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Cardiac Dysfunction in Adolescents with Type 1 Diabetes Mellitus

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Iris Plani

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Assoz. Prof. Priv.-Doz. Dr.med. MMedSci PhD Nandu Goswami
Prof. Dr. Domenique Hansen

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Preword

“And now here is my secret, a very simple secret:
It is only with the heart that one can see rightly;
what is essential is invisible to the eye.”
—Antoine de Saint-Exupéry, The Little Prince

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Abbreviations

ALA	Alpha-Lipoic Acid
BMI	Body mass Index
CS	Circumferential Strain
DCM	Diabetic Cardiomyopathy
DM	Diabetes Mellitus
EF	Ejection Fraction
Fas-L	Factor Fas-Ligand
GAD- Antibodies	Glutamic Acid Decarboxylase Autoantibodies
GAD- Antibodies Test	Glutamic Acid Decarboxylase Autoantibodies Test
GLUT2	Glucose Transporters
HbA1c	Glycosylated Haemoglobin
HF	Heart Failure
OGTT	Oral Glucose Tolerance Test
IA-2- Antibodies	Autoantibodies against Tyrosine Phosphatase
IAAs- Antibodies	Autoantibodies against Insulin Molecule
IR	Insulin Resistance
IVSd	Intra Ventricular Septum Dimension
LA	Left Atrium
LADA	Latent Autoimmune Diabetes of Adulthood
LAP	Mean Left Atrium Pressure
LS	Longitudinal Strain
LV	Left Ventricular
LVEDP	Left Ventricle End Diastolic Pressure
LVH	Left Ventricle Hypertrophy
LVM	Left Ventricle Mass
LVW	Left Ventricle Wall
MDA	Malondialdhyde
MMP-2	Matrix Metallproteinase 2
MV	Mitral Valve
NO	Nitric Oxide
PCWP	Mean Capillary Wedge Pressure
T1D	Type 1 Diabetes Mellitus
T2D	Type 2 Diabetes Mellitus
TNF-alpha	Tumor Necrosis Factor-Alpha

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Zusammenfassung

Hintergrund: Kardiale Funktionsstörungen sind bei Erwachsenen als Komplikation eines Diabetes mellitus bekannt, allerdings bestehen zum jetzigen Zeitpunkt noch große Lücken im Hinblick auf das pathophysiologische Verständnis der Herzfunktionsstörung bei Jugendlichen mit Typ-1-Diabetes mellitus (T1D).

Ziele und Objektiven: Ziel dieser Diplomarbeit ist es, mithilfe einer Literaturrecherche die bekannten Auswirkungen von T1D auf die Herzfunktion bei Jugendlichen zu erläutern, sowie bestehende therapeutische Intervention zu beleuchten. Weiterfürend dient diese Diplomarbeit dazu, ein Bewusstsein für die Notwendigkeit weiterer Forschung zu diesem Thema zu schaffen.

Methodik: Die Überprüfung der aktuellen Literatur umfasste primäre und sekundäre Quellen. Als medizinische Datenbank diente Pubmed. Inklusionskriterien waren Studien, die in den letzten 10 Jahren am Menschen im Alter von 8-18 Jahren durchgeführt wurden, welche in englischer oder deutscher Sprache verfasst wurden und bei denen eine kostenlose Volltextverfügbarkeit vorhanden war. Darüber hinaus wurden nur Veröffentlichungen über die Herzfunktion aufgenommen. Studien über die Gefäßfunktion wurden ausgeschlossen. Die Ergebnisse kürzlich veröffentlichter Studien wurden systematisch analysiert.

Ergebnisse und Diskussion: Insgesamt 9 Studien erfüllten die Inklusionskriterien. Die Analyse der aktuellen Literatur zeigte, dass Jugendliche mit T1D eine diastolische Dysfunktion der linken Ventrikel, sowie eine linksventrikuläre Hypertrophie aufweisen. Die Erkenntnisse über den Zusammenhang der glykämischen Kontrolle mit der Herzfunktion waren sehr widersprüchlich. Ein höherer Body-Mass-Index ist mit einer Verringerung der Myokardleistung verbunden. Eine zusätzlich zur Insulin Verabreichung durchgeführte Therapie mittels Alpha-Liponsäure führte zu einer Verbesserung der linken Ventrikelfunktion und zu einer Abnahme mehrerer biochemischer Marker, die am Mechanismus des hyperglykämischen oxidativen Stresses beteiligt waren.

Dieser Oxidativer Stress ist verantwortlich für die Entwicklung der diabetischen Kardiomyopathie.

Schlussfolgerungen und zukünftige Richtungen: Jugendliche mit T1D zeigen frühe Anzeichen einer Entwicklung der diabetischen Kardiomyopathie. Eine mögliche Prävention könnte die Gabe von Alpha-Liponsäure darstellen.
Für ein weiterreichendes pathophysiologisches Verständnis kardialer Funktionsstörung bei Jugendlichen mit T1D benötigt es zusätzliche Forschungsansätze. Das Ziel ist die Früherkennung kardialer Veränderungen zur möglichst gezielten therapeutischen Intervention, um eine Krankheitsprogression zu verhindern und die Lebensqualität der jungen betroffen Menschen zu verbessern.

Abstract

Background: Cardiac abnormalities are known complications in adult with diabetes mellitus; however, wide gaps still exist in understanding the evolution of cardiac dysfunction in adolescents with type 1 diabetes mellitus (T1D).

Aims and objectives: The aim of this diploma thesis is to carry out a literature review on the known effects of T1D in cardiac function in adolescents, as well as early therapeutic interventions and raise awareness on further research on the matter.

Methodology: The review of the current literature included primary and secondary sources. Medical database was obtained from Pubmed. Inclusion criteria were studies conducted in the last 10 years, on humans, 8-18 years of age, written in English or German and with a free full text availability. Moreover, only publications about the cardiac function were included, whether studies about vascular function were excluded. Findings of recently published studies were systematically analyzed.

Results and discussion: A total of 9 studies fulfilled the inclusion criteria. Analysis of the current literature showed that adolescents with T1D have left ventricle diastolic dysfunction, as well as left ventricle hypertrophy. The contradictory findings about the association of glycemic control with cardiac function in T1D adolescents, indicate that further research is required. A higher Body- Mass- Index is associated with a reduction of myocardial performance. Additional therapy with alpha-lipoic acid besides insulin, resulted in an increase of left ventricle function and decrease of several biochemical markers involved in the mechanism of hyperglycemic oxidative stress, which is responsible in the development of diabetic cardiomyopathy.

Conclusions and future directions: Adolescents with T1D have early signs of the development of diabetic cardiomyopathy. Alpha lipoic-acid may play a role in its prevention. However, further research is needed on detection of cardiac

abnormalities in adolescents with T1D, on understanding its mechanisms and on possible beneficial therapeutic interventions. Introduction

1.1 Type 1 diabetes mellitus

1.1.1 Definition and Pathogenesis

Type 1 diabetes mellitus (T1D) is alongside with type 2 diabetes mellitus (T2D) one of the most common types of diabetes mellitus (DM) defined as an absolute insulin deficiency. This is due to an autoimmune response that leads to the destruction of insulin-producing beta (ß) cells in the pancreas. ß-cells are synthetized in the Langerhans islets in which a chronic inflammatory infiltration of T-cell lymphocytes and macrophages occurs, causing chronic hyperglycemia (elevated blood glucose levels) and ketoacidosis (a buildup of acids in the blood). However, this results when approximately 80% of the ß-cells is destroyed and the Langerhans islets become atrophic. This period usually lasts months to years. Despite being functionally and embryologically similar to ß-cells, all other cell types (alpha, gamma, and pancreatic polypeptide cells) are not affected by this pathophysiologic process. Usually, it is diagnosed at an early age and is classified in two types: the autoimmune (type 1A, the antibodies have been identified) and idiopathic (is type 1B, the pathogenesis unclear, antibodies are absent and seems to have a strong hereditary component).(1,2) T1D can also be manifested in adulthood, whom the sufficient residual of ß-cell function permitted them to avoid dependence on insulin until the later years.(3)

The common symptoms of T1D are polyuria, polydipsia, as well as weight loss, and fatigue. These results due to the impaired insulin-dependent glucose homeostasis: Glucose molecules are transported to liver, muscle, and adipose tissue by glucose transporters (GLUT2). Because glucose utilization is damaged by the progressive insulin deficiency, GLUT2 remain activated causing hyperglycemia. In state of hyperglycemia (> 180 mg/dL), glucose is excessively excreted into urine (glucosuria), leading to an osmotic diuresis that causes polyuria, which then stimulates polydipsia to maintain euvolemia. The lack of insulin production triggers lipolysis from fat cells as well as protein breakdown to provide alternative sources of energy and resulting in weight loss and hyperphagia along the caloric loss from glucosuria.(1,4,5)

1.1.2 Diagnosis

The clinical symptoms (polyuria, excessive thirst, weight loss and fatigue) are usually the first indications of a DM suspicion. However, to confirm the diagnosis the oral glucose tolerance test (OGTT) is the gold standard. Alternative parameters might also be plasma glucose levels or the determination of glycated hemoglobin (HbA1c).(1,4,6)

1.1.2.1 OGTT

Different factors such as malnutrition, hunger, drugs, steroids, and others can affect glycemia and therefore affect the performance of the OGTT. The test is conducted in three steps: At first proceeds the determination of fasting plasma glucose values after a fasting period of eight hours. Next an oral intake of glucose solution (adults 75 g; children 1,75 g/kg, maximum 75 g) will be given. The third step is the establishment of plasma glucose levels two hours after the solution has been consumed. Plasma glucose levels <140 mg/dL indicate normal glucose tolerance, whereas levels >200 mg/dL define the diagnosis of DM.(1,4,6)

1.1.2.2 Determination of fasting Plasma Glucose

The fasting plasma glucose test must be conducted from the venous plasma in the morning after a fasting period of eight to ten hours. Normal glucose levels are defined as <110 mg/dL (<6.1 mmol/L), levels between 111 mg/dL (6.2 mmol/L) and 125 mg/dL (6.9 mmol/L) suggest pre-DM and two plasma glucose levels above 126 mg/dL (> 7.0 mmol/L) are typical for DM.(1,4,7)

1.1.2.3 HbA1c

The assessment of HbA1c identifies average blood glucose concentration over a period of three-months, the same as the lifespan of an erythrocyte (120 days). The reference for HbA1c concerning all age-groups is defined by a value less than 7.5 % (58 mmol/mol). However, the values of HbA1c are generally not recommended for diagnosis at the moment since it can be influenced by various factors such as age, ethnicity, pharmaceuticals such as cephalosporins or high-dose long-term therapy with acetylsalicylic acid, long-term consumption of vitamin E, diseases affecting the spleen, liver, kidney or after splenectomy or phlebotomy, hemolysis, iron deficiency anemia, pregnancy and others. After the diagnosis has been established, HbA1c is also used as a marker for glycemic control and should be measured every three months, followed by an accordingly adjustable therapy.(1,4,6)

1.1.2.4 Differential Diagnosis Criteria for T1D and T2D

To differentiate between T1D and T2D different laboratory parameters can be helpful such as evidence of insulin production, antibodies and c-peptide levels.(6) C-peptide test determines the insulin production, and it is a useful marker not only for distinguishing T1D or T2D, but also to detect causes of hypoglycemia, to observe insulin production after a pancreatic tumor removal and to investigate the presence of insulin resistance. C-peptide molecules are equivalent in number to insulin molecules and are released simultaneously as insulin. However, C-peptide molecules tend to remain longer in the blood than insulin and blood sugar is not influenced by it. The test must be performed after a fasting period eight to 12 hours followed by an injection of glucagon, when to diagnostically differentiate T1D and T2D. Normal values are defined 0.51 to 2.72 ng/mL (0.17-0.90 nmol/L). Low C-peptide and high blood glucose levels may suspect T1D, whether high C-peptide and low blood glucose levels could be an indicator of either T2D or Cushing’s syndrome.(8)

A glutamic acid decarboxylase autoantibodies test (GAD antibodies test) is also used to differentiate between T1D or latent autoimmune diabetes of adulthood (LADA) and whether gestational diabetes may be T1D as well as to estimate the progression of T1D or indicate a risk of T1D or LADA. The test should be

performed before the intake of insulin. The presence of the GAD antibodies suggest T1D, however the absence of the antibodies is not exclusive of no T1D.(9)

Table 1: Differential diagnosis criteria for T1D and T2D

	T1D	T2D
Aetiology	Autoimmune, genetic predisposition	Genetic predisposition, multifactorial
Heredity	variable	variable
Frequency among all diabetes types	5–10%	90–95%
Pathogenesis	Autoantibodies, absolute insulin deficiency	Insulin resistance and secretion disorder up to insulin deficiency
Typical age of manifestation	Childhood to adulthood	Adulthood
Clinical manifestation	Acute polyuria, polydipsia, severe hyperglycemia, ketoacidosis	Slow onset, often secondary diseases, moderate hyperglycemia
Tendency to ketoacidosis	Yes	No
Weight	Normal weight/weight loss	Overweight
Comorbidities	Autoimmune thyroiditis, celiac disease	Visceral obesity, hypertension, Diabetes (also called Metabolic Syndrome)
Plasma insulin/C-peptide HOMA-B2	Reduced to lacking	Often high at the beginning, then reduced
autoantibodies	Yes	No
Insulin resistance HOMA-R3	No	Yes
Therapy	Insulin	Lifestyle modification measures, oral antidiabetics, Insulin

Type 1 diabetes mellitus (T1D); Type 2 diabetes mellitus (T2D);
HOMA-B or Homa-R Homeostasis Model Assessment to quantify the β- cell reserve and insulin resistance

Reference:(6)

1.1.3 Epidemiology

The process of cell destruction is epidemiologically heterogenous and may be influenced by a combination of genetic, immunologic, and environmental factors. However, the identity of specific environmental triggers is still unconfirmed or unidentified. It has been shown, that up to 20 % of individuals who had a congenital rubella infection developed T1D.(5)

1.1.4 Complications

T1D has various disease- associated complications, both acute such as diabetic Ketoacidosis as well as chronic complications such as renal, retinopathic, cardiovascular, and others.

The most common acute complication of T1D is diabetic Ketoacidosis. It develops as a result of a profound insulin deficiency causing hyperglycemia and hyperketonemia. The lack of insulin releases free fatty acids that are converted into ketone bodies via beta oxygenation, which induces metabolic acidosis, dehydration, and loss of electrolyte. It is presented with symptoms such as excessive thirst, nausea, vomiting, abdominal pain, shortness of breath, fruity-scented breath, fatigue, and confusion. Diabetic Ketoacidosis might also be the first presentation in a person who diabetic has not yet been diagnosed. It is associated with great risks since 10 % of diabetic Ketoacidosis lead to coma. Therefore, an immediate treatment is necessary. Intravenous insulin therapy, fluid- and electrolyte replacement is the primary therapy.(1,4)

Usually, chronic complications occur due to chronic hyperglycemia as a predominantly consequence of a not well controlled DM.(4) Diabetic retinopathy is a microvascular complication and the primary cause for blindness in developed countries. However, it is unobserved before a diabetes duration of five to ten years. Risk factors include also poor metabolic control, increased blood pressures, smoking, albuminuria, and increased lipid values as well as pregnancy. Diabetic nephropathy is also a microvascular complication often resulting in hemodialysis and diabetic neuropathy. Hypertension should be treated aggressively as it accelerates the progression of nephropathy. In children and adolescents with T1D a symptomatic peripheral or autonomic diabetic neuropathy is uncommon. However, after a diabetes duration of four to five years, changes in nerve conduction may be visible. The frequency of diabetic neuropathy increases with diabetes duration and degree of hyperglycemia. Therefore, neuropathic symptoms may improve by improving glycemic control. Coronary heart disease, stroke and peripheral artery disease are macrovascular complications caused by arterial hypertension, hypercoagulability, hyperlipidemia, and smoking. However, the association of glycemic control with this complications is limited.(1,4,5)

One of the prominent barriers to target glycemic control in children and adolescents is hypoglycemia, especially the fear (patient, parental or both) of hypoglycemia and especially nocturnal hypoglycemia. Mild hypoglycemia can result in altered cognitive function, while severe hypoglycemia has devastating effects on neurological functions causing seizures and coma. In children with T1D, exercise is also strongly associated with hypoglycemia, especially nocturnal hypoglycemia because the insulin sensitivity is greater after exercise.(10) A longer diabetes duration and a lower HbA1c are besides a younger age, other risk factors for hypoglycemia, which must be taken into consideration when managing T1D children and adolescents with insulin.(11)
Complications can also occur from an improper insulin application such as hypoglycemia and lipohypertrophy (accumulation of adipose tissue) due to an unfrequently change of the injected sides. This causes an undependable and slow absorption of insulin at the affected side.(1)

1.1.5 Therapy and Management

T1D treatment is insulin therapy, which is injected subcutaneously by an insulin pen, insulin syringe or as continuous subcutaneous insulin infusion via an insulin pump. To date the most common treatment is basal bolus insulin, by aiming to supplement the requirements of basal insulin under fasting conditions maintaining euglycemia. In certain clinical situations other regimes such as pre-mixed insulin is also used. Insulin doses is administrated depending on current blood glucose levels, planned meal intake, activity level, pubertal stage, and health condition (e.g., infection).(1,2)
The aim of T1D management is to avoid acute and minimize chronic complications and to allow a normal lifestyle.(1,2) However, even though it is necessary to achieve and maintain tight metabolic control, the adjusted therapy should also support the growth and development of children and adolescents with T1D. In order for insulin treatment to be affective, it must be provided in line with the needs, preferences, and resources of the individual and the family.(12) Control examinations should be performed every 3 months to review glycemic control and strategies to avoid recurrences in case acute complications occur in the interval between visits.(5)

According to the International Society of Pediatric and Adolescent Diabetes, Screening for retinopathy and microalbuminuria should begin from age 11 (with two years diabetes duration) and from nine years of age with five years diabetes duration and after two years diabetes duration in an adolescent. After this, an annually screening should be performed. Persistent micro-or macroalbuminuria should be treated with medication (Angiotensin-converting enzyme or Angiotensin II receptor blocker) as it not only affects the end stage renal failure but is also associated with a high risk of macrovascular complications. Soon after children over 12 years of age have been diagnosed with T1D, they should be screened for fasting blood lipids. This should be repeated every 5 years if the attained results are within the normal range. Blood pressure measurements should be performed annually.(13)

Patients and their families need to be well educated in order to succeed on diabetes self-management, which is very fundamental and important. However, education should not be limited only in self-glucose monitoring and insulin administration but it is also necessary to advice patients about effective lifestyle interventions (exercise, nutrition, no smoking).(5)

1.2 Cardiac Anatomy and Function

The heart is a muscular pumping organ of vital importance by furnishing the body with blood. It is located in the middle of mediastinum and is divided into the left and right side, each consisting of two chambers, atrium and ventricle. On the left side, atrium and ventricle are divided by mitral valve, and on the right side by tricuspid valve. The left and right heart sides are divided by a septal wall (inter-atrial septum between right and left atria and inter-ventricular septum between right and left ventricles.).(14)

The Heart wall consists of three layers: epicardium (visceral layer of pericardium, outside layer), myocardium (middle muscle layer and the thickest layer, responsible for hearts pumping action), and endocardium (inner layer, thin layer of endothelium).(14)

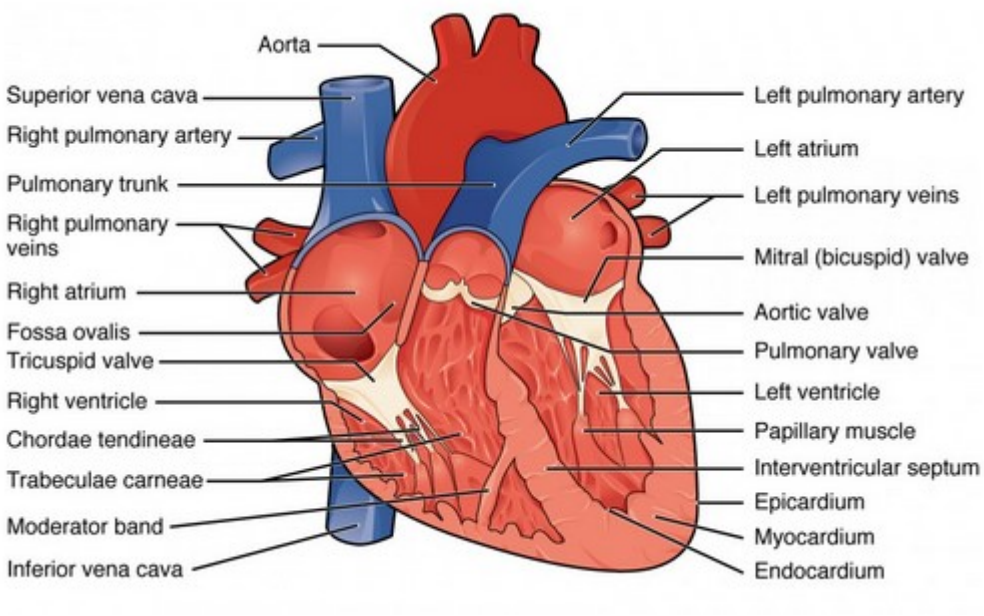

Figure 1: Anterior view of the heart

Reference: (15)

Blood flow: The heart furnishes the body continuously with blood through the circulatory system. The circulation system consists of two parts: the pulmonary circulation (blood flowing to and from the lungs exchanging carbon dioxide for oxygen) and the systemic circulation (blood flowing to the body transporting

oxygen and returning relatively deoxygenated blood with carbon dioxide to the heart so it can be sent back to the pulmonary circulation).(16)

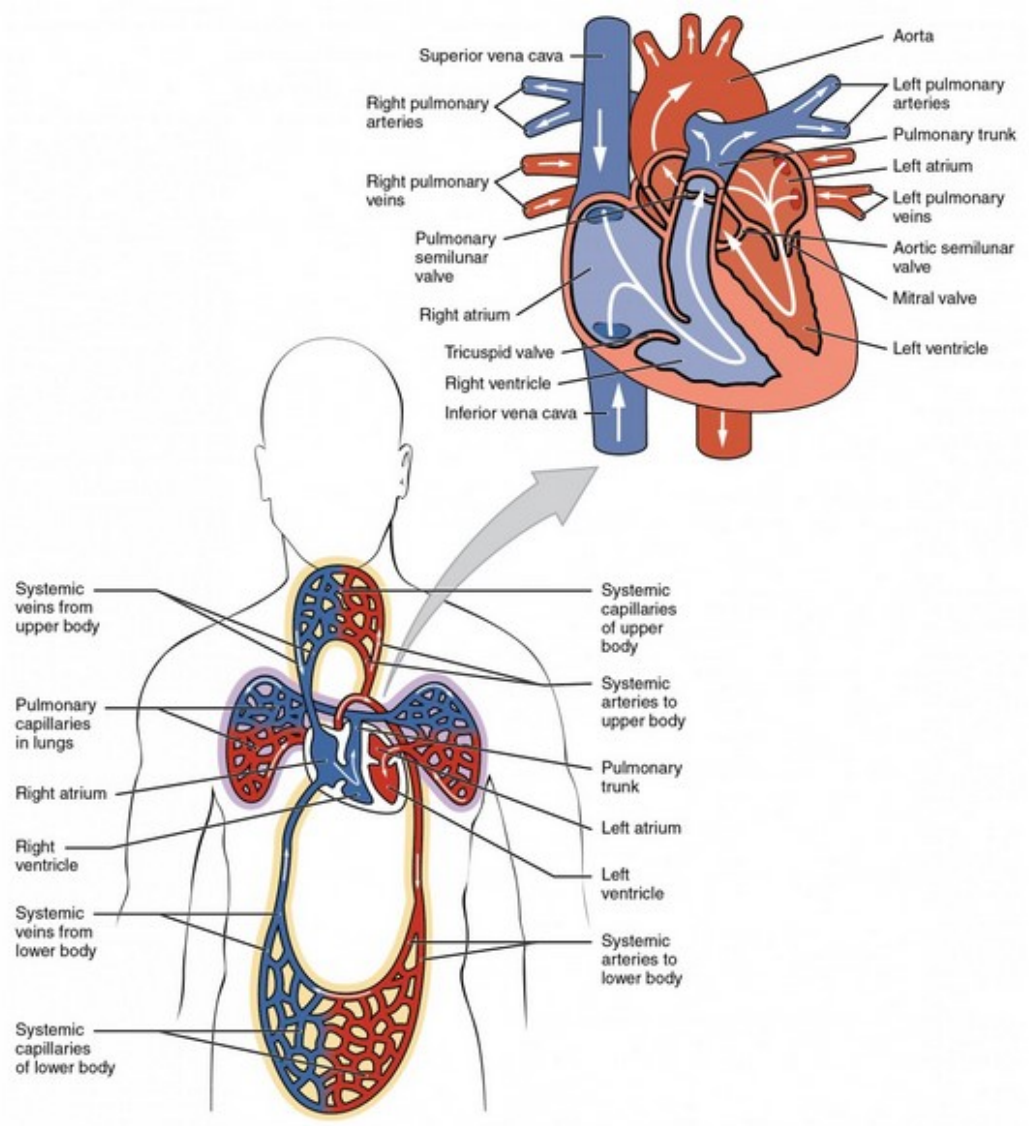

Figure 2: The Circulatory System

Reference: (15)

Cardiac cycle: It is the rhythmic alteration between heart contraction (systole) and heart relaxation (diastole). This is powered by the electrical system known as cardiac conduction, in which heart nodes send nerve impulses dispersed through the heart wall and contracting the heart muscle.(17)

Systole: Contraction of the ventricles pumping blood out of the heart through the opened aortic and pulmonary valve to the aorta and pulmonary trunk respectively.(17)

The ventricles contract due to the received impulses from the heart nodes. Oxygenated blood is pumped from the left ventricle to the aorta, whether simultaneously the deoxygenated blood is pumped from the right ventricle to the pulmonary artery. The semilunar valves prevent the blood from flowing back to the ventricles.(17)

Diastole: The relaxation and expansion of atria and ventricles, while refilling with blood returning to the heart into both left and right ventricles through the opened atrioventricular valves.(17)

The deoxygenated blood flows through the inferior and superior vena cavae to the right atrium, whether the oxygenated blood flows from the pulmonary veins to the left atrium. The impulses dispersed from the sinoatrial to the atrioventricular node, trigger both atria to contract and empty their content into the right and left ventricle through the opened tricuspid and mitral valve, respectively. The atrioventricular valves prevent the blood from flowing back to the atria.(17)

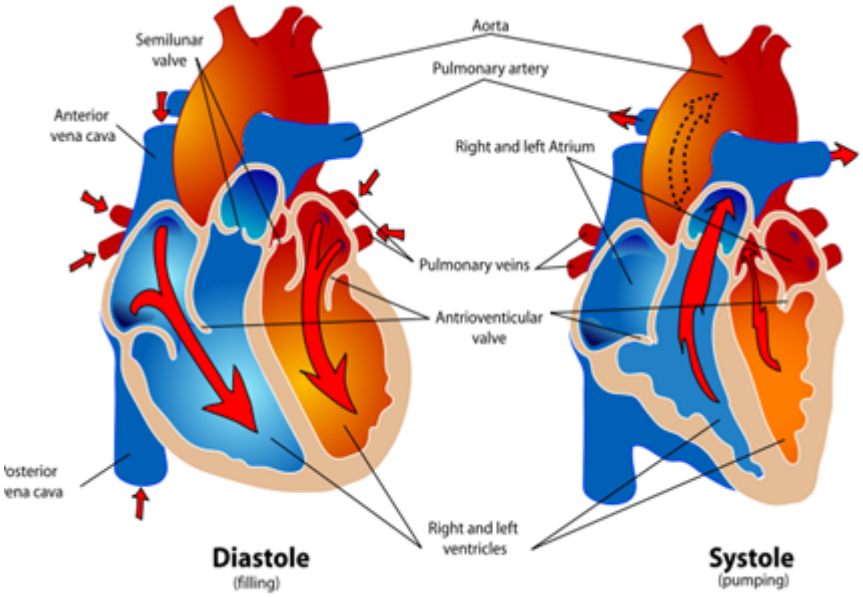

Figure 3: The Cardiac Cycle

Reference:(17)

1.3 Diabetic Cardiomyopathy

Diabetic cardiomyopathy (DCM) is a pathophysiological condition and known complication of DM. It can lead to heart failure (HF) even in the absence of coronary artery disease, hypertension, and valvular heart disease.(18)
The development and progression of HF results from structural and functional changes of the myocardium, due to longstanding DM, that leads to left ventricular dysfunction. It induces absolute and relative increases in left ventricle (LV) wall (LVW) thickness and left ventricle mass (LVM) independently of other factors like obesity and hypertension that could also cause such structural changes of the LV. The increased LVM reduces diastolic filling, prolongs isovolumetric relaxation, and increases atrial filling and LV end diastolic pressure (LVEDP), causing diastolic dysfunction and the development of systolic dysfunction in a later step. Most of the DM patients with left ventricle hypertrophy (LVH) are asymptomatic in the early stage. In an advanced stage it progresses to HF with maintained and in late stage with reduced ejection fraction (EF) and systolic dysfunction.(18)
Early and mild diastolic dysfunction could be well detected in rigorous doppler methods. In the subclinical phase of DCM patients, even though asymptomatic, stress situations such as exercise can reveal a subtle systolic dysfunction possible in association with diastolic dysfunction, which then proceeds to the final stage of systolic dysfunction with reduced EF.(18)

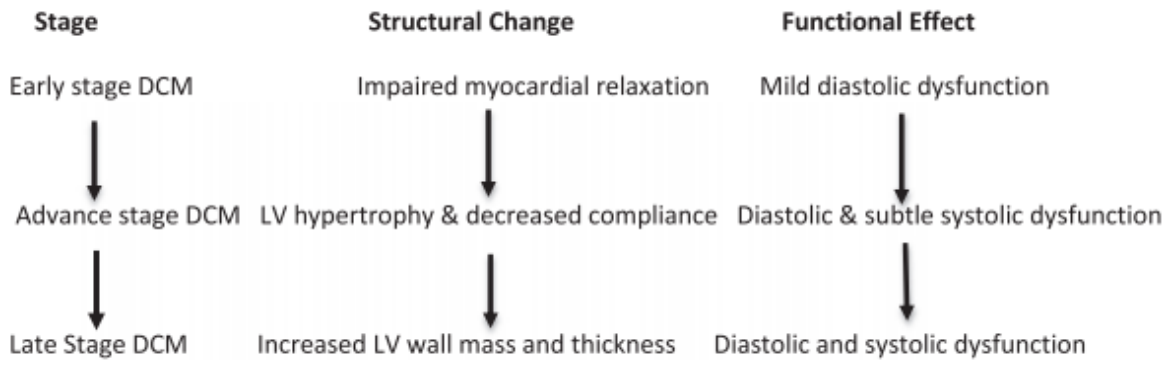

Figure 4: Flow chart showing clinical stages of DCM
Diabetic cardiomyopathy (DCM); Left ventricle (LV)

Reference:(18)

1.3.1 Risk factors

The development of DCM is multifactorial. Structural and functional changes associated with DCM have been proposed to be explained by different pathophysiological mechanisms. However, hyperglycemia, hyperinsulinemia, and insulin resistance are considered the three major risk factors of DCM. Advanced glycation products contribute strongly to myocardial fibrosis, which is one of the early signs of DCM. Different studies have supported the fact that an above range accumulation of advanced glycation products is present in patients with high HbA1c levels.(18) Another study has shown that, HbA1C correlated directly with diastolic dysfunction. Therefore, the risk of developing HF may be reduced by lowering the levels of HbA1C.(19)
Also, with duration of DM and age, the risk of DCM increases. This necessitates an improvement in early detection that can help prevent the progression of the disease.(18)

1.3.2 Role of oxidative stress, inflammation, and myocardial fibrosis in the pathogenesis of DCM and their connection to hyperglycemia

Oxidative stress promotes development as well as progression of DCM and HF. Along hyperglycemia and inflammation, oxidative stress is the main cause for inducing cardiac cell apoptosis in the diabetic heart. It causes direct cellular damage of proteins and DNA.(20)
Oxidative damage happens because of abnormal insulin metabolic signaling, which also induces a decrease of endothelial nitric oxide synthase, whether the production of nitric oxide (NO) increases to modulate the cardiac function, which on the other hand, induces an overload of intracellular Ca^{2+} promoting an increased stiffness and impaired relaxation of myocardium.(18)
Hyperglycemia is also associated with inflammation, which also plays a pivotal role in the pathogenesis of DCM. This mechanism induces pro-inflammatory cytokines such as Interleukin-6 (IL-6), tumor necrosis factor-α (TNF-alpha), monocyte chemoattractant protein-1 and nuclear factor-κB (NF-kB).(18)
Cardiac fibrosis is one of the primary structural changes in DCM. It is induced from abnormal expression of genes in the diabetic heart, such as transforming growth

factor-ß (TGF-ß) due to activation of NF-kB, as well as the remodeling of extracellular matrix and abnormal fibroblast activity by decreasing the synthesis of collagen and increasing the activity of matrix metalloproteinase-2 (MMP-2).(18,21)

1.3.3 Diastolic dysfunction and cardiac imaging

To detect structural and functional changes in the LV, echocardiography would be the standard modality and the most sensitive test.(18)

Doppler echocardiography: Is used for a comprehensive evaluation of DCM by assessing diastolic dysfunction, LV filling pressure and myocardial perfusion. Usually, LV diastolic dysfunction is due to impaired LV relaxation resulting in reduced early and prolonged diastolic flow, and in an advanced stage, early diastolic filling and rapid velocity deceleration as well as increased LV chamber stiffness, which increase cardiac filling pressure.(18,22)

> *"LV filling pressures can refer to mean capillary wedge pressure (PCWP) (which is an indirect estimate of LV diastolic pressures), mean left atrial (LA) pressure (LAP), LV pre-A pressure, mean LV diastolic pressure and LV end-diastolic pressure (LVEDP)."(22 Nagueh et al. 2016)*

Usually, LVEDP is the only abnormal increased pressure in the early stages of diastolic dysfunction due to a large atrial pressure wave.(22)
Doppler echocardiography can be normal in between early and late diastolic dysfunction. To differentiate the pseudo normal pattern, is used the Valsalva maneuver and the pulmonary venous flow. The mitral E/A ratio is a reliable established marker to predict the prognosis by identifying the filling patterns, whether it is normal (E > A), impaired (E > A), pseudo normal (E/A appears normal) or restrictive (E/A ratio often > 2) .(18,22)

Color M-mode Doppler echocardiography: Measures LV relaxation by measuring mitral inflow velocity from annulus to apex.(18)

Tissue doppler imaging: Is a reliable method to detect diastolic dysfunction in patients with normal systolic function and especially in patients with normal E/A

ratio in Doppler echocardiography by improving the diagnostic accuracy in case of a pseudo normal pattern.(18) Tissue Doppler E/e´ (transmitral flow to mitral annular velocity ratio) is a variable to assess an increased LVEDP. It has been associated with HbA1C and therefore glycemic control in diabetic patients with diastolic dysfunction.(23)

Speckle tracking echocardiography: It is a method with high sensitivity, which is especially useful to detect early global changes in LV function. Therefore, it is also a preferable method for diagnostic in children and adolescents with T1D. In asymptomatic DM patients, is observed a subclinical LV longitudinal dysfunction with reduction in circumferential (CS) and longitudinal strain (LS) rate. These changes can be detected early in the first few weeks post-DM onset by helping the prevention of further progression of DCM.(18)

Table 2: Different echocardiographic variables used to access LV diastolic dysfunction, recommended from the American Society of Echocardiography and the European Association of Cardiovascular Imaging

Variable	Utility and physiologic background	Analysis
Mitral E velocity	Reflects the LA-LV pressure gradient during early diastole and is affected by alterations in the rate of LV relaxation and LAP	Peak E-wave velocity (cm/sec): Peak modal velocity in early diastole (after ECG T wave) at the leading edge of spectral waveform
Mitral A velocity	reflects the LA-LV pressure gradient during late diastole, which is affected by LV compliance and LA contractile function	Peak A-wave velocity (cm/sec): Peak modal velocity in late diastole (after ECG P wave) at the leading edge of spectral waveform
Mitral E/A ratio	Is used to identify the filling patterns: normal, impaired, pseudo normal and restrictive filling	Mitral E velocity divided by mitral A velocity
Pulsed-wave TDI-derived mitral annular early diastolic velocity: e´	The hemodynamic determinants of E´ velocity include LV relaxation, restoring forces and filling pressure.	Pulsed-wave TDI e´ velocity (cm/sec): Peak modal velocity in early diastole at the leading edge of spectral waveform
Mitral E/e´ ratio	E´ velocity can be used to correct for the effect of LV relaxation on mitral E velocity, and E/e´ ratio can be used to predict LV filling pressures.	MV E velocity divided by mitral annular e´ velocity
LA maximum volume index	LA volume reflects the cumulative effects of increased LV filling pressures over time. Increased LA volume is an independent predictor of death, heart failure, AF, and ischemic stroke.	(mL/BSA) LA volume should be measured in dedicated views in which LA length and transverse diameters are maximized
CW Doppler TR systolic jet velocity	A significant correlation exists between systolic PA pressure and noninvasively derived LAP. In the absence of pulmonary disease,	Peak modal velocity during systole at leading edge of spectral waveform

	increased systolic PA pressure suggests elevated LAP.	
Valsalva maneuver	Helps distinguishing normal from PN filling patterns. A decrease of E/A ratio of >50% or an increase in A wave velocity during the maneuver, not caused by E and A fusion, are highly specific for increased LV filling pressures.	Change in MV E velocity and E/A ratio during peak strain and following release
Color M-mode Vp (cm/sec)	Vp correlates with the time constant of LV relaxation (T) and can be used as a parameter of LV relaxation. E/Vp ratio correlates with LAP.	Slope of inflow from MV plane into LV chamber during early diastole at 4-cm distance

Left atrium (LA); Left ventricle (LV); Left atrial pressure (LAP); Tissue Doppler imaging (TDI); Body surface area (BSA); Pulmonary artery (PA); Pseudonormal (PN); Tricuspid regurgation (TR); Mitral valve (MV)

Reference: (22)

To diagnose a LV diastolic dysfunction, four variables are recommended*:*

'annular e´ velocity (septal e´ < 7 cm/sec, lateral e´ < 10 cm/sec), average E/e´ ratio > 14, LA maximum volume index > 34 mL/m2, and peak tricuspid regurgation (TR) velocity > 2.8 m/sec'. (22 Nagueh et al. 2016)

If more than half of these parameters have abnormal values, this would indicate a LV diastolic dysfunction.(22)

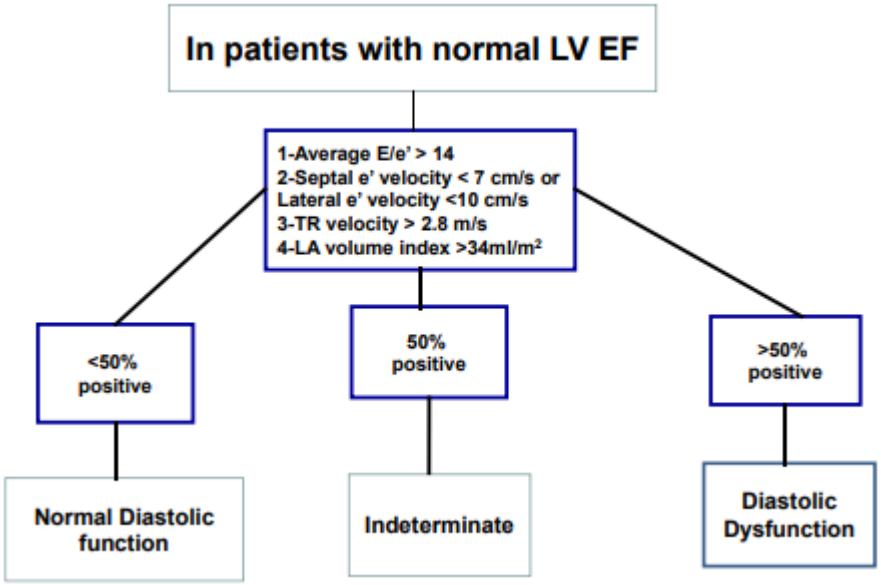

Figure 5: Agorithm for diagnosis of LV diastolic dysfunction in patients with normal LVEF
Left ventricle (LV); Ejection fraction (EF); Left atrium (LA); Tricuspid regurgation (TR);

Reference: (22)

1.3.4 LVH and cardiac imaging

Pathological LVH is linked to increased LV stiffness and diastolic dysfunction. Like myocardial fibrosis, it is also one of the earliest morphological remodeling visible in patients with pre- and early stages of DM. These structural changes of LV can be a helpful tool to differentiate normal from abnormal diastolic dysfunction. Echocardiographic parameters show enlarged LVW, LV posterior wall and interventricular septal thickness.(18,22)

2 Aims and Objectives

Cardiovascular disease is a chronic complication and a major death cause in adults with diabetes mellitus. However, the knowledge about the evolution of early cardiac structural and functional abnormalities in youth with T1D is still limited. Therefore, the aim of this diploma thesis is to provide an overview of the known effects of T1D in cardiac function in adolescents, as well as early therapeutic interventions, and raise awareness on further research on the matter.
For this purpose, a review of the current literature was carried out to present the cardiac outcomes in T1D adolescents including a possible therapeutic delay of the natural progress of the disease.

3 Materials and Methods

3.1 Search strategy

The following search strategy was applied:
PubMed was used to identify the studies representing the objective. The search was carried out on 24.07.2020 and was advanced with the three terms ‘Diabetes Mellitus’, ‘Cardiac Dysfunction’ and ‘Adolescents’. The search in PubMed was as follows:
((type 1 diabetes mellitus) AND (cardiac dysfunction)) AND (adolescents)
First there were shown an overwhelming number of 481 articles. The publication date was set at a limit of 10 years (2010-2020) to set the focus on the latest findings. Further restrictions contained:

- Text availability: free full text
- Species: human
- Language: English, German

First, the relevance of the suggested articles was roughly determined by reading the articles´ abstracts. Thereafter, the articles were read thoroughly, and their results were structured and compared.

3.2 In- and exclusion criteria

The database selection included all studies with the characteristics numerated above. 56 articles fulfilled the selection criteria which were all considered. Nine Publications were included in my manuscript, which additionally fulfilled the criteria of a Patient’s age range of 8-18 years old. Initially the age range was set to 12-18 years old but only three results were shown, therefore the range was widened starting from the eighth year of age. The other 47 were excluded due to the following reasons:

- Age <8 and >18: 17 studies
- Renal function and T1D: 7 studies

- Vascular changes and T1D: 10 studies
- Retinopathy and T1D: 3 studies
- Neurocognitive Function and T1D: 2 studies
- Physical activity and T1D: 2 studies
- Pharmacology and T1D: 1 study
- Pattern of presentation of T1D: 1 study
- Pulmonary diffusing capacity: 1 study
- Helicobacter Pylori and T1D: 1 study
- Dietary intake and T1D: 1 study
- Pregnancy and T1D: 1 study

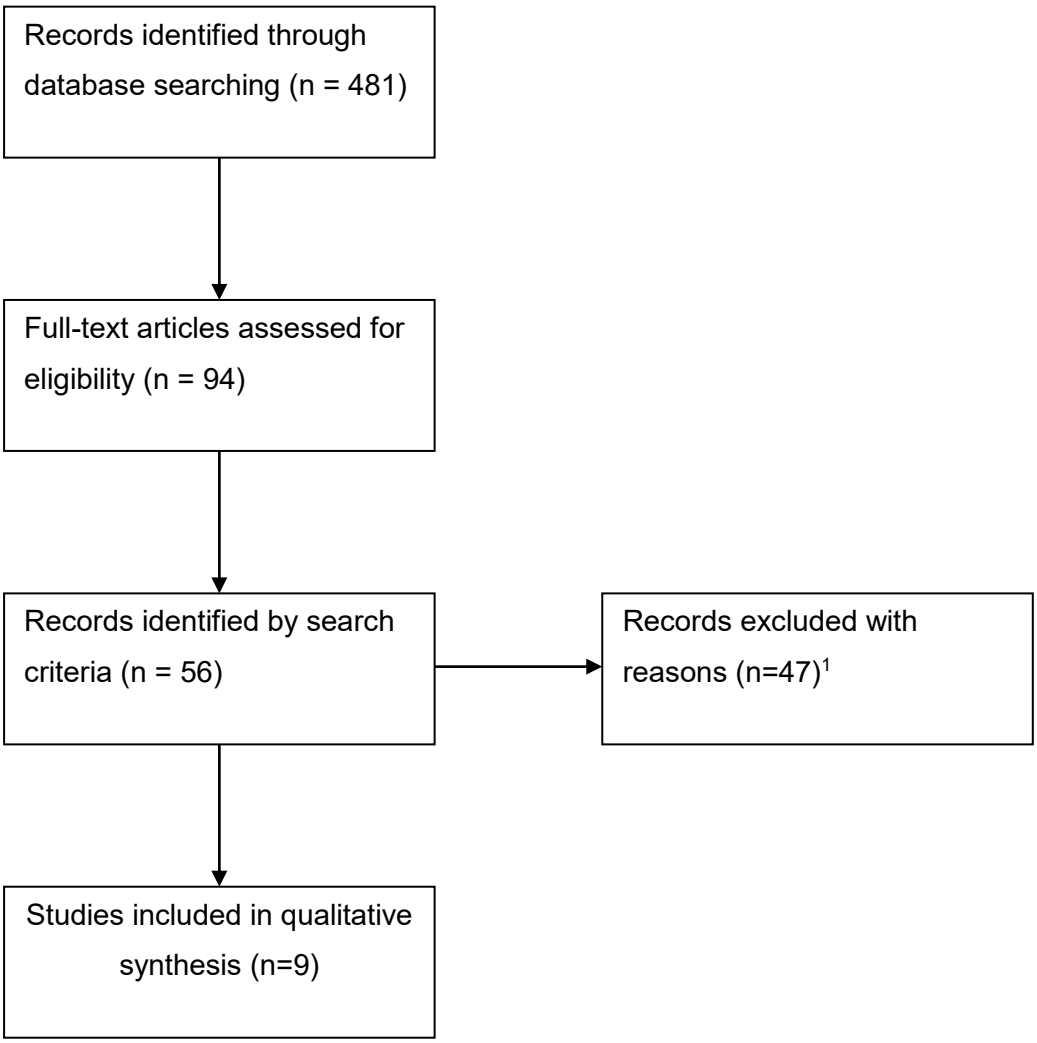

Figure 6: Flow Chart Overview of the selection progress
1 The excluded studies are described thoroughly in the section 'In-and Exclusion Criteria'

In the Introduction Section was included additional literature obtained from Textbooks, accessed primarily from the library of the Medical University of Graz as well as personal approaches. Included were also current guidelines from the International Society for Pediatric and Adolescent Diabetes guidelines, American Heart Association, American Diabetes Association, American Society of Echocardiography, and the European Association of Cardiovascular Imaging. Relevant images and figures on this topic were primarily obtained from papers and from webpages by using Google as a search engine.

To save my references, I used Mendeley by importing them from Pubmed to my Mendeley account. The Vancouver style was my choice of format.

3.3 Data extraction

To enable a better review of the characteristics as well as a better comparability of the studies, two tables were created, each including the Author and year of publication, study design, country, objectives, and results. Table 1 lays out studies reporting cardiac abnormalities in T1D adolescents as well as their correlations with diabetes duration, glycemic control, BMI, and sex differences. Table 2 presents the findings of a study regarding therapeutical improvement of the myocardial dysfunction. The data Base was checked again after the first collection to verify the accuracy and completeness.

4 Review of the current literature

The thorough process of obtaining the results has been previously explained in the section 'data extraction'. The research articles were categorized as following:
Section A deals with cardiac impairment as well as correlations with body mass index (BMI), glycemic control, diabetic duration, and cardiac sex differences in adolescents with T1D. The outcomes of eight studies were included, compared, and discussed in this section (see Table 3).
Section B elaborates the possible beneficial effect of alpha-lipoic acid on the improvement of cardiac dysfunction in adolescents with T1D. The relevant information was provided from one study on this topic. (see Table 4).

4.1 Section A: Cardiac dysfunction in adolescents with T1D and its' associations

Table 3: Articles dealing with cardiac dysfunction in adolescents with T1D and its' correlations

Author	Study details	objectives	Results
Bradley *et al.* (2016)	**Cross-sectional Observational** Greater Toronto Area (Ontario, Canada)	Early changes in cardiovascular structure and function in adolescents with T1D	▪ **Small Increased LV systolic function at rest in T1D** ▪ **LV diastolic dysfunction in T1D (Higher E/e´, Left ventricular mid CS and lower global LS in T1D)** ▪ **Higher systolic and diastolic blood pressure** ***
Brunvand *et al*. (2016)	**Cross-sectional** Oslo, Norway	Early reduced myocardial diastolic function in children and adolescents with T1D	▪ **Systolic Function did not differ** in any of the measurements ▪ **Reduced myocardial diastolic function in T1D** ▪ **In the highest BMI-group both T1D and controls had the lowest E/A-ratio** ▪ **Higher systolic and diastolic blood pressure**
Brunvand *et al*. (2017)	**Longitudinal, follow up** Oslo, Norway	Associations between early reduced diastolic function and elevated levels of HbA1c.	**E/A ratio <2.0** ▪ **Higher E/e` ratio** ▪ **Higher BMI** ▪ **Higher systolic and diastolic blood pressure** ▪ **No association of HbA1C with diastolic**

			function
Bjornstad *et al.* (2016)	**Cross-sectionl** Colorado, USA	Difference in myocardial strain in adolescents with and without T1D	▪ *T1D*: **lower CS**, no diff in LS; **Hypertrophy** (Higher LVM, LVPW, LVIDd) ▪ *Boys T1D*: **lower LS,** no diff. in CS
Hensel *et al.* (2015)	**Observational** Wuppertal, Germany	To investigate the influence of real-time blood glucose on the echocardiographic LV performance parameters strain and strain rate in pediatric patients with uncomplicated T1D	▪ **T1D with higher blood sugar levels: significantly greater LV CS, SR, global LS**
Gusso *et al*. (2012)	**Observational** Auckland, New Zealand	Whether adolescents with T1D have left ventricular functional changes at rest and during acute exercise and whether these changes are affected by metabolic control and diabetes duration.	▪ **Lower exercise capacity (correlated with glycemic control)** ▪ **Reduced stroke volume and end-diastolic volume at rest and during exercise. (correlated with glycemic control)** ▪ **End-systolic volume reduced at rest (correlated with diabetes duration)** ▪ **High systolic and diastolic blood pressure**
El Dayem *et al.* (2012)	**Prospective longitudinal** Cairo-Egypt	To evaluate progression of the LV structural and functional changes in T1D and effect of glycemic control	▪ **LVH** ▪ **Diastolic dysfunction** ▪ **No improvement with glycemic control, however no glycemic control leads to increased LVPW and IVS**
Nadeau *et al.* (2010)	**Cross sectional** Colorado, USA	Whether cardiopulmonary fitness would be reduced in T1D youth in association with IR and cardiovascular dysfunction	▪ **Strong correlation between IR and reduced cardiopulmonary fitness** ▪ **LVH and diastolic dysfunction** ▪ **T1D with longer diabetes duration had higher IVSd** *****

Diff. (Difference); Left ventricular (LV); Type 1 diabetes (T1D); Circumferential strain (CS); Longitudinal strain (LS); Strain rate (SR); Peak late mitral inflow velocity (E/A); Left ventricular mass (LVM); Left ventricular posterior wall (LVPW); Left ventricular end-diastolic dimension (LVIDd); Left ventricular end-systolic dimension (LVIDs); Intra ventricular septum dimension (IVSd); Left ventricle hypertrophy (LVH); Insulin resistance (IR)

* Findings about vascular function have not been included in this literature review.

Reference: (24–31)

4.1.1 DCM in adolescents with T1D

DCM is known to be a diabetes mellitus complication and is defined as a development of LV dysfunction regardless of ischemic, valvular, or hypertensive heart disease that can result in HF.(32,33)

The abnormalities in LV are reported in the structure such as hypertrophy and function primarily reflecting a diastolic dysfunction, which has been described by many studies as an early sign of DCM and in a later stage systolic damage as well.(32) However, only a few studies presented data on left ventricular function and structure abnormalities and the outcomes in adolescents with T1D.

Nadeau et al. (2010) studied by two-dimensional and tissue Doppler echocardiography, 17 T1D adolescents (diabetes duration 1-12 years) compared to 12 controls, similar in age, pubertal stage, activity level, BMI, and blood pressure.T1D hat significantly evidence of LVH (greater interventricular septal dimension (ILVSd) in diastole and indexed (LVM) and diastolic dysfunction (peak early mitral annular septal velocity (E/e´ septal), higher E/A ratio, shorter velocity of propagation (Vp) and higher E/Vp).(24)

Gusso et al. (2012) assessed exercise capacity and LV functional changes at rest and during acute exercise using magnetic resonance imaging, as well as their correlation with metabolic control and diabetes duration in 53 adolescents with T1D and 22 controls similar in sex ratio, weight, height, body fat percentage, BMI, and lipid profile. The presented data showed a reduced LV function at rest and during acute exercise. Moreover, a reduced stroke volume at rest and during exercise, reflected a lower end-diastolic volume, suggesting that the diastolic impairment may reduce the functional activity. Therefore, indicating that the abnormalities in the LV relaxation and filling velocities may have led as a result to a lower end-diastolic volume. At rest, a compensation of a smaller end-systolic volume was found, suggesting recruitment of the systolic reserve to improve systolic function. Therefore, compensating for the diastolic dysfunction during exercise. In addition, the systolic and diastolic blood pressures were both higher in T1D at rest but also during acute exercise.(26)

Bradley et al (2016) investigated early changes in cardiovascular structure and function in 199 T1D adolescents with mean diabetes duration 6.2 (2.0-12.8 years) and 178 healthy control subjects paired for sex, age, and height. Compared to the

controls, T1D had a significantly decreased mitral valve lateral e´ and A myocardial velocities and increased E/e´ as well as a higher isovolumic relaxation time of mitral flow and pulmonary venous flow by pulse wave Doppler imaging, suggesting an early decreased LV diastolic function in T1D. Similarly, to Gusso et al (2012), T1D had significantly higher systolic and diastolic blood pressure.(26) By myocardial deformation imaging, T1D had higher left ventricular mid CS and lower global LS.(31) Conversely, Bjornstad et al. (2016) provided evidence by speckle tracking that 41 adolescents with T1D had significantly lower CS but no difference in LS compared to the 48 controls similar in age, BMI, pubertal stage, level of habitual physical activity, and sex. Other differences in echocardiographic parameters showed that the LV end-systolic linear dimension, as well as LVM and diastolic septal and posterior wall thickness, were significantly higher in the T1D. These findings indicate a LVH.(28)

In the previous smaller cohort Nadeau et al (2010) presented more distinctions in traditional tissue Doppler imaging, reporting early diastolic dysfunction. On the other hand, in the previous study, the diabetes duration of the participants was significantly longer. However, both studies presented findings of LVH.(24)

Brunvand et al (2016) reported myocardial diastolic dysfunction in 146 T1D patients (diabetes duration 5.6 years) and 56 age-matched controls by color tissue doppler imaging examination. The findings showed a higher peak of maximal late velocity of the annulus (A) and a lower E/A-ratio in all registrations (mean mitral E/A 2.3 in T1D and 2.7 in controls, p<0001), confirming that even young children and adolescents with T1D have a small but significant reduction of the diastolic myocardial function. In comparison to Gusso et al (2012) there was no difference in systolic function in any of the measurements.(26) No differences in E/e`-ratio was shown either, probably because the diastolic dysfunction was small. Moreover, a negative association of the E/A-ratio with systolic and diastolic blood pressure was indicated.(29)

In the follow-up study (Brunvand et al. 2017) the 146 T1D patients were stratified into two groups (E/A-ratio <2.0 and E/A-ratio >2.0) according to diastolic function. The group with E/A <2.0 showed higher systolic and diastolic blood pressure as well as a higher E/e` ratio.(30)

4.1.2 BMI, glycemic control, and diabetes duration correlation with cardiac dysfunction in adolescents with T1D

The association between LVH and diastolic dysfunction and metabolic control is still very debatable.(32)

Brunvand et al (2016) stratified all participants into three BMI groups (<25, 25-75, > 75 centile). It was shown that in the lower and the middle BMI group the E/A-ratio of T1D was significantly lower than the controls. However, in the highest BMI group both T1D and controls presented the lowest E/A-ratio, showing that a higher BMI is linked to a reduction of the cardiac function.(29)

The follow-up study (Brunvand et al 2017) reported that the low diastolic function group of the T1D had not only a higher BMI but also higher levels of the advanced glycation product MG-H1, although this association did not reach statistical significance as a risk factor for the cardiac dysfunction. There was no association between HbA1c and diastolic function.(30)

Gusso et al. (2012) found that a reduced exercise capacity and a decreased LV performance was associated with glycemic control because participants with higher HbA1c presented worse fitness level. However, there was no association to the diabetes duration except for the end-systolic volume at rest.(26) Previously Nadeau et al. (2012) reported that insulin resistance may be a stronger correlate than HbA1c to a lower exercise capacity. T1D had no metabolic syndrome but they had insulin resistance, which had a strong association with reduced exercise capacity. Only E/A correlated with HbA1c, whereas mitral valve E/e´ correlated contrarily with glucose disposal rate. T1D participants with longer diabetes duration had higher evidence of LVH (higher IVSd) but no other echocardiographic parameters associated with diabetes duration.(24)

El Dayem et al. (2012) evaluated clinically and by echocardiography 48 patients (diabetes duration 5-14 years) three times every two years to evaluate the effect of glycemic control on the progression of the left ventricular structural and functional changes. LVH and diastolic dysfunction were high among T1D; however, no significant correlation was found between these parameters and BMI, HbA1c, and insulin dose. Indicating that glycemic control could not improve LV hypertrophy or diastolic dysfunction, but on the other hand, no improvement in glycemic control led to a worsening of cardiac structure such as an increase in the interventricular

septum and left ventricular posterior wall.(25) Similarly to Nadeau et al (2010) patients with LVH had significantly higher diabetes duration.(24,25)
In the study conducted by Hensel et al (2015) was hypothesized that real time blood glucose levels have an influence on left ventricular myocardial strain and strain rate in pediatric patients with uncomplicated T1D. 39 T1D participants (mean age 11,5 ± 3,5 years) were subcategorized into two groups according to blood sugar levels (A < 150 mg/dl, B >150 mg/dl) and compared within the diabetes groups as well as with 44 sex and age-matched healthy controls. By speckle tracking echocardiography, T1D with higher blood glucose level, had higher LV strain rate, CS rate as well as LS rate. Therefore, when investigating myocardial function with sensitive methods such as speckle tracking echo, real-time blood sugar levels should be also considered.(27)

4.1.3 Cardiac sex-differences in adolescents with T1D

Bjornstad et al. (2016) provided by M-Mode and two-dimensional echocardiography evidence of significant sex differences in adolescents without T1D for greater left ventricular end-systolic and end-diastolic volume, index LVM and diastolic septal and posterior wall thickness in boys. These parameters observed in the control group were lacking in the T1D. However, in the speckle tracking analysis and adjusted for Tanner stage, boys with T1D had significantly lower LS than girls with T1D but no difference in CS was observed. No significant relationship between HbA1c and LS and CS was observed.(28)

4.2 Section B: Therapeutic options of cardiac dysfunction in adolescents with T1D

Table 4: Articles dealing with therapeutic options of cardiac dysfunction in adolescents with T1D

Author	Study details	objectives	Results
Hegazy *et al* (2013)	**Randomized controlled trial** Tanta, Egypt	The possible beneficial effect of alpha-lipoic acid (ALA) on LV dysfunction in children and adolescents with asymptomatic T1D	**T1D:** ▪ **↓Glutathione** ▪ **↑MDA, NO, TNF-alpha, Fas-L, MMP-2, Troponin-I, TGF-beta** ▪ **Significant correlation of mitral E/A ratio and left**

			ventricular global peak systolic strain with glytathione Alpha-lipoic-acid: ▪ **↑Glutathione** ▪ **↓MDA, NO, TNF-alpha, Fas-L, MMP-2, Troponin-I, TGF-beta** ▪ **↑mitral E/A ratio and left ventricular global peak systolic strain**

Malondialdhyde (MDA); Nitric Oxide (NO); Tumor Necrosis Factor-Alpha (TNF-alpha); Fas Ligand (Fas-L); Matrix Metallproteinase 2 (MMP-2); Transforming Growth Factor Beta (TGF-beta)

Reference: (34)

As explained above, hyperglycemia induces oxidative stress, which promotes the development of myocardial dysfunction in the diabetic heart.(18)
Hegazy et al (2013) studied the protective role of antioxidant alpha-lipoic acid (ALA) in diabetic cardiac dysfunction. The study evaluated thirty T1D patients (aged 10-14) who were randomized into two groups. For four months one group received insulin treatment (n=15), whereas the other one received insulin plus ALA 300 mg twice daily (n=15). Before and after the therapy intervention, cardiac parameters were assessed using conventional 2-dimensional echocardiographic examination, pulsed tissue Doppler, and 2-dimensional longitudinal strain echocardiography. A healthy control group similar in age and sex was also studied. The study also evaluated several biochemical markers such as glutathione, malondialdehyde (MDA), NO, TNF-alpha, Fas ligand (Fas-L), MMP- 2, and troponin-I. These biochemical markers were correlated to echocardiographic parameters such as E/A ratio and LV global LS.(34)
It was shown that in the patients who received additional treatment with alpha-lipoic acid the levels of glutathione (the most abundant intracellular antioxidant in all cells) increased, whether MDA, NO, TNF-alpha, Fas-L, MMP-2, troponin-I levels, and TGF-beta gene expression significantly decreased. Moreover, the above-mentioned cardiac parameters were increased. These results indicate that ALA could be a good therapeutic prevention in the development of DCM in T1D patients.(34)

4.3 Limitations

The primary limitation of this literature review is the small number of studies related to cardiac dysfunction in adolescents with T1D. Initially, in addition to the inclusion criteria, only four studies did fit the age range (12-18 years). Therefore, to extend the literature for a wider review, the age range was changed to 8-18 years, which included five more studies. Consequently, it is necessary to take into notice that since the pubertal stage has been included too, this might affect the results. However, the total number of the reviewed articles was still small, affecting the comparison between them. The most recent study in the area was conducted in 2017 also restraining the accurateness of the review. About the therapeutic options of the cardiac dysfunction in T1D adolescents, only one study conducted in 2013 fulfilled the inclusion criteria for the last 10 years, therefore limiting the interpretation.

5 Conclusions and future directions

In conclusion, T1D adolescents display a reduction in cardiac function associated with a high prevalence of abnormalities in LV function (diastolic dysfunction) and structure (hypertrophy), as well as high systolic and diastolic blood pressure.
LV diastolic dysfunction was evaluated with high mitral inflow pattern and diastolic tissue velocities, whereas LVH with greater interventricular septal and posterior wall thickness in diastole and indexed LVM, representing the early stages of the development of DCM.
Moreover, the contradictory results of the reviewed studies on the association of glycemic control and LV functional and structural changes indicate that further investigation is required.
One study presented findings that boys with T1D had a lower longitudinal strain than girls with T1D, but no other cardiac differences were shown. Also, a higher BMI is associated with a reduction of myocardial performance.
The outcomes of another study showed that Alpha-lipoic acid may be a good therapeutic intervention to improve LV dysfunction and reduce myocardial damage in the early stages of DCM by decreasing several biochemical markers involved in the process of hyperglycemic oxidative stress and increasing cardiac parameters such as mitral E/A-ratio and LV global longitudinal strain.
Taken together, further studies are needed on the early assessment of cardiac abnormalities in T1D adolescents. Further research is also necessary to fully comprehend the pathophysiologic mechanism of cardiac dysfunction in order to develop new targeted treatment approaches, which would delay the natural progression of the disease and reduce the risk of developing heart failure. Therefore, ensuring the young, affected patients a better quality of life.

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