mann DL, Zipes DP, Libby P (eds), Elsevier, pp 456-459.

Buse JB, Ginsberg HN, Bakris GL, Clark NG, Costa F, Eckel R, Fonseca V, Gerstein HC, Grundy S, Nesto RW, Pignone MP, Plutzky J, Porte D, Redberg R, Stitzel KF, Stone NJ; Primary prevention of cardiovascular diseases in people with diabetes mellitus: a scientific statement from the American Heart Association and the American Diabetes Association. Diabetes Care (2007):30(1):162-172.

Ceriello A. Cardiovascular effects of acute hyperglycaemia: pathophysiological under pinnings. Diab Vasc Dis Res (2008);5(4):260-268.

Chang SH, Wu LS, Chiou MJ, Liu JR, Yu KH, Kuo CF, Wen MS, Chen WJ, Yeh YH, See LC. Association of metformin with lower atrial fibrillation risk among patients with type 2 diabetes mellitus: a population-based dynamic cohort and in vitro studies. Cardiovasc Diabetol (2014);13:123.

Chao EC. SGLT-2 Inhibitors: A New Mechanism for Glycemic Control. Clinical Diabetes (2014);32(1):4-11.

Connelly KA , Zhang Y, Advani A, Advani SL, Thai K, Yuen DA, Gilbert RE. DPP-4 inhibition attenuates cardiac dysfunction and adverse remodeling following myocardial infarction in rats with experimental diabetes. Cardiovasc Ther (2013);31(5):259-267.

Corriere M, Rooparinesingh N, Kalyani RR. Epidemiology of Diabetes and Diabetes Complications in the Elderly: An Emerging Public Health Burden. Curr Diabetes Rep (2013);13: 805-813.

De Ferranti SD, de Boer IH, Fonseca V, Fox CS, Golden SH, Lavie CJ, Magge SN, Marx N, McGuire DK, Orchard TJ, Zinman B, Eckel RH. Type 1 diabetes mellitus and cardiovascular disease: a scientific statement from the American Heart Association and American Diabetes Association. Diabetes Care (2014);37(10):2843-2863.

DeFronzo RA. Pharmacologic Therapy for Type 2 Diabetes Mellitus. Ann Intern Med (1999);131(4):281-303.

Dimitropoulos G, Tahrani AA , Stevens MJ. Cardiac autonomic neuropathy in patients with diabetes mellitus. World J Diabetes (2014);5(1):17-39.

Dries DL, Sweitzer NK, Drazner MH, Stevenson LW, Gersh BJ. Prognostic impact of diabetes mellitus in patients with heart failure according to the etiology of left ventricular systolic dysfunction. J Am Coll Cardiol (2001);38(2):421-428.

Düfer M , Noack K, Edalat A, Krippeit-Drews P, Drews G. Glitazones exert multiple effects on β-cell stimulus-secretion coupling. Mol Pharmacol (2013);83(1):51-60.

Engström G , Stavenow L, Hedblad B, Lind P, Eriksson KF, Janzon L, Lindgärde F. Inflammation-sensitive plasma proteins, diabetes, and mortality and incidence of myocardial infarction and stroke: a population-based study. Diabetes (2003);52(2):442-7.

Eurich DT, Weir DL, Majumdar SR, Tsuyuki RT, Johnson JA, Tjosvold L, Vanderloo SE, McAlister FA. Comparative Safety and Effectiveness of Metformin in Patients With Diabetes Mellitus and Heart Failure. Circulation: Heart Failure. (2013);6:395-402.

Forst T, Hanefeld M, Jacob S, Moeser G , Schwenk G, Pfützner A, Haupt A. Association of sulphonylurea treatment with all-cause and cardiovascular mortality: A systematic review and meta-analysis of observational studies . Diab Vasc Dis Res (2013);10(4):302-314.

Gilbert RE. Sodium-glucose linked transporter-2 inhibitors: potential for renoprotection beyond blood glucose lowering? Kidney Int (2014);86(4):693-700.

Goldfine AB, Beckman JA. Life and death in Denmark: lessons about diabetes and coronary heart disease. Circulation (2008);117(15):1914-1917.

Grace AA, Roden DM. Systems biology and cardiac arrhythmias. Lancet 2012;380(9852): 1498–1508.

Grundy SM, Benjamin IJ, Burke GL, Chait A, Eckel RH, Howard BV, Mitch W, Smith SC Jr, Sowers JR. Diabetes and cardiovascular disease: a statement for healthcare professionals from the American Heart Association. Circulation (1999)7;100(10):1134-46.

Grundy SM. Pre-diabetes, Metabolic Syndrome, and Cardiovascular Risk. J Am Coll Cardiol 2012;59(7):635-643.

Gutzwiller JP, Tschopp S, Bock A, Zehnder CE, Huber AR, Kreyenbuehl M, Gutmann H, Drewe J, Henzen C, Goeke B, Beglinger C. Glucagon-like peptide 1 induces natriuresis in healthy subjects and in insulin-resistant obese men. J Clin Endocrinol Metab (2004);89(6):3055-3061.

Ha KH, Kim DJ. Association of metabolic syndrome with coronary artery calcification. Korean J Intern Med. (2015);30(1):29-31.

Haffner SM, Greenberg AS, Weston WM, Chen H, Williams K, Freed MI. Effect of Rosiglitazone Treatment on Nontraditional Markers of Cardiovascular Disease in Patients With Type 2 Diabetes Mellitus (2002);106:679-684.

Hartog JWL, Voors AA, Bakker SJL, Smit AJ, van Veldhuisen DJ. Advanced glycation end-products (AGEs) and heart failure: Pathophysiology and clinical implications, Eur J Heart Fail (2007);9(12):1146–1155.

Hawkins JW, Dunn MI. Ischemic Heart Disease: The Old Versus the New. J Am Coll Cardiol (1990);16(2):311-312.

Hayashino Y, Jackson JL, Hirata T, Fukumori N, Nakamura F, Fukuhara S, Tsujii S, Ishii H. Effects of exercise on C-reactive protein, inflammatory cytokine and adipokine in patients with type 2 diabetes: a meta-analysis of randomized controlled trials. Metabolism (2014);63(3):431-440.

Hirshberg B, Raz I. Impact of the U.S. Food and Drug Administration Cardiovascular Assessment Requirements on the Development of Novel Antidiabetes Drugs. Diabetes Care (2011); 34(Suppl 2): S101–S106.

Home P, Riddle M, Cefalu WT, Bailey CJ, Bretzel RG, del Prato S, Leroith D, Schernthaner G, van Gaal L, Raz I. Insulin Therapy in People With Type 2 Diabetes: Opportunities and Challenges? Diabetes Care (2014);37(6):1499-1508.

Huang B, Yang Y, Zhu J, Liang Y, Zhang H, Tian L, Shao X, Wang J. Clinical Characteristics and Impact of Diabetes Mellitus on Outcomes in Patients with Nonvalvular Atrial Fibrillation. Yonsei Med J (2015);56(1):62-71.

Hugenholtz PG, Goldman BS (eds). Unstable Angina, Current Concept and Management. Schattauer, Stuttgart (1985), pp 151.

Inzucchi SE, Zinman B, Wanner C, Ferrari R, Fitchett D, Hantel S, Espadero RM, Woerle HJ, Broedl UC, Johansen OE. SGLT-2 inhibitors and cardiovascular risk: proposed pathways and review of ongoing outcome trials.Diab Vasc Dis Res (2015);12(2):90-100.

Iyngkaran P, Anavekar N, Majoni W, Thomas MC., The role and management of sympathetic overactivity in cardiovascular and renal complications of diabetes. Diabetes Metab (2013);39(4):290-298.

Janka HU , Michaelis D. Epidemiology of diabetes mellitus: prevalence, incidence, pathogenesis, and prognosis. Z Arztl Fortbild Qualitätssich (2002);96(3):159-65.

John RM, Tedrow UB, Koplan BA, Albert CM, Epstein LM, Sweeney MO, Miller AL, Michaud GF, Stevenson WG. Ventricular arrhythmias and sudden cardiac death. Lancet (2012);380:1520–1529.

Joseph JJ , Donner TW. Long-term insulin glargine therapy in type 2 diabetes mellitus: a focus on cardiovascular outcomes. Vasc Health Risk Manag (2015);11:107-116.

Joshi M, Kotha SR, Malireddy S, Selvaraju V, Satoskar AR, Palesty A, McFadden DW, Parinandi NL, Maulik N. Conundrum of pathogenesis of diabetic cardiomyopathy: role of vascular endothelial dysfunction, reactive oxygen species, and mitochondria. Mol Cell Biochem (2014);386(1-2):233-249.

Kassi E, Pervanidou P, Kaltsas G, Chrousos G. Metabolic syndrome: definitions and controversies. BMC Med (2011);5(9):48.

Khan MA, Deaton C, Rutter MK, Neyses L, Mamas MA. Incretins as a novel therapeutic strategy in patients with diabetes and heart failure. Heart Fail Rev (2013);18(2):141-148 .

Kolluru GK, Bir SC, Kevil CG. Endothelial dysfunction and diabetes: effects on angiogenesis, vascular remodeling, and wound healing. Int J Vasc Med. (2012):918267.

Koska J, Sands M, Burciu C, Reaven P. Cardiovascular effects of dipeptidyl peptidase-4 inhibitors in patients with type 2 diabetes. Diab Vasc Dis Res (2015);12(3):154-163.

LevyAP. Genetics of diabetic cardiovascular disease: identification of a major susceptibility gene. Acta Diabetol (2003);40:S330-333.

Levy AP. Haptoglobin: A Major Susceptibility Gene for Diabetic Cardiovascular Disease. Isr Med Assoc J (2004);6:308-310.

Li X , Ren H, Xu ZR, Liu YJ, Yang XP, Liu JQ. Prevalence and risk factors of prolonged QTc interval among Chinese patients with type 2 diabetes. Exp Diabetes Res (2012):234084.

Lim GB. Diabetes: Cardiovascular safety of 'gliptin' therapy. Nat Rev Cardiol (2013);10(11): 616.

Lionetti V, Stanley WC, Recchia FA. Modulating fatty acid oxidation in heart failure. Cardiovasc Res (2011);90(2):202-209.

Liu WJ, Xie SH, Liu YN, Kim W, Jin HJ, Park SK, Shao JM, Park TS. Dipeptidyl Peptidase IV Inhibitor Attenuates Kidney Injury in Streptozotocin-Induced Diabetic Rats. J Pharmacol Exp Ther (2012);340(2):248-255.

Lorber D. Importance of cardiovascular disease risk management in patients with type 2 diabetes mellitus. Diabetes Metab Syndr Obes (2014);23;7:169-83.

Lüscher TF, Creager MA, Beckman JA, Cosentino F. Diabetes and Vascular Disease Pathophysiology, Clinical Consequences, and Medical Therapy: Part II. Circulation (2003)108:1655-1661.

Mahalle N, Garg MK, Naik SS, Kulkarni MV. Association of metabolic syndrome with severity of coronary artery disease. Indian J Endocrinol Metab (2014);18(5):708–714.

Martins e Silva J (2006). Ischemic myocardial disease as an example of a thrombotic event. A historical note. Rev Port Cardiol (2006);25(5):537-43.

Martín-Timón I, Sevillano-Collantes C, Segura-Galindo A, Del Cañizo-Gómez FJ. Type 2 diabetes and cardiovascular disease: Have all risk factors the same strength? World J Diabetes (2014);5(4):444-470.

McDonald CG, Majumdar SR, Mahon JL, Johnson JA. The effectiveness of beta-blockers after myocardial infarction in patients with type 2 diabetes. Diabetes Care (2005);28(9):2113-2117.

Mytas DZ, Stougiannos PN, Zairis MN, Foussas SG, Pyrgakis VN, Kyriazis IA. Diabetic myocardial disease: pathophysiology, early diagnosis and therapeutic options. J Diabetes Complications (2009);23(4):273–282.

Nadal JF, Gutiérrez PC. Type 2 diabetes mellitus and cardiovascular risk factors: is comprehensive treatment required? Med Clin (Barc) (2013);141 Suppl 2:7-13.

Nakou ES, Mavrakis H, Vardas PE. Are diabetic patients at increased risk of arrhythmias? Hellenic J Cardiol (2012);53(5):335-339.

Nashar K, Egan BM. Relationship between chronic kidney disease and metabolic syndrome: current perspectives. Diabetes Metab Syndr Obes (2014);18(7):421-435.

Nasir S, Aguilar D. Congestive Heart Failure and Diabetes: Balancing Glycemic Control with Heart Failure Improvement. Am J Cardiol (2012);110(9 Suppl):50B–57B.

Nathan DM. The Role of Glycemia Management in the Prevention of Cardiovascular Disease—Starting Over? Ann Intern Med. (2009);151(12):888-889.

Nathanson D, Ullman B, Löfström U, Hedman A, Frick M, Sjöholm Å, Nyström T. Effects of intravenous exenatide in type 2 diabetic patients with congestive heart failure: a double-blind, randomised controlled clinical trial of efficacy and safety. Diabetologia (2012);55(4):926-935.

O'Donnell ME, Reid JA, Lau LL, Hannon RJ, Ulster BL. Optimal Management of Peripheral Arterial Disease for the Non-Specialist, Med J. 2011 Jan; 80(1): 33–41.

O'Keefe JH, Abuannadi M, Lavie CJ, Bell DSH. Strategies for Optimizing Glycemic Control and Cardiovascular Prognosis in Patients With Type 2 Diabetes Mellitus. Mayo Clin Proc (2011);86(2):128–138.

Patel A, Chalmers J, Chaturvedi V, Currie R, Monaghan H, Neal B. Diabetes and vascular disease: a new international trial. Asian Cardiovasc Thorac Ann (2003);2:180-184.

Patel P, Macerollo A. Diabetes Mellitus: Diagnosis and Screening, Am Fam Physician (2010);81(7):863-870.

Pattyn N, Cornelissen VA, Toghi Eshghi SR, Vanhees L. The Effect of Exercise on the Cardiovascular Risk Factors Constituting the Metabolic Syndrome. Sports Med (2013); 43:121–133.

Peterson LR , McKenzie CR, Schaffer JE. Diabetic cardiovascular disease: getting to the heart of the matter. J Cardiovasc Transl Res (2012);5(4):436-445.

Rao AD, Shah RV, Garg R, Abbasi SA, Neilan TG, Perlstein TS, Di Carli MF, Jerosch-Herold M, Kwong RY, Adler GK. Aldosterone and myocardial extracellular matrix expansion in type 2 diabetes mellitus. Am J Cardiol (2013);112(1):73-8.

Raposeiras-Roubín S, Rodiño-Janeiro BK, Grigorian-Shamagian L, Seoane-Blanco A, Moure-González M, Varela-Román A, Álvarez E, González-Juanatey JR. Evidence for a role of advanced glycation end products in atrial fibrillation. Int J Cardiol (2012);157(3):397–402.

Rask-Madsen C, Kahn CR. Tissue-specific insulin signaling, metabolic syndrome and cardiovascular disease. Arterioscler Thromb Vasc Biol (2012);32(9):2052–2059.

Roguin A, Koch W, Kastrati A, Aronson D, Schomig A, Levy AP. Haptoglobin genotype is predictive of major adverse cardiac events in the 1 year period after percutaneous transluminal coronary angioplasty in individuals with diabetes. Diabetes Care (2003);26(9):2628-2631.

Romeo GR, Lee J, Shoelson SE. Metabolic syndrome, insulin resistance, and roles of inflammation-mechanisms and therapeutic targets. Arterioscler Thromb Vasc Biol (2012); 32(8):1771-1776.

Rosenwasser RF, Sultan S, Sutton D, Choksi R, Epstein BJ. SGLT-2 inhibitors and their potential in the treatment of diabetes. Diabetes Metab Syndr Obes (2013) 6:453-467.

Ruderman NB , Carling D, Prentki M, Cacicedo JM. AMPK, insulin resistance, and the metabolic syndrome. J Clin Invest (2013);123(7):2764-2772.

Rydén L, Grant PJ, Anker SD, Berne C, Cosentino F, Danchin N, Deaton C, Escaned J, Hammes HP, Huikuri H, Marre M, Marx N, Mellbin L, Ostergren J, Patrono C, Seferovic P, Uva MS, Taskinen MR, Tendera M, Tuomilehto J, Valensi P, Zamorano JL. ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD: the Task Force on diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and developed in collaboration with the European Association for the Study of Diabetes (EASD). Eur Heart J (2013);34(39):3035-3087.

Rydén L, Grant PJ, Anker SD, Berne C, Cosentino F, Danchin N, Deaton C, Escaned J, Hammes HP, Huikuri H, Marre M, Marx N, Mellbin L, Ostergren J, Patrono C, Seferovic P, Uva MS, Taskinen MR, Tendera M, Tuomilehto J, Valensi P, Zamorano JL. Task Force on diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC); European Association for the Study of Diabetes (EASD), ESC guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD - summary. Diab Vasc Dis Res (2014);11(3):133-173.

Satoh N , Ogawa Y, Usui T, Tagami T, Kono S, Uesugi H, Sugiyama H, Sugawara A, Yamada K, Shimatsu A, Kuzuya H, Nakao K. Antiatherogenic effect of pioglitazone in type 2 diabetic patients irrespective of the responsiveness to its antidiabetic effect. Diabetes Care (2003);26(9):2493-2499.

Schauer IE, Snell-Bergeon JK, Bergman BC, Maahs DM, Kretowski A, Eckel RH, Rewers M. Insulin Resistance, Defective Insulin-Mediated Fatty Acid Suppression, and Coronary Artery Calcification in Subjects With and Without Type 1 Diabetes The CACTI Study. Diabetes (2011);60:306–314.

Schernthaner G , Currie CJ, Schernthaner GH. Do we still need pioglitazone for the treatment of type 2 diabetes? A risk-benefit critique in 2013. Diabetes Care (2013);36 Suppl 2:S155-161.

Scirica BM, Bhatt DL, Braunwald E, Steg PG, Davidson J, Hirshberg B, Ohman P, Frederich R, Wiviott SD, Hoffman EB, Cavender MA, Udell JA, Desai NR, Mosenzon O, McGuire DK, Ray KK, Leiter LA, Raz I. Saxagliptin and Cardiovascular Outcomes in Patients with Type 2 Diabetes Mellitus. N Engl J Med (2013); 369:1317-1326.

Shargel L, Mutnick AH, Ewanson LN, Souney PF. Comprehensive Pharmacy Review (2004), Lippincott Williams and Wilkins, pp 787-808.

Singh BN, Dzau VJ, Vanhoutte PM, Woosley RL (eds). Cardiovasc Pharmacol Ther (1994) Churchill Livingstone, New York, pp 399-404.

Sokos GG, Nikolaidis LA, Mankad S, Elahi D, Shannon RP. Glucagon-Like Peptide-1 Infusion Improves Left Ventricular Ejection Fraction and Functional Status in Patients With Chronic Heart Failure. J Card Fail (2006);12(9):694–699.

Sotoye TDM, Maclean RA, Osaretin JO. Left ventricular dysfunction in normotensive type II diabetic patients in Port Harcourt, Nigeria. Vasc Health Risk Manag (2013);9:529–533.

Spallone V, Ziegler D, Freeman R, Bernardi L, Frontoni S, Pop-Busui R, Stevens M, Kempler P, Hilsted J, Tesfaye S, Low P, Valensi P. Cardiovascular autonomic neuropathy in diabetes: clinical impact, assessment, diagnosis, and management. Diabetes Metab Res Rev (2011);27(7):639-653.

Stolar MW. Defining and Achieving Treatment Success in Patients With Type 2 Diabetes Mellitus; Mayo Clin Proc. 2010 Dec; 85(12 Suppl): S50-S59.

Stratmann B , Tschöpe D. Atrial fibrillation and diabetes mellitus. Correlation, co-existence, and coagulation therapy. Herz. (2012);37(3):258-263.

Subbiah RN, Campbell TJ, Vandenberg JI. Inherited cardiac arrhythmia syndromes: What have they taught us about arrhythmias and anti-arrhythmic therapy? Proc Austr Physiol Pharmacol Soc (2004);34:133-140.

Trevisan R , Vedovato M, Tiengo A. The epidemiology of diabetes mellitus. Nephrol Dial Transplant (1998);13(Suppl 8):2-5.

Turner RC, Cull CA, Frighi V, Holman RR. Glycemic Control With Diet, Sulfonylurea, Metformin, or Insulin in Patients With Type 2 Diabetes Mellitus: Progressive Requirement for Multiple Therapies (UKPDS 49). UK Prospective Diabetes Study (UKPDS) Group. JAMA (1999);281(21):2005-2012.

Vinik AI , Maser RE, Mitchell BD, Freeman R. Diabetic autonomic neuropathy. Diabetes Care (2003);26(5):1553-1579.

Voulgari C, Papadogiannis D, Tentolouris N, Diabetic cardiomyopathy: from the pathophysiology of the cardiac myocytes to current diagnosis and management strategies, Vasc Health Risk Manag (2010);6:883-903.

Wändell P, Carlsson AC, Sundquist J, Johansson S-E, Bottai M, Sundquist K. Effects of prescribed antithrombotics and other cardiovascular pharmacotherapies on all-cause mortality in patients with diabetes and atrial fibrillation – a cohort study from Sweden using propensity score analyses. Diabetol Metab Syndr (2014);6(1):2.

Wang Y , Xuan YL, Hu HS, Li XL, Xue M, Cheng WJ, Suo F, Yan SH. Risk of ventricular arrhythmias after myocardial infarction with diabetes associated with sympathetic neural remodeling in rabbits. Cardiology (2012);121(1):1-9.

Wilson JF, Laine C, Goldmann D. In the clinic. Peripheral arterial disease. Ann Intern Med (2007);146(5):ITC3-1-ITC3-16.

Won K-B, Chang H-J, Sung J, Shin S, Cho I-J, Shim C-Y, Hong G-R, Kim YJ, Choi BW, Chung N. Differential association between metabolic syndrome and coronary artery disease evaluated with cardiac computed tomography according to the presence of diabetes in a symptomatic Korean population. BMC Cardiovasc Disord (2014);14: 105.

Wong AKF, Ruth S, Alzadjali MA, Ang DSC, Ogston S, Choy AM, Petrie JR, Struthers AD, Lang CC. The effect of Metformin on insulin resistance and exercise parameters in patients with heart failure. Eur J Heart Fail (2012);14(11):1303–1310.

Yadav D, Mishra M, Tiwari A, Bisen PS, Goswamy HM, Prasad GB. Prevalence of Dyslipidemia and Hypertension in Indian Type 2 Diabetic Patients with Metabolic Syndrome and its Clinical Significance. Osong Public Health Res Perspect (2014);5(3):169–175.

Zachariah S, Sheldon B, Shojaee-Moradie F, Jackson NC, Backhouse K, Johnsen S, Jones RH, Umpleby AM, Russell-Jones DL. Insulin detemir reduces weight gain as a result of reduced food intake in patients with type 1 diabetes. Diabetes Care (2011);34(7):1487-1491.

Zhang Q, Li G, Liu T. Receptor for advanced glycation end products (RAGE): Novel biomarker and therapeutic target for atrial fibrillation. Int J Cardiol (2013);168(5):4802-4804.

Zimmet P. The Global Epidemiology of Diabetes Mellitus. Tohoku J Exp Med (1983);141:41-54.

15. LEBENSLAUF

Rabab HAMID

Persönliche Daten:

Geburtsdaten	4. Oktober 1969 in Baghdad, Irak
Staatsbürgerschaft	Irak
Familienstand	verheiratet, zwei Kinder (14 und 12 Jahre alt)

Ausbildung:

1975 bis 1981	Grundschule
1981 bis 1987	Höhere Schule mit Matura
1987 bis 1992	Universität: Studium der Pharmazie in Baghdad

Weiterbildung

1998	Deutschkurs an der Universität Wien.
1999	Beginn der Nostrifizierung des Pharmaziestudiums an der Universität Wien.
2001	Nostrifizierung des Pharmaziestudiums in Abu Dhabi.
2008	Nostrifizierung des Pharmaziestudiums in Auckland, Neuseeland: Theoretischer Teil.
2010	General Business Englisch (Wifi) in Wien.
2011	Marketing Kompakt (Wifi) in Wien.
Seit Oktober 2014	Fortsetzung der Nostrifizierung in Wien

Berufliche Tätigkeit

1992 bis 1996	Krankenhaus Al-Jarrah, Baghdad: • Beratung des Ärzteteams für Medikation • Versorgung und Betreuung der Patienten mit Medikamenten • Herstellen von Salben und Tabletten
2004 bis 2006	Pharmazie, Abu Dhabi: • Selbständige Leitung der Filiale • Beratung und Verkauf von Medikamenten

Weitere Kenntnisse:

Arabisch (Mutter Sprache)
Deutsch (sehr gute Kenntnisse in Wort und Schrift)
Englisch (gute Kenntnisse in Wort und Schrift)