Cardiovascular Effects of Diabetes Mellitus in Paediatrics

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1 Introduction

Diabetes mellitus (DM) is a chronic metabolic disorder which affects in one way or another all the stages of childhood. Diabetes effects start in utero and affect neonates, infants, children and adolescent. Its cardiovascular complications constitute a considerable portion of morbidity in such an active age because of the metabolic derangement, associated dyslipidemia, atherosclerosis, hypertension and autonomic dysfunction. Gestational diabetes (GD) may have overwhelming effects on the embryonic heart as well as the infant born to a diabetic mother (IDM). The neonates and infants who may suffer this metabolic disease may also have considerable cardiovascular effects. Both types of diabetes can occur in children and it can affect various cardiac functions as well as cardiac remodelling in adolescents and young youth. In this chapter we will shed some light on the pathogenesis and the various cardiovascular effects of diabetes in the pediatric population (Abraha et al., 1999; Rodriguez et al., 2006; Gillian et al., 2009).

2 Pathogenesis

Vascular dysfunction is present in children with both types of diabetes and is a critical precursor of atherosclerosis. The cardiovascular mortality rate is higher in diabetic patients than non diabetic with the same cardiovascular risk factors. Diabetes has an additive role when combined with one or more risk factors. It is usually associated with one or more of cardiovascular risk factors like increased low density lipids (LDL), decreased high density lipids (HDL) increased glycosylated haemoglobin (Hb A1c), elevated systolic blood pressure, hyperglycaemia, hyperinsulinemia and insulin resistance, dyslipidemia, increased plasma oxidative stress, enhanced fibrinolysis and abnormal vasodilator function. Type 2 diabetes (T2 DM) has more cardiovascular risk than type 1. T2 DM has early occurrence of cardiovascular diseases with a higher rate of multi-vessel disease and poorer outcomes than in type 1 diabetes (T1 DM). The pathogenesis of diabetic vascular diseases is complex, incompletely understood and still in need for a thorough investigation. Table 1 showed summary of the different pathogenesis mechanisms of diabetic vascular diseases.

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Table 1: Summary of the different pathogenesis mechanisms of diabetic vascular diseases.

2.1 Endothelial Cell Dysfunction

The vascular endothelium is a single cell layer lining of the intimal surface of the blood vessels. This active layer acts as a controlling barrier between the circulation and body tissues. It secretes a variety of substances that cause vasodilatation (e.g. Nitric oxide [NO], prostanoids, endothelin, and angiotensin II).
It controls the vascular tone and blood flow and maintains a balance between vasodilatation and vasoconstriction. It also controls the nutrient delivery and waste removal, controls local inflammation, inhibits leucocyte migration and influences the platelet activation. So, disturbance of the endothelial functions will lead to increased vasoconstriction, inflammation, thrombosis, impaired platelet function and abnormal coagulation (Wheaton & Pinkstaff, 2006; Kampoli et al., 2009; Goligorsky, 2005).

The diabetes-induced endothelial dysfunction results from the oxidative stress that arises from the abnormal cluster of hyperglycemia, elevated free fatty acids, increased production of glycosylated end-products; and insulin resistance which characterizes DM. All act together in a harmony to target the endothelial cell (Aljada, 2003). Elevated levels of free fatty acids also reduce NO production, and promote the formation of oxidized low-density lipoproteins (Ox-LDL), which can damage endothelial cells and induce the expression of adhesion molecules such as P-selectin as well as chemotactic factors such as monocyte chemoattractant protein-1 and macrophage colony stimulating factor which increase endothelial dysfunction in DM and hence initiate the process of atherosclerosis. (Hsueh & Quinones, 2003; Hsueh et al., 2004) Nitric oxide (NO) is produced by endothelial nitric oxide synthase (eNOS). Endothelial Nitric Oxide is an anti-inflammatory, anti-oxidant, and potent vasodilator that counteracts smooth muscle cell proliferation and decreases platelet adhesiveness (Moncada & Higgs 2002).

Chronic hyperglycemia induced endothelial damage result from glucose auto-oxidation, activation of poly-alcohol pathway with production of sorbitol, production of diacylglycerol and activation of protein kinase enzyme; with production of glycation end products. All these changes will increase the oxidative stress and cause endothelial damage (Du et al., 2003). In diabetes associated endothelial dysfunction; there is a decrease in nitric oxide (NO) production and release and increased NO inactivation especially with presence of insulin resistance. The decrease in the vasodilator function of nitric oxide (NO) together with the increased secretion of the vasoconstrictor endothelin-1 cause dysregulation of vascular tone; hyper-constrictive state; hypertension and its concomitant complications that result from vasoconstriction (Koh et al., 2005). So, endothelial dysfunction provides an environment that allows the development of vascular disease, offering a link between DM and microvascular and macrovascular disease.

### 2.2 Vascular Smooth Muscle Dysfunction

Vascular smooth muscle is an important component of the blood vessel and contracts and relaxes in response to certain stimuli. Its main function is to regulate the blood flow inside the blood vessel. The endothelial nitric oxide is the main vasodilator stimulus while the endothelin-1 is the main vasoconstrictor stimulus (Clark & Pyne-Geithman, 2005). Alteration of vascular smooth muscle functions is an important mechanism for the development of cardiovascular complications in diabetes. Hyperglycemia can cause vascular smooth muscle dysfunction by increased oxidative stress and abnormal apoptosis in the same way of endothelial damage. Hyperglycemia increases also Angiotensin II which causes vasoconstriction and smooth muscle proliferation (Amiri et al., 1999). There is a decrease in vascular smooth muscle response to the relaxing effect of nitric oxide, as well as presence of an exaggerated contractility response to nor-epinephrine. These changes may be due to an enhanced intracellular Ca2+ signaling of the vascular smooth muscle cells to contractile stimuli as a result of changes in subcellular Ca2+ distribution on cell activation (Fleischhacker et al., 1999). Patients with T2 DM show decreased vasoconstriction in response to infusion of endothelin-1 and Angiotensin. The degree of alterations in vascular reactivity to vasoconstrictor phenylephrine is significantly influenced by the duration of diabetes (Suzuki et al., 2001; Hassan et al., 2011). Role of vascular smooth muscle cells in the development of atherosclerosis is essential. When macrophage-rich fatty streak forms, the vascular smooth muscle cells in the medial layer of the
arteries start to migrate into the nascent intimal lesion, replicate, and lay down a complex extracellular matrix, important steps in the progression to advanced atherosclerotic plaque. Arterial vascular smooth muscle cells cultured from patients with T1 DM demonstrate enhanced migration (Beckman et al., 2002).

2.3 Thickening of the Basement Membranes (BM) and Medial Calcification

The vascular basement membrane is a specialized extracellular matrix secreted by endothelial cells to provide support -cell regulatory- and filtering sieving functions. Capillary BM thickening is an ultra-structural hallmark in diabetic patients which occurs with prolonged hyperglycaemia and since 1970's to 1980's; diabetes was considered as a basement membrane disease (Melvin et al., 2005). Thickening of BM affects its ability and selectivity to transport the metabolic products and nutrients between the circulation and the tissue (Hayden et al., 2005). Various high glucose-induced mechanisms have been investigated and excess synthesis of BM components has been identified as a major contributing factor to BM thickening. Several vascular BM components have been identified whose expression is up-regulated in diabetes. Hyperglycaemia cause altered extracellular matrix (ECM) synthesis and accumulation due to increase cellular fibronectin and type IV collagen fragments which ends by thickening of vascular basement membrane. Enzymes responsible for the degradation of BM components have been reported to exhibit reduced activity. Thickening of capillary BM is integrally involved with profound cardiovascular and microvascular complications of diabetes (Chronopoulos et al., 2011; Roy & Sato, 2000).

2.4 Insulin Resistance and Compensatory Hyperinsulinemia

Insulin resistance was first described by Reaven as "syndrome X". The complete form of this syndrome includes hyperinsulinaemia, glucose intolerance, dyslipidaemia, elevated blood pressure and fibrinolytic impairment (Fontbonne, 1996). Insulin resistance commonly precedes hyperglycemia in diabetic patients. Insulin resistance and compensatory hyperinsulinemia may increase atherogenic risk through several different mechanisms. In insulin resistance, the ability of insulin to induce vasodilation is low, suggesting an impairment or inactivation of nitric oxide. The insulin resistance-associated hyperinsulinemia induces smooth- muscle cell hypertrophy and hyperplasia and increased extracellular proteins which is an important factor contributing to atherogenesis. Studies have indicated a connection between hyperinsulinaemia and activation of both atherogenic and anti-atherogenic pathways (Nigro et al., 2006). Also; insulin per se seems to have the capacity to both increase and decrease vascular tone (Muniyappa et al., 2007).

2.5 Inflammation

Inflammation is a process by which the body try to heal itself or fight off infection in response to tissue injury or pathogen exposure. This response engages activation of leukocytes and release of certain inflammatory cytokines and chemokines. Inflammation seems to fuel the atherogenic process and is strongly linked to DM and insulin resistance. Immune activation in diabetes initiates state of chronic low-level inflammation which even may precede insulin resistance in diabetic and pre-diabetic states and is an important risk factor for the diabetes-associated cardiovascular complications. The reason for this chronic state of inflammation may be due to the reduced production of the potent vasodilator NO and an increased secretion of the vasoconstrictor and growth factor endothelin-1. These changes enhances the release of pro-inflammatory cytokines which cause or exacerbate injury by a variety of mechanisms including enhanced vascular permeability, programmed cell death (apoptosis), recruitment of invasive leuko-
cytes, and the promotion of reactive oxygen species (ROS) production (Pradhan et al., 2001; Festa et al., 2000).

Association of obesity in diabetic patients also plays a role in triggering inflammation. Obesity is associated with increased levels of a number of adipokines (cytokines released from adipose tissue), including tumor necrosis factor-α, interleukin 1β, interleukin 6, and plasminogen activator inhibitor 1 (PAI-1); all linked to the inflammatory response. On the other hand, adipokine adiponectin, which has anti-inflammatory properties; is decreased in obese subjects, exacerbating the chronic inflammatory nature of obesity (Dokken, 2008; Trayhurn & Wood, 2005). Both hyperglycemia and insulin resistance are correlated directly with markers of inflammation and hence the poor vascular outcomes. In the same way, improvements in insulin resistance and glycemic control reduce inflammation and consequently the cardiovascular complications. These benefits are translated to the vasculature. Reductions in inflammation through medication or by reducing visceral adiposity, improve endothelial function and soluble markers of endothelial cellular activation (Yatagai et al., 2004).

2.6 Diabetes-associated-Hypoglycaemia

With the intense glycemic control; there is an increased rate of hypoglycemia in diabetic patients. The body responds by release of counter-regulatory hormones and substance to return blood glucose to the normal non-pathologic levels. There is an excess secretion of glucagon, epinephrine, nor-epinephrine, cortisol, pancreatic polypeptide, growth hormone, corticotrophin, as well as activation of the autonomic nervous system in response to hypoglycemia. The level of this excess is directly proportional to the severity of hypoglycaemia. Hypoglycemia was linked to the development of cardiac and cerebral ischemia and cardiac arrhythmias (Wright & Frier, 2008). It can induce significant several acute inflammatory thrombotic, and fibrinolytic and increases the oxidative-stress which may further contribute to atherosclerotic processes. Hypoglycemia significantly increases soluble vascular cell adhesion molecule 1, soluble intercellular adhesion molecule 1, soluble E-selectin and soluble P-selectin (a marker of platelet activation). Hypoglycemia increases plasminogen activator inhibitor 1, (a major inhibitor of fibrinolysis), while plasma tissue plasminogen activator concentrations does not change, with the result that hypoglycaemia induced acute reductions in fibrinolytic balance. Hypoglycaemia also is related to impaired vascular endothelial function in children with type 1 diabetes. (Joy et al., 2010; Wright et al., 2010; Younk & Davis, 2011; Boulton et al., 2005)

2.7 Peripheral Neuropathy

Pryce described the degenerative lesions of the peripheral nerves in the extremities of diabetic patients for the first in 1887. It occurs as a micro-vascular complication of diabetes. Peripheral neuropathy may be a cause or a result of the cardiovascular changes that occur in diabetes. Endothelial dysfunction has also been considered an important event in the development of diabetic neuropathy. Vascular endothelial dysfunction results in vascular damage of the small blood vessels supplying the peripheral nerves causing peripheral neuropathy. Injury to the peripheral nerves can result from polyol accumulation, injury from advance glycation end products (AGEs), and oxidative stress (Kalani, 2008). Arteriovenous shunting leading to impaired blood flow through nutritive capillaries results in sympathetic neuropathy due to both hemodynamic and metabolic disturbances. Microvascular dysfunction is seen at an early stage in the peripheral nerve, which contributes to impaired endoneural blood flow, leading to destruction of neuronal and Schwann cells and, and finally, nerve degeneration (Bhowmik et al., 2009). In diabetic peripheral neuropathy; there may be loss of normal vascular tone that can cause severe venous swelling and even
leads to ulceration and infection with lack of healthy blood flow. Diabetic peripheral neuropathy can induce autonomic dysfunction which can be manifested by orthostatic hypotension or fainting when standing up (Peña et al., 2012).

2.8 Cardiac Autonomic Neuropathy

The autonomic nervous system adjusts the cardiac electrical and contractile activity through the balance between sympathetic and parasympathetic activity. Cardiac autonomic neuropathy occurs in parallel to the development of peripheral neuropathy as a part of the neuropathy which begins distally and progressing proximally. Diabetic associated cardiovascular autonomic neuropathy causes abnormalities in heart rate control, as well as defects in central and peripheral vascular dynamics. (Maser & Lenhard, 2005) The degree of cardiac autonomic neuropathy depends on degree of glycemic control, disease duration, age-related neuronal attrition, and systolic and diastolic blood pressure (Witte et al., 2005). There are different pathogenic mechanisms which help to develop cardiac autonomic neuropathy. These include: formation of AGEs, increased oxidative/nitrosative stress with increased free radical production, activation of the polyol and protein kinase C pathways, activation of polyADP ribosylation, and activation of genes involved in neuronal damage (Edwards et al., 2008).

2.9 Disturbance of Thrombosis and Coagulation Process

Diabetes is often associated with a hypercoagulable state which increases the risk of ischemic cardiovascular events as well as cerebrovascular events which are the cause of death in about 80% of diabetic patients (Gu et al., 1998). In diabetes; there is an increased platelet aggregation, increased plasma levels of platelet coagulation products and clotting factors including fibrinogen, factor VII, factor VIII, factor XI, factor XII, kallikrein, and von Willebrand factor. Platelet hyperactivity is indicated by higher plasma levels of beta-thromboglobulin, platelet factor 4, and thromboxane B2. Coagulation activation markers, such as prothrombin activation fragment 1+2 and thrombin–anti-thrombin complexes are also elevated in diabetes. Another cause of disturbance of thrombosis, and coagulation process is the diminished fibrinolytic activity due to abnormal clot structures that are more resistant to degradation, and also because of an increase in PAI-1. The increase in coagulation and thrombosis potentiates thrombus formation after plaque rupture and makes the development of arterial occlusion and clinical events more likely (Carr, 2001).

2.10 Autoimmune Disorders (e.g. Hypothyroidism and Hyperthyroidism)

Type 1 diabetes results from the body’s failure to produce insulin due to autoimmune or idiopathic destruction of cells. There is an increased frequency of other autoimmune diseases in T1 DM e.g. thyroid dysfunction, vitamin B12 deficiency, or celiac disease. Auto-immune thyroid disease is the most common autoimmune disorder associated with diabetes, occurring in 17–30% of patients with T1 DM. The presence of thyroid auto-antibodies is predictive of thyroid dysfunction, generally hypothyroidism but less commonly hyperthyroidism. Plus the increased risk cardiovascular complications in diabetic patients; the presence of these autoimmune disorders further increases this risk (Gerstein, 2007; Nathan et al., 2007).

2.11 Disturbances of Angiogenesis

Angiogenesis is a physiological process of new vessel formation (neo-vascularisation). A balanced angiogenesis is important for both embryonic and postembryonic vascular development. It is essential for embryological growth, tissue development, and wound healing in damaged tissues. Defect in angiogene-
sis could affect the body ability to grow or to regenerate the damaged tissue while increased angiogenesis is also an important step in the transition of tumors from a confined locale to malignancy (Carmeliet, 2000). There are numerous mechanisms for aberrant angiogenesis in diabetes. Reduced angiogenesis and the ability of collateral formation are due to reduced vascular endothelial growth factor-A (VEGF), fibroblast growth factor (FGF), endothelial progenitor cells (EPC) circulation, cytokines, the extracellular matrix (ECM)/vascular basement membrane (BM) {ECM/BM} degradation; and increased AGEs and matrix metalloproteinase (MMP). Angiogenesis also is reduced by vascular occlusion and inflammation which occur due to increased free fatty acids, polyol pathway, cytokines, ICAM, and VCAM. Impaired angiogenesis also reduces wound healing probably due to reduced VEGF and growth factors; sorbitol-inositol imbalance; increased ACE, Ang-II and tissue factor mRNA. In gestational diabetes, embryonic vasculopathy with anomalous vasculogenesis and angiogenesis; occurs due to reduced VEGF, IL-1, and transforming growth factor beta (TGF-β). On the other hand excessive angiogenesis can also occur in diabetic patients. Retinal capillary occlusion occurs due to elevated intraocular pressure. Increased VEGF can cause increased vascular permeability while vascular remodelling occurs due to increased laminin, fibronectin, collagen IV, ECM components, and lipidosis. Capillary sprouting also can occurs due to elevated levels of VEGF, FGF, PDGF; cytokines (TGF-β); and integrins (Kolluru, 2012).

3 Fetal Effects of Maternal Diabetes

The fetal heart is a target organ for the congenital effects of pre-existing as well as gestational maternal diabetes. Cardiac anomalies and myocardial hypertrophy are about three times more prevalent in the offspring of women with DM. Maternal DM significantly affect the fetal heart and fetal–placental circulation in both structure and function. The diversity of cardiac abnormalities in foetuses of diabetic mothers suggests a complex pathogenesis, though it is similar to the general pathogenetic mechanisms of cardiovascular effects of diabetes but with some specific fetal effects. The teratogenic effect of DM is likely to be multi-factorial. The higher is the maternal Hb A1C values during early pregnancy, the more the risk of malformations. Glycosylated haemoglobin (Hb A1C) > 6.3% in the first trimester is associated with a significant increased risk of congenital heart abnormalities. Hyperglycaemia and hyperketonemia are toxic factors for the developing embryo and can induce and modify multiple biochemical and signal transduction pathways which include reduction in cellular levels of myoinositol and arachidonic acid and increase in production of reactive oxygen species. Hyperglycaemia induces proliferation and migration of neural crest cells which are critical to heart and brain development. High plasma triglycerides, ketones, branched chain amino acids, and creatinine increase resorption rates and malformation rates among affected pregnancies (Kumar, et al., 2007).

Maternal DM increases the expression of certain placental genes concerned with chronic stress and inflammation which play major role in evolution of maternal diabetes-induced embryopathy (Suhonen et al., 2000). Down-regulation of genes involved in development of cardiac neural crest could contribute to pathogenesis of maternal diabetes-induced congenital heart defects (Hornberger, 2006). Hypoglycaemia is a common side effect of diabetes therapy and is a potential teratogen. Hypoglycaemia interferes with normal cardiogenesis and alters morphology, function, metabolism, and expression of certain proteins in the developing heart. It is likely that these factors contribute to heart defects observed in the diabetic embryopathy, but the definitive link has yet to be made (Smoak, 2002). Intrauterine hyperglycaemia that occurs in type-I diabetic pregnancies are associated with congenital cardiac malformations, fetal cardiomy-
opathy, fetal venous thrombosis, altered placental villi vascularization, and pathological fetal heart rates even with tight maternal glucose control. Hyperglycaemia exerts its teratogenic effects during the period of organogenesis—the first 42 days of pregnancy. Intrauterine hyperglycemia induces reflex fetal hyperinsulinemia. Chronic fetal hyperinsulinemia can cause increased total body weight and selective organomegaly as a result of hypertrophy of insulin-sensitive tissues including the heart and increased expression and affinity of insulin receptors. Chronic fetal hypoxemia is also common in foetuses of diabetic mothers due to relative immaturity of the placenta, with an increased distance over which oxygen diffusion has to occur from maternal to fetal side. Chronic fetal hypoxemia is commonly seen in cases of increased maternal and fetal glucose levels. This chronic fetal hypoxemia causes higher haemoglobin levels in newborns of diabetic mothers and elevated number of nucleated red blood cells which in turn causes compensatory changes in fetal circulation (Lisowski et al., 2003).

In presence of diabetic associated fetal macrosomia, there is an increase in the cardiac mass due to a larger mass of myocardial nuclei, increased cell number and hypertrophy of myocardial fibers. Reduced left ventricular filling was also observed in infants of mothers with gestational diabetes. Underdevelopment of ventricular compliance in foetuses of diabetic mothers occurs secondary to cardiac wall thickening or other factors which can influence diastolic function as a result of DM (e.g. hypoxemia, polycythemia and altered in utero metabolic environment). This decrease of ventricular compliance can present with impairment of cardiac diastolic function as expressed by the ratio between early and late diastolic ventricular filling at the level of both mitral and tricuspid valves (Tsyvian, 1998). Interventricular septal hypertrophy may be associated with functional cardiac changes during pregnancy as well as in the neonatal period and seems to normalize within the first 6 months after birth. Ventricular hypertrophy can occur as early as before 20 weeks of gestation. However there is accelerated growth of the fetal heart in the mid and third trimesters when compared to foetuses of non-diabetic pregnancies. Lisowski et al. found that the expected decrease of the ratio of the right to left ventricular output that usually takes place with the progress of pregnancy does not occur which indicates a dominant role for the right ventricle until the end of pregnancy, whereas in normal pregnancy right and left ventricles transport half each of the cardiac output until the end of gestation. They explained this right ventricle dominance because the head of the foetuses of women with diabetes is relatively smaller than the body. As a result of the placental immaturity, more blood has to be transported to the placenta and the right ventricle is responsible for delivery of blood to the placenta. These changes in fetal circulation may suggest the existence of a compensatory mechanism which increases cardiac output and causes cardiac hypertrophy (Lisowski et al., 2003).

### 3.1 Pre-Gestational Diabetes

The prevalence of pre-gestational DM among women early in their reproductive years is increasing. The fetal effect of pre-gestational DM begins during the early embryonic development in the first trimester, with altered cardiac morphogenesis and placental development. It continues to affect the fetal circulation through the second and third trimesters and into the perinatal and neonatal period (Hornberger, 2006). Turan et al showed that foetuses of poorly controlled diabetic mothers had significant decrease in first-trimester diastolic myocardial function and myocardial performance than in non-diabetic controls. The decrease in myocardial performance is more marked with increasing HbA1c and appears to be independent of preload and after load (Turan, 2011). Good glycemic control in foetuses of diabetic mothers results in normal cardiac growth and ventricular diastolic filling. Progression of diastolic filling is abnormally delayed, however, and is presumably more exaggerated in poorly controlled diabetics (Weber et al.,
The ability to document these cardiac functional changes early in pregnancy opens potential new avenues to understand the consequences of maternal glycemic status.

### 3.2 Gestational Diabetes

Gestational diabetes mellitus (GDM) is diabetes which diagnosed during pregnancy and is not clearly overt diabetes. Chu et al showed that foetuses of GDM mothers have some cardiac function impairments. In GDM foetuses; cardiac ventricular walls were thicker and left atrial shortening fraction was smaller than foetuses of non-diabetic mothers. Left atrial shortening was negatively correlated with thicknesses of left ventricular walls and interventricular septum in foetuses of diabetic mother with poor glycemic control. However; good maternal glycemic control may delay the impairments, but cannot reduce the degree. Some cardiac changes in GDM foetuses were similar to those in pre-gestational diabetic pregnancies except for several parameters and their changing time. (Chu, et al., 2012)

### 3.3 Types of Cardiac Anomalies Associated with Gestational Diabetes

There is a wide range of cardiac anomalies observed in foetuses in pregnant diabetic women. Most types of cardiac structural lesions have been associated with diabetes mellitus, ranging from small septal defects to major heart disease. Table 2 summarizes the most encountered cardiac anomalies observed in foetuses of pregnant diabetic mothers.

<table>
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<tr>
<th>Hypertrophic cardiomyopathy (adaptive hypertrophy)</th>
<th>Transposition of the great vessels</th>
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<tr>
<td>Pericardial effusion (15%)</td>
<td>Coarctation</td>
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<tr>
<td>Intermittent or persistent bradycardia</td>
<td>Single umbilical artery</td>
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<tr>
<td>Cardiomegaly</td>
<td>Hypoplastic left ventricle</td>
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<tr>
<td>Patent ductus arteriosus</td>
<td>Persistent truncus arteriosus</td>
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<tr>
<td>Patent foramen ovale</td>
<td>Visceral heterotaxia</td>
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<tr>
<td>Ventricular septal defect</td>
<td>Single ventricle</td>
</tr>
<tr>
<td>Atrial septal defect</td>
<td>Diabetic fetopathy associated heart failure</td>
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<tr>
<td>Tetralogy of Fallot</td>
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</table>

**Table 2**: The most encountered cardiac anomalies observed in foetuses of pregnant diabetic mother

### 3.4 Fetal ECG Signs in Diabetes Mellitus

Gestational diabetes mellitus has a noticeable impact on the fetal heart rate and ECG. The alteration is slight but evident and reflects fetal wellbeing and correlate with neonatal reactivity. Only cCTG may allow detecting those slight but significant differences. Fetal ECG during delivery showed that significant ST depression is more prevalent in foetuses of diabetic mothers during delivery than in foetuses of non-diabetic mothers. These changes probably are not indicating hypoxia but an altered ability of the myocardium to respond to the stress of labour. Presence of these changes could give a significant add on information to predict moderate fetal acedemia (Yli et al., 2011; Veille et al., 1992).

### 3.5 Fetal Echocardiography Features in Diabetes Mellitus

The effectiveness of routine fetal echocardiographic screening in diabetic mothers has been thoroughly studied. However; selective fetal echocardiography should be considered after an abnormal detailed ana-
tomogramic survey as a screening strategy for cardiac defects in pregnant diabetics. It can be done as early as in the first trimester of pregnancy which can help to alleviate a lot of anxiety the parents could have if the fetus is at high risk of having cardiac abnormalities such as in diabetic pregnancy. In most patients the resolution of images is sufficient to allow assessment of basic cardiac anatomy, when normal, or detection of complex malformations, when present. Fetal echocardiography can show structural defects in the fetal heart as well as the ability to look at rhythm abnormalities and other functional aspects of the fetal heart. In fetal echocardiography, the four-chamber view and the outflow-tract view are usually used to diagnose cardiac anomalies. Four-chamber view is technically very easy to obtain.

M-mode and 2-D echocardiography can show cardiomegaly (30%), asymmetric septal hypertrophy and fetal ventricular walls thickness. It may be manifested similar to idiopathic hypertrophic subaortic stenosis and increase progressively with advancing gestation. A diabetic cardiomyopathy has been proposed as a unique entity that is characterised by localised septal hypertrophy and accompanying cardiac dilatation (Veille et al., 1992). This is in contrast to the prenatal symmetrical hypertrophy of the ventricular walls and may be explained by peri-natal changes of ventricular geometry. Fetal cardiac systolic function indicated by ejection fraction (EF) may be significantly increased in the presence of GDM independently of maternal glycemic control (Ren et al., 2011). However, one disadvantage of the conventional M-mode derived cardiac function is that ventricular minor axis function is usually preserved in the fetal heart until there is overt myocardial dysfunction. Furthermore, ventricular filling velocities are affected by heart rate, packed cell volume, and myocardial thickness, all of which may be increased in foetuses of diabetic mothers (FDM) (Rizzo et al., 1994). Doppler echocardiography can detect ventricular inflow and outflow velocities and altered fetal myocardial function in foetuses of diabetic mothers from the late first and mid trimesters. There is an accelerated increase in maximum and mean temporal velocities across atrioventricular valves through gestation relative to normal pregnancies with increased left and right ventricular output adjusted for fetal weight (Lisowski et al., 2003). Lowered E/A wave ratio was observed in poor maternal glycaemic control, which may be indirectly due to changes in fetal heart rate, ventricular wall thickness and haematocrit (Rizzo et al., 1994).

Tissue Doppler is a better technique to assess long-axis atrial and ventricular function than the conventional methods. Gardiner et al found that the absolute age related values of ventricular systolic and diastolic long-axis function is greater in foetuses of diabetic mothers than in foetuses of non-diabetic mothers which may reflect improved age-related cardiac performance. They demonstrated a significant increase in myocardial shortening velocities and long-axis amplitude of motion of the LV and septal free wall. Late lengthening myocardial velocities in the LV and RV free walls were also significantly increased, possibly in keeping with improved ventricular diastolic performance, despite the presence of increased ventricular and septal wall thickness. So, they considered this increase in cardiac function associated with cardiac hypertrophy as a form of functional adaptation. So; they suggest to rename the “fetal diabetic cardiomyopathy” as “adaptive hypertrophy (Gardiner et al., 2006).

4 Effect of Diabetes on Neonates and Infants

Neonates and infants could be the victim of maternal diabetes or they could suffer from the effects of diabetes that primarily affects them. The increased risk of cardiovascular problems associated with maternal diabetes is well recognised with an incidence of 1.7–4.0%. These problems can be categorized in 3 main groups which include cardiovascular mal-adaptation to extra-uterine life, congenital heart defects and
hypertrophic cardiomyopathy. It is essential to be able to differentiate between these categories as the treatment is different for each one. Which could be helpful for one category may be harmful for another. For example using digoxin may be helpful in case of heart failure due to structural heart defects but harmful if used in cases with hypertrophic cardiomyopathy. The incidence of malformations is highest in mothers who were on insulin at the time of conception. (Day & Insley, 1976)

4.1 Cardiovascular Mal-adaptation to Extra-uterine Life

Adaptation to the extra-uterine life is a critical process in the neonatal life. Full-term healthy newborns demonstrate a predictable pattern of physiologic adaptations during the first 6 to 8 hours of life which is referred to as the transitional period during which the newborn makes dramatic adaptations to extra-uterine life required for neonatal survival. The most important changes are seen in the cardiovascular system that occurs when the fetal bypass shunts close and blood begins to circulate normally. Lungs filled with alveolar fluid must clear the fluid and adjust to the mechanics of breathing air with improving lung compliance. The pressure and concentration of blood gases and the binding properties of haemoglobin must also adjust, as well as the acid-base balance established by those factors. In addition, the newborn must gain the feedback mechanisms for respiratory control. The myocardial wall tension acutely increases because of the high systemic arterial pressure. During the fetal life the myocardium contracts against a low systemic pressure, whereas after delivery the systemic arterial pressure increase immediately due to obliteration of the umbilical blood flow and initiation of respiration (Bimbek et al., 1999).

Adaptations to each of these aspects of respiration occur during prenatal, natal and postnatal periods. Each stage is characterized by specific pulmonary physiology to which certain adjustments are made. Right ventricular systolic time intervals have been used in neonates to demonstrate both normal and abnormal cardiovascular adaptation to extra-uterine life. It was noted that IDM who presented with respiratory distress had prolonged isometric contraction phase of RV with elevated RV pre-ejection period (RVPEP)/RV ejection time (RVET) ratio (RVPEP/ RVET Ratio). This ratio correlates closely with pulmonary vascular resistance (PVR) and pulmonary artery diastolic pressure. This may suggest an abnormality of the transitional pulmonary circulation. There were also delayed closure of the ductus arteriosus and delayed postnatal decrease in pulmonary artery pressure in these neonates which could explain the increased frequency of respiratory disorders as well as the delay in the recovery of such infants. Primary pulmonary hypertension may be due to increased muscularization of small pulmonary arteries. It also associated with and aggravated by polycythemia which is frequently present in these neonates (Narchi & Kulaylat, 2000).

4.2 Congenital Heart Defects (CHD)

Infants of diabetic mother (IDM) are at a significant risk for CHD which occur in about 5% of them. “Overt” diabetes was present in 0.5% of mothers of babies with CHD. The highest relative risk for major cardiovascular defects occurs if the mother has gestational diabetes and develops insulin resistance in the 3rd trimester. The most frequent CHD in IDMs include ventricular septal defect (VSD), transposition of great arteries (TGA) and aortic stenosis. Defects involving the great arteries, including truncus arteriosus and double outlet right ventricle (DORV), are also more prevalent in IDMs (Narchi & Kulaylat, 2000). Mills and colleagues reported a number of cardiac malformations in infants of diabetic mothers in 1988. The abnormalities included anomalous origin of the left coronary artery from the pulmonary artery, coarctation of the aorta, and atrial septal defect (ASD), malformations that are not usually apparent at this early age (Mills et al., 1988). Abu-Sulaiman and Subaih found in study included 100 consecutive IDMs
that the most common echocardiographic findings were patent ductus arteriosus (PDA; 70%), patent foramen ovale (68%), ASD (5%), small muscular VSD (4%), mitral valve prolapse (2%), and pulmonary stenosis (1%). Hypertrophic cardiomyopathy (HCMP) was observed in 38% of cases, mainly hypertrophy of the interventricular septum. Severe forms of CHD encountered were D-transposition of great arteries, Tetralogy of Fallot (TOF), and hypoplastic left heart syndrome (1% each). Isolated aortic stenosis and coarctation of aorta were not encountered in this series. Overall incidence of congenital heart disease was 15% after excluding PDA and HCMP (Abu-Sulaiman & Subaih, 2004). Maternal diabetes increases the risk of having “conotruncal” defects (that included truncus arteriosus, TOF, TGA, and DORV) than in normal population. (Becerra et al., 1990) These “conotruncal” malformations are dependent upon neural-crest-cell-derived ectomesenchymal tissues; these are precisely the conotruncal abnormalities that result from experimental ablation of the neural crest in chick embryos.

4.3 Hypertrophic Cardiomyopathy (HCMP)

Hypertrophic cardiomyopathy has been well documented in infants of diabetic mothers (IDMs). It was first observed in a stillborn infant of a diabetic mother by Maron et al (Maron et al., 1978). Clinically manifest HCMP is present in 12.1% of IDMs, but the ratio rises up to 30% when routinely searched for with an echocardiographic scan. The severity of IDM-HCMP can vary from an incidental finding on echocardiography to an infant with severe symptoms of congestive heart failure. Fatal cases HCMP may occur in an infant of a diabetic mother. HCMP is a condition characterised by stiff, hypertrophied ventricular muscle, predominant thickening of the ventricular septum, impaired relaxation, and powerful but in-coordinate contraction. Functional subaortic obstruction may occur in severe cases and this is referred to as idiopathic hypertrophic subaortic stenosis (IHSS). Previous reports have suggested that a unique form of IHSS may occur transiently in infants of diabetic mothers and when it occurs it is generally benign and transient (Sheehan et al., 1986). Natural history of IDM-HCMP appears to be benign, with a resolution of symptoms within 2-4 weeks and a resolution of septal hypertrophy within 2-12 months. Most of the infants need only supportive care. If pharmacologic intervention is deemed necessary, propranolol appears to be the drug of choice. Natural history of this entity is that of spontaneous regression of symptoms and septal hypertrophy irrespective of therapy (Way et al., 1979). However, fatal cases of HCMP were observed in cases with diabetic fetopathy. In the diabetic fetopathy; the affected neonates are macrosome, suffer from respiratory distress syndrome due to delayed lung maturity, acidosis, hypoglycaemia, electrolyte-imbalances and polycythaemia. Severe hypertrophy of the right ventricle is associated with intrauterine heart failure. However; HCMP could normalize within 6 weeks after birth without further treatment (Krautzig et al., 1979). Echocardiography in such cases can demonstrate cardiomegaly, increases in thickness of the interventricular septum and RV and LV free wall with disproportionate septal hypertrophy in about one quarter of cases.

This increased myocardial thickness cannot be simply explained by being macrosomic infants because this thickness was also observed in small infants born to diabetic mothers and because the myocardial thickness in the large normal babies never exceeded the upper limit of normal value (Deorari et al., 1999). Neonatal asymmetric septal hypertrophy is not specific for any disorder. It may present in normal infants when the ratio of septum:ventricular posterior wall >1.3. This can be distinguished from other pathological causes because there is no absolute increase in septal thickness. Asymmetric septal hypertrophy may be observed in familial cases, glycogen storage disease (type II), and any cause of right ventricular hypertension. In diabetes; the hypertrophy may be asymptomatic and regress over months. In Pompe's disease it presents at about 3-4 months of age. (Maron et al., 1974)
4.4 Neonatal Diabetes Mellitus

Neonatal DM, defined as insulin-requiring hyperglycemia within the first month of life. Neonatal DM was also described in association with CHD. Permanent neonatal DM due to pancreatic Partial agenesis/hypoplasia with congenital heart defects has been reported. Pancreatic agenesis can be associated with intra-uterine growth retardation, dysmorphic features, non-specific immunodeficiency, and malformations of the heart, the biliary tract, and the cerebellum. Transient neonatal DM is caused by over expression of a gene cluster at 6q24. CHD may be one of the anomalies associated with transient neonatal DM; plus severe intrauterine growth retardation, structural brain anomalies, macroglossia, developmental delay, and umbilical hernia (Balasubramanian et al., 2008; Taha et al., 2010).

5 Effect of Diabetes on Childhood and Adolescence

Diabetes mellitus is one of the most severe chronic diseases of childhood and adolescence. Most pediatric patients with diabetes are of T1 DM. For the age between 10-19 years; T1 DM is more common than T2 DM. The prevalence rate is 2.28 per 1,000 for T1 DM and 0.42 per 1,000 for those with T2 DM (Faulkner, 2010). In the United States; each year more than 13,000 children are diagnosed with T1 DM. Fifty percent of subjects with T1 DM are diagnosed within the first 15 years of life. While most new pediatric diabetic cases are of T1 DM, there are increasing numbers of older children and adolescents with T2 DM in response to childhood obesity and sedentary life with increasing detection of more cases of T2 DM among children (Krishnan & Short, 2009). With the increasing number of children and young youth being diagnosed with DM; there is an increasing incidence of premature heart disease in early adulthood. Both types of diabetes often coexists with other multiple cardiovascular risk factors, including hyperlipidemia, hypertension, and obesity and may be associated with poor cardiovascular outcome.

5.1 Cardiovascular Complications Associated with Childhood and Adolescent’s Diabetes

The following cardiovascular complications are usually associated with childhood and adolescent’s diabetes:

5.1.1 Impaired Vascular Functions and Accelerated Atherosclerosis

Endothelial dysfunction in children with DM is an indicator of future cardiovascular events and atherosclerotic changes were observed to occur much earlier than the appearance of clinical diabetes. Children and adolescents with T1 DM have more rate of endothelial dysfunction than non-diabetic age-matched control children, as measured by flow-mediated dilation (FMD) in the brachial artery. These children have adverse carotid remodelling which increase the future cardiovascular risk (Järvisalo et al., 2004). Early signs of abnormal vascular homeostasis including impaired endothelial function; increased carotid intima-media thickness; and increased markers of systemic inflammation may appear in prepubertal children with T1 DM. So, diabetic children are at increased risk of early asymptomatic atherosclerosis, and cardiovascular morbidity and mortality are substantially increased in this group of patients. The atherosclerotic process starts in childhood and proceeds silently over a long period of time before clinical events occur. Several studies in children and adolescents with T1 DM have consistently reported increased carotid artery intima-media thickness (c-IMT) compared with healthy control subjects. cIMT is a reliable surrogate marker of generalized atherosclerosis because it correlates to coronary artery disease and pre-
dicts future cardiovascular events. cIMT correlates well with cardiovascular risk factors and coronary atherosclerosis and is an independent predictor of future cardiovascular disorders (CVD) (Margeirsdottir et al., 2010). With the limited available data about markers of subclinical atherosclerosis in pediatric populations, there is a need for more studies, including those of a longitudinal design.

Dyslipidemia is a disorder of lipoprotein metabolism that results in increased total cholesterol, high low density lipoprotein cholesterol (LDL-C), low high-density lipoprotein cholesterol (HDL-C), and high triglycerides (TG). Although dyslipidemia is an established risk factor for CVD in adults, no long-term studies directly link dyslipidemia in childhood with subsequent CVD (Hong, 2010). There was a trend of increased HDL cholesterol levels and significantly reduced cholesterol–to–HDL cholesterol ratios in preadolescent children with T1 DM. Despite the athero-protective effect of the higher plasma HDL cholesterol levels but in the setting of T1 DM, this HDL cholesterol may be dysfunctional in combating the adverse, pro-inflammatory, and pro-atherogenic effects of oxidized LDL cholesterol. The presence of dysfunctional HDL cholesterol would make type 1 diabetic subjects more vulnerable to oxidative vascular damage despite higher absolute levels (Babar et al., 2011).

These atherosclerotic changes affect both small and large blood vessels. Small vessel affection increases the risk for tissue injury in organs supplied by an endarterial system due to microangiopathy. These microvascular complications include nephropathy, retinopathy, and neuropathy while macrovascular disease including heart disease and stroke (Moore et al., 2009). Improved glycaemic control obtained by intensive insulin treatment is associated with delayed atherosclerosis development and fewer cardiovascular events. Prevention and screening for vascular complications are important in the care of children and adolescents with T1DM. Target levels to reduce the risk of microvascular and macrovascular complications in children and adolescents with T1 DM are the following: HbA1c <7.5%, lipids in normal range, blood pressure <90th percentile by age, sex and height, BMI <95th percentile, no smoking and adequate physical activity (Fröhlich-Reiterer & Borkenstein, 2010).

5.1.2 Hypertension

Hypertension is considered as a major cardiovascular risk factor in young patients with T1 DM. Both pre-hypertension and hypertension are common disorders in young patients with diabetes. The prevalence of pre-hypertension is associated with older age, longer duration of diabetes and the shift of the sympathetic-vagal balance toward sympathetic activation (Szadkowska et al., 2006). Hypertension is 2–3 times more frequent in children and adolescent with diabetes compared with the general population especially nocturnal hypertension when compared to diurnal hypertension. Persistently elevated blood pressures can induce serious complications on both the micro- and macrovascular level. On the other hand; children with T2 DM often have several risk factors for elevated blood pressures, such as obesity, family history, and generally poor cardiovascular health. Nocturnal hypertension is a risk factor of diabetic nephropathy. It is related to higher BMI and triglycerides and with lower HDL cholesterol. Type I diabetic patients have high incidence of non-dipping hypertension which related to increase in target organ damage such as diabetic nephropathy and cardiovascular events. The onset of renal pathology seen in diabetes is usually noted around the time when blood pressure elevations begin. In diabetic nephropathy; the patients initially develop microalbuminuria which progress to gross proteinuria with widespread microvascular nephropathy. Elevated blood pressure occurs with development of glomerular damage. However, it has also been shown that increases in systolic blood pressure during sleep can precede the onset of microalbuminuria in patients with T1 DM which may denote other mechanisms implicated in the pathogenesis of hypertension other than diabetic nephropathy (Moore et al., 2009; Basiratnia et al., 2012).
Lee et al showed significant increase in carotid intima-media thickness (c-IMT) and daytime blood pressure in diabetic children and adolescents with nocturnal hypertension. c-IMT is a good measure for identifying subclinical atherosclerosis. This means that subclinical atherosclerosis is another possible mechanism for the diabetes-associated hypertension (Lee et al., 2011). Children with T1 DM and hypertension have a higher level of vascular endothelial growth factor (VEFG) in serum compared with Children with T1 DM without hypertension, and the healthy control group. The VEGF may have an important function in the modification of tissue damage and its acceleration. It induces vascular endothelial cell proliferation and migration and increases the permeability of renal glomerular and retinal capillaries. So; measurement of VEGF serum levels allows for the identification of groups of patients who have the highest risk of hypertension and, subsequently, progression of vascular complications (Zorena et al., 2011).

Also children with diastolic hypertension have higher level of E-selectin which is an early atherosclerosis biomarker. Diastolic BP z-scores were associated with E-selectin level in children with T1 DM. Polymorphism of angiotensin-converting enzyme (ACE) gene was observed in some T1 DM children with pre-hypertension or with nocturnal BP abnormalities even if they are normotensive and normoalbuminuric. (Maggio et al., 2012) Poor glycaemic control and male gender are risk factors for abnormal systolic BP as measured by 24-hour ambulatory blood pressure monitoring. So, it is important to evaluate renal function and BP even when they are in normal range to minimize the deleterious effects of hypertension in the development of nephropathy and cardiovascular disease.

5.1.3 Cardiac Dysfunction and Diabetic Cardiomyopathy

Diabetes mellitus can induce a pattern of myocardial pathology known as specific diabetic cardiomyopathy, even if this is not clearly specified. Diabetic cardiomyopathy is responsible for the increased incidence of heart failure in diabetic patients even in absence of coronary atherosclerosis or arterial hypertension. This diabetic cardiomyopathy has been suggested to cause systolic and/or diastolic dysfunction. The cause of this cardiomyopathy is debatable. The dysfunction of autonomic nervous system can cause higher heart rate in diabetic patients than observed in normal subjects and may affect the cardiac haemodynamics. Hypertrophy, increased diastolic stiffness and noncompliance of LV with increased LV wall thickness and mass are other possible causes of diastolic dysfunction which occurs early in the course of T1 DM even in absence of hypertension. There is reduction of LV end-systolic wall stress which is used as an indicator of LV after-load which can be roughly approached by certain non-invasive measurements, including systolic blood pressure and aortic pulse wave velocity, which are related to LV after-load. Also, the impairment of ventricular relaxation may be related to cardiac fibrosis, abnormal calcium transport in the sarcoplasmic reticulum, and the increased levels of advanced glycation end products, formed by non-enzymatic glycation of proteins or lipids. These advanced glycation end products can increase the cross linking of proteins like collagen and elastin, causing reduced tissue elasticity and decreased protein turnover (Tavares et al., 2012; Suys et al., 2004).

Even with normal systolic ventricular functions, the diabetic children may suffer diastolic dysfunction as expressed by reduced LV compliance which could serve as an early marker of diabetic cardiomyopathy even before clinical symptoms appear. The degree of diastolic dysfunction correlates with the severity of the diabetic complications. More pronounced diastolic dysfunction was found in presence of severe vascular complications. Girls are more liable to diabetic cardiomyopathy and more significant changes in LV dimensions than boys. These sex differences may be related to the significant higher BMI or HbA1c in girls or related to the role of hormonal changes. However, some studied showed no correlation of diabetes duration and HbA1c with the cardiovascular changes. Children and young adolescents
rarely have good health education and proper insight regarding their disease, and their diet is accordingly difficult to control. Therefore, alteration of myocardial function induced by diabetes may begin earlier than is generally thought and these changes may be accelerated when glycemic control is poor. Early manifestations of diabetic cardiomyopathy have been suggested to contribute to depressed levels of aerobic fitness described in children and adolescents with this disease. These early manifestations produce certain echocardiographic abnormalities in asymptomatic young diabetic adolescents and can be elucidated by post-exercise echocardiography. This test is a non-invasive procedure that can easily be done in the adolescent population and is useful for evaluating subclinical cardiomyopathy. Diabetic cardiomyopathy could occur in both types of diabetes. However, Adolescent-onset T2 DM is often coexists with multiple other cardiovascular risk factors, including hyperlipidemia, hypertension, and obesity and is associated with poor cardiovascular outcome. This explains the more prevalence of diabetic cardiomyopathy in children and adolescents with T2 DM than those with T1 DM. ACE inhibitors and non-selective B-blockers have been proposed to prevent or treat diabetic cardiomyopathy (Baum et al., 1987; Eun et al., 2010; Gillian et al., 2009).

5.1.4 Cardiac Autonomic Dysfunction

Cardiac autonomic neuropathy (CAN) is a common complication in T1 DM and is frequent in subclinical stages. Its prognostic value has been demonstrated and is associated with an increased morbidity and mortality. Sudden death and cardio-respiratory arrest in patients with T1 DM and T2 DM have been attributed to cardiac autonomic dysfunction. It is a part of the well studied diabetic autonomic neuropathy which is a well recognized complication of T1 DM. It can induce different functional cardiac changes, especially a reduction in LV contractility and changes in ventricular repolarisation. It is also associated with changes in the daily variations in blood pressure (Valensi, 2000). Cardiac autonomic neuropathy involves both parasympathetic and sympathetic systems. There is an early parasympathetic impairment that may raise the heart rate, but as the duration of the diabetes increases, sympathetic involvement occurs that may relatively slow the heart rate (Elamin et al., 2009).

The development of autonomic complications depends on the diabetes duration, glycemic control and patient age. Rapid progression of the diabetic autonomic neuropathy could occur with the pubertal spurt. Chronic hyperglycemia and microvascular abnormalities induce certain enzymes activation that play important roles in the progressive nerve fibers damage in patients with longstanding T1 DM. Early neuropathic changes as endoneurial edema or intra-axonal sodium accumulation could be reversed by intensified glycaemic control. Hormonal changes during puberty and prolonged periods of poor metabolic control could induce irreversible neuropathic changes which emphasize for the importance of early detection of cardiac autonomic dysfunction and motivation of the patients to improve their diabetes control that hopefully could delay the development of complications with strict follow up especially during the puberty stage (Massin et al., 1999).

Clinically; diabetic cardiac autonomic neuropathy could be detected early by the increased resting heart rate, decreased heart rate variation to deep breathing (deep breathing test), and diminished heart rate response to standing or sustained handgrip tests. There was impairment of the parasympathetic control of heart rate in young patients with diabetes as detected by deep breathing test. Study of heart rate variations during deep respiration (which test parasympathetic function), active orthostatism (which test sympathetic function) or Valsalva manoeuvre, is still the reference. Heart rate variability (HRV) is a sensitive, reproducible, non-invasive method and is able to determine early cardiac autonomic neuropathy independent of the patient’s cooperation. It depends on the influence of sympathetic and vagal activity on the sinus
node and can easily be determined from 24-h Holter recordings. It is one of the first indices of cardiac dysautonomia observed in young diabetic patients. Squat test (1-min standing, 1-min squatting, 1-min standing) can be used with continuous monitoring of HR and BP, using a Finapres device. This active test imposes greater postural stress than the passive head-up tilt test, and provokes large changes in BP and HR that can be analyzed to derive indices of cardiac autonomic neuropathy. In healthy subjects, squatting is associated with increase in BP and decrease in HR, whereas the squat-stand transition is accompanied by a deep but transient drop in BP associated with sympathetic-driven tachycardia. In diabetic patients with cardiac autonomic neuropathy, BP increases are accentuated during squatting whereas reflex bradycardia is reduced. When standing from squatting position, the fall in BP tends to be more pronounced and orthostatic hypotension is more prolonged, while reflex tachycardia is markedly dampened (Philips et al., 2011). Another sign of cardiac autonomic neuropathy is a reduced gain of the baroreflex regulation of the heart period. Prolonged Q-Tc intervals were also found in presence of cardiac autonomic neuropathy. Impaired circadian blood pressure (BP) variation with impaired nocturnal BP reduction has been associated with autonomic dysfunction. Orthostatic hypotension is a late sign of sympathetic nervous system disease. Spectral analysis of blood pressure variations on orthostatism or the study of cutaneous blood flow during activating the sympathetic system can help in identifying autonomic neuropathy. Diabetic children also showed reduced baroreceptor sensitivity (BRS). The degree of BRS impairment was related to the degree of autonomic imbalance and with positively correlated with the disease duration (Dalla Pozza, Bechtold et al., 2007).

Microalbuminuria is an independent predictive of autonomic dysfunction as same pathological processes, such as microvascular complications may lead to both neuropathy and nephropathy. Pupillometry and studying urinary bladder function may indicate presence of autonomic dysfunction in type 1 diabetic child but do not reflect cardiac autonomic dysfunction. However, there is a high risk of development of diabetic cardiac autonomic neuropathy in children with T1 DM in the presence of the autonomic dysfunction syndrome (Manukian et al., 2011). It has been shown that the early treatment of functional disturbances of the autonomic nervous system using transcranial magnetic stimulation is necessary to prevent the manifestation of diabetic cardiac autonomic neuropathy.

5.1.5 Impaired Physical fitness and Cardiovascular Endurance

There is a reciprocal relationship between glucose tolerance, physical fitness and cardiovascular endurance. Higher levels of fitness at baseline are protective against the development of impaired glucose tolerance. Also, impairments in glucose regulation are associated with lower fitness levels. The protective effect of fitness on glucose homeostasis could be due to exercise induced alterations in skeletal muscle substrate metabolism with specific adaptations to skeletal muscle such as increased mitochondrial volume and density and oxidative enzyme capacity which in turn lead to improvements in glucose metabolism. Physical activity directly improves insulin sensitivity through increased skeletal muscle glucose uptake, and indirectly through improvements in body composition. Despite the fact that exercise stimulates glucose uptake, a certain amount of insulin is required. In children with T1 DM, exercise occasionally may result in a worsening of their glucose control if the endogenous insulin is not enough. However, patients with T2 DM have sufficient endogenous insulin available and very rarely develop hyperglycemia with ketosis in response to exercise. Children with good metabolic control should respond well to exercise. (Shaibi et al., 2006; Kollipara & Warren-Boulton, 2004)

Children and adolescents with T1 DM may have some impaired fitness-related components and alterations in their cardio-respiratory responses to exercise. The maximal aerobic power and physical work
capacity are reduced especially with fair to poor metabolic control. This may be due to reduced level of habitual activity, a smaller body stature, or impairment in cardio-respiratory or skeletal muscle function. Other possible causes may be due to associated high systolic blood pressure, lower O₂ pulse, a thickening of capillary basement membrane in skeletal muscle, impairments in the regulation of skeletal muscle blood flow and impaired nerve conduction velocity (Riddell & Iscoe, 2006). On the other side; low cardiorespiratory fitness is observed in patients with impaired glucose tolerance and T2 DM. Despite the education on the importance of increased physical activity for diabetes management given to the diabetic youth; they spent nearly 60% less time per day in moderate to vigorous activities compared to their non-diabetic counterparts. Lower fitness was observed in overweight and severely insulin resistant diabetic adolescents. This lower fitness is due to impairments in oxidative capacity of skeletal muscle as a result of mitochondrial dysfunction and hence impaired oxidative metabolism and because of the circulatory defects which limit oxygen delivery to exercising muscle. However; children with T1 DM have better cardio-respiratory fitness than those with type 2 (Shaibi et al., 2006).

Gender, BMI, metabolic control, and physical activity were strong predictors of cardiovascular endurance, regardless of type of DM. Females are exhibiting at least 20% lower capacity than males. This decrease in the levels of cardiovascular endurance in females versus males increases as they age into later adolescence. There is a significant inverse relationship between cardiovascular endurance and most lipid profile's components and systolic blood pressure in poor controlled T1DM children and adolescents; found independently of body adiposity (Lobstein et al., 2004). American Diabetes Association (2010) presently recommends that Hb A1C values to be maintained below 7.5% to improve long-term health outcomes (American Diabetes Association, 2010). The Physical Activity Guidelines for (2008) and the Exercise in Medicine initiative of the American College of Sports Medicine (2010) emphasize at least 60 minutes of moderate to vigorous activity on most days for adolescents (Group SfDiYS, 2006). Physically fit adolescents with T1 DM can have better overall glucose control and a reduction in serum lipids (Miculis et al., 2012).

5.1.6 Cardiac Effects of Diabetes-associated Obesity

Diabetes and obesity are related to each other. Adolescents with T2 DM have a higher tendency towards obesity and obese children are more prone to develop T2 DM. The increased risk of T2 DM in obese children is not well understood. It could be due to the increased body fat; and possibly specific depots of body fat such as visceral fat which have unique effects on insulin resistance. The increased frequency of obesity in T2 DM may be due to poor cardiorespiratory fitness coupled with a sedentary lifestyle. Obese diabetic children are associated with various risk factors for cardiovascular disease and early development of atherosclerotic lesions. They are 4.5 times more likely to have adverse levels of cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides, and blood pressure, respectively, than normal weight subjects. In addition, obese children have elevated levels of hemostatic and inflammatory factors, including fibrinogen, plasminogen activator inhibitor 1, and C-reactive protein which contribute to endothelial dysfunction and early atherosclerosis. Syndrome X or the Insulin Resistance Syndrome is a combination of obesity, hyperglycemia, hyperinsulinemia, dyslipidemia, and hypertension. This collection of risk factors increases the chance of developing heart disease (Goran et al., 2003). With the increasing level of insulin in insulin resistant syndrome; the insulin will stimulate renal sodium retention while increasing free water clearance. Insulin resistance is also associated with increased sympathetic nervous system activity and stimulation of vascular smooth muscle growth which is an important risk factor for hypertension and early atherosclerosis (Steinberger et al., 2003).
5.2 Risk Factors for Cardiac Complications in Childhood and Adolescent Diabetes

5.2.1 Type of Diabetes Mellitus

Children and adolescents with T2 DM have more cardiovascular risk factors than those with T1 DM. Rodriguez et al showed that about 14% of youths with T1 DM and about 92% of youths with T2 DM have two or more traditional cardiovascular disease (CVD) risk factors present in addition to glucose intolerance (Rodriguez et al., 2006). Faulkner conducted a study on 151 diabetic adolescents which showed significantly greater body mass index and age-adjusted BMI percentile for adolescents with type 2 than for those with T1 DM, denoting more characteristic overweight noted with the former group. Systolic and diastolic blood pressure and triglycerides were significantly higher in those with T2 DM; whereas, HDL-c, CV fitness, and physical activity expenditure (METS) were significantly lower than for those with T1 DM (Faulkner, 2010). Cardiovascular endurance and heart rate variability were significantly lower in adolescents with T2 DM in comparison to those with T1 DM. (Faulkner et al 2005)

5.2.2 Age at Onset of the Disease

Pozza et al found a direct correlation between the cIMT and risk factors for CVD with the age at onset of diabetes. The earlier the onset of T1 DM is, the more the intima-media thickness (Dalla Pozza, et al., 2007). Also Schwab et al showed in a study involved more than 27,000 German children and young adults with T1 DM that the presence of cardiovascular risk factors increased with age, suggesting the need for early screening and counselling to prevent their occurrence and early treatment if present (Schwab et al., 2006).

5.2.3 Gender Difference

Girls with T1 DM had significantly increased mean Hb A1C levels, body mass index, LDL cholesterol, and C-reactive protein, compared with boys who have the disease. In a study done by Zhou et al, the male group showed that BMI z–scores have significant positive correlations with insulin resistance and diastolic blood pressure while in the female group, BMI z–scores showed significant positive correlations with insulin resistance and systolic blood pressure (Zhou et al., 2010). Study performed in adults with T1 DM, showed unexpected increased female risk for microvascular complications in T1 DM (Monti et al., 2007). Also female adolescents showed lower levels of cardiovascular endurance than male adolescents (Faulkner et al 2005). Girls with T1 DM are particularly at risk of being overweight. They need larger insulin dose, and their HbA1c and cholesterol levels are higher than boys with T1 DM suggesting that girls are at increased insulin resistance and cardiovascular risk (Davis et al., 2012).

5.2.4 Puberty

Puberty is another risk factor that enhances development of vascular complications in diabetic children and the majority of the complications initially present or become more significant after the onset of puberty. This increased risk is due to numerous factors associated with puberty as impaired compliance with treatment during adolescent stage, the increase in blood pressure, and the effect of the increasingly produced sex steroids on hyperglycemia (Moore et al., 2009).
5.2.5 Body Mass Index

There is an increased prevalence of obesity among diabetic children and adolescent especially those with T2 DM. Obesity itself is associated with increased cardiac dimensions and higher LV mass. Adolescent obesity has been previously associated with increased LV volumes and mass (Chinali et al., 2006). It is also associated with diastolic dysfunction and may independently lead to heart failure (Kenchaiah et al., 2002). Obesity is an important factor contributing to structural changes in the heart augmenting the cardiovascular changes that occur in diabetes as impaired diastolic and systolic function, increased LV filling pressure, as well as increase left atrial volume which is used as a marker of long-standing diastolic disease. The higher LV mass in obese diabetic children and adolescents may reflect normal physiological growth in response to higher fat-free mass (FFM) as LV mass is related to body composition, in particular FFM. There is also increase risk of hypertension among the obese children. Patients with a higher BMI had a higher systolic and diastolic BP, and also higher total and LDL cholesterol levels. A significant thickening of the endothelial wall has been demonstrated in obese children. Obesity increases the risk of insulin resistance in the young diabetics which increases the risk of hypertension, and abnormal lipid profile. So; it is reasonable to suggest that lifestyle modification and weight control in childhood could reduce the risk of developing the insulin resistance syndrome, T2 DM, and cardiovascular disease. As obesity is associated with hypertension and dyslipidemia, a patient’s poor nutritional status is of high risk of developing diabetic vascular complications. (Whalley et al., 1999; August et al., 2008; Villa et al., 2000)

5.2.6 Metabolic Control (HbA1c)

Poor metabolic control among adolescents is related to their changing physiology (pubertal growth and development) as well as to behavioral and adherence issues. Young diabetics with poorer metabolic control tended to have lower levels of cardiovascular endurance (Faulkner et al., 2005). Poor metabolic control can lead to early onset of diabetic neuropathy and development of severe consequences including cardiovascular autonomic dysfunction and ventilatory dysfunction during sleep. Good metabolic control is crucial for the prevention of long-term diabetic complications. Good metabolic control and intensified insulin therapy are associated with a better health-related quality of life (Wagner et al., 2005). Lower HbA1c was significantly associated with better adolescent-rated quality of life (Hoey et al., 2001). Metabolic control is an important determinant of lipid profile in diabetic children. Metabolic control may contribute to the subsequent risk of cardiovascular disease and possibly the development of incipient diabetic nephropathy (Abraha et al., 1999).

5.2.7 Exercise Beliefs and Physical Activity

Cardiovascular fitness is the direct measure of maximal oxygen uptake during a participant's exercise of progressive intensity. Exercise is an essential component in blood glucose regulation for T1 DM patients, along with insulin management. Adolescents with T1 DM, being more physically fit can lead to better overall glucose control and a reduction in serum lipids. Exercise fitness was associated with improved lipids, Hb A1c, health perception, cardiovascular fitness, and athletic competence in adolescents with T1 DM (Faulkner, 2010). Physical activity is a strong predictor of cardiovascular fitness and exercise beliefs consistently predicted both frequency and time domain heart rate variability (HRV) measures (Faulkner et al., 2005). Early findings of poor physical fitness; lower HRV; fewer positive beliefs about exercise, and less active lifestyles highlight the importance of developing culturally sensitive interventions for assisting youth to make lifelong changes in their physical activity routines. Females, those with poorer met-
abolic control, and minority youth with T2 DM may be particularly vulnerable to later cardiovascular disease (Faulkner et al., 2005).

5.3 Electrocardiography (ECG) Finding in Diabetic Children

5.3.1 Heart Rate Variability

Heart rate variability (HRV) is good tool to measure the cardiac autonomic control, and disturbances in HRV have been documented in patients with diabetic autonomic neuropathy. HRV can be determined using 24-h Holter recordings. HRV depends on the balanced effects of both sympathetic and vagal activity on the sinus node. HRV analysis can characterize and quantify variations in sympathetic and vagal activity and has been used to foster a better understanding of physiological and pathological processes in adults and children (Massin et al., 1999). In diabetic children with mean Hb A1c >10%; a reduction in HRV was predictive for onset of symptomatic autonomic neuropathy (Rollins et al., 1992). Therefore, all T1 DM patients should be screened by HRV analysis for that complication beginning at the first stage of puberty regardless of illness duration, microalbuminuria, and level of metabolic control.

5.3.2 P wave Dispersion

Another tool to evaluate the cardiovascular autonomic function is P wave dispersion. P wave dispersion is an ECG index that measures the difference between the longest and the shortest P wave duration recorded from multiple different ECG surface leads. It shows a diurnal variation in healthy subjects such as shortest in summer and longest in winter. It has a good predictive value for assessment the risk of having atrial fibrillation (AF) in various subclinical cardiac disorders (Kose et al., 2002). In diabetic children; there was an increase in the dispersion of the p wave that could reveal the onset of cardiac electrophysiological heterogeneity before it is possible to detect autonomic (both parasympathetic and sympathetic) dysfunction with other tests (Imamoglu et al., 2008).

5.3.3 Corrected QT interval (QTc)

Prolonged QTc interval and a larger QTc dispersion were found in a significant proportion of children and adolescents with diabetes. QT interval was found to be prolonged in diabetic children and adolescents, with no interrelationship in patients between Hb A1c, diabetes duration and length of QTc. However, moderate correlation was found between dose of insulin administered in 24 hours and length of QTc (Riabykina et al., 2007). The same finding was confirmed by Shiono et al who studied children and adolescents aged 7-20 years with poor glycaemic control (Hb A1c > 10%) with signal-averaged ECG; they found a prolonged filtered QRS duration and a significantly low root mean square voltage, demonstrating subclinical cardiac impairment (Shiono et al., 2001). In difficult controlled diabetes, hyperinsulinemia-induced hypoglycaemia can prolong the QTc interval and decrease T-wave area and amplitude. Murphy et al showed that young subjects with T1 DM had prolonged QTc which occurred frequently with spontaneous overnight hypoglycaemia which may be related to insulin-induced hypokalaemia. Prolonged QTc also occurs frequently during DKA and is correlated with ketosis. This abnormal cardiac repolarisation occurs consistently during insulin-induced hypoglycaemia. Potassium infusion or beta-blockade prevents increased QT dispersion but only partially prevents QT lengthening (Murphy et al., 2004).
5.4 Echocardiographic Finding in Diabetic Children

Children and early adolescents with DM rarely have insight on the significance of DM, and their diet is difficult to control. An alteration of myocardial function induced by DM may begin earlier than generally thought, and these changes are accelerated when glycaemic control is poor. These impose the need for early detection of the cardiac dysfunction among those children. Doppler echocardiography is a reliable simple non-invasive and reproducible tool to assess early impairment of cardiac function and for serial follow up of such patients. Diastolic dysfunction was twice as common as systolic dysfunction. The diabetes induced myocardial damage affects diastolic function before systolic function. Diastolic abnormalities could be observed even in absence of other complication but both diastolic and systolic dysfunction usually observed in presence of severe cardiac complications. Early diastolic dysfunction showed an early impairment of LV filling and is expressed by reduced LV compliance. Diastolic dysfunction is manifested by significant reduction of E wave and E/A ratio with more contribution of atrial component to the LV filling greater than 0.25. Diastolic dysfunction is also associated significant prolongation of isovolumic relaxation time. These changes are more evident during isometric exercise.

Stress Doppler echocardiography is a reliable tool to detect early diastolic dysfunction in diabetic patients. The diastolic dysfunction related to diabetes duration, cardiac autonomic dysfunction and genetic factors but its relation to glycaemic control or microvascular complications is controversial. A reduced LV cavity size and increased atrial ejection were noted in children with insulin-dependent diabetes even in absence of hypertension, nephropathy or ischaemic heart disease, suggesting the existence of a metabolically-induced cardiomyopathy. Using M-mode echocardiography, morphological parameters and systolic time-intervals (fractional shortening; ejection fraction) could be determined. M-mode echocardiography showed a high prevalence of echocardiographic abnormalities in diabetic patients that increased with age. Mean dimensions of the left atrium, RV, and LV (systolic and diastolic) could be increased significantly in diabetic individuals. Hypertrophy of the interventricular septum was present in some patients older than 12 yr of age. Echocardiographic abnormalities in asymptomatic young diabetic adolescents can be elucidated by post-exercise echocardiography (Kim et al., 2010; Baum et al., 1987).

6 Prevention of Complications of Diabetes Mellitus

6.1 Measures to Decrease Effects of Diabetes on Fetal Cardiovascular System

If the pregnancy is planned, the most important aim is to achieve the best possible glycaemic control in women entering their reproductive years before pregnancy to prevent major forms of cardiac and non-cardiac anomalies. Implementation of preconception counselling, emphasizing strict glycaemic control before and throughout pregnancy reduces the rate of perinatal mortality and malformations. Intensive glucose management should be initiated with a goal to keep Hb A1C around 6.1%. Dietary and diabetic counselling should be offered with daily multivitamin with at least 400 g of folic acid. Unfortunately; unplanned pregnancy occurs in about two-thirds of women with diabetes leading to a persistent excess of malformations in their infants (Vargas et al., 2010). Counselling against pregnancy should be done in patients with Hb A1C ≥10%. Comprehensive ophthalmologic examination and thyroid function tests should be performed with strict follow up of renal functions. Pre-pregnancy care from specialised multi-disciplinary clinics, involving optimisation of glycaemic control and prescription of folic acid, could con-
siderably decrease the observed rates of malformation. It is now routine practice to advice women to take 5 mg of folic acid daily before conception and for the first trimester (Taylor & Davison., 2007).

During pregnancy; adequate glycaemic control should be maintained. Fluctuations in glucose values rather than basal state may be more important determinants of fetal cardiac and general somatic growth in maternal diabetes. Diabetic counselling should be readily available to help manage rapidly changing insulin requirements. Insulin pump should be considered if proper glycaemic control is not attainable. Repeating ophthalmologic assessment should be done at 16-18 weeks if baseline retinal examination was abnormal and at 28 weeks if ophthalmologic assessment was normal at baseline. Fetal anatomy scan with 4-chamber cardiac imaging should be performed at 18-20 weeks for early detection of major cardiac anomalies. Monthly fetal ultrasound to assess growth and amniotic fluid levels should be performed after 28 weeks of gestation with daily fetal movement counts. Biweekly fetal monitoring (NST) can be started at 32 weeks of gestation, or earlier if needed. Maternal immune-stimulation and maternal antioxidant therapy in fetal protection against exposure to teratogens such as DM are not yet completely elucidated and are worth research attention (Punareewattana et al., 2004). Delivery at about 38 weeks’ gestation is advised for women with DM to minimise the risk of unexplained late fetal death. The timing and mode of delivery should be determined on an individual basis based on best possible assessments of risk to mother and baby.

6.2 Measures to Decrease Effects of Diabetes on Neonates and Infants

Strict diabetes control before and during pregnancy may reduce the severity of HCMP. However, other studies found no relationships between the echocardiographic results and the metabolic control of pregnancy or fetal characteristics, suggesting that strict maternal diabetes control may not prevent accelerated fetal cardiac growth and abnormal development of cardiac function (Sheehan et al., 1986). The high incidence of the cardiac manifestations in IDM and the risk of occurrence of some severe problems, require a complete cardiac examination from the first few days of life and a follow-up schedule until the normalization of the cardiac parameters (Dimitriu et al., 2004).

6.3 Measures to Decrease Effects of Diabetes on Children and Adolescents

Controlling weight gain, and enhancing physical activity, and improvement in glycemic control are important aspects to decrease the cardiovascular complication in diabetic children and adolescents. It is important to keep LDL-cholesterol in diabetic children and adolescents less than 100 mg/dl. They have to follow a meal plan developed by a registered dietician, diabetes educator, or physician. Those children need to practice regular physical activity, ideally a total of 60 minutes each day. Physical activity helps to lower blood glucose levels and increase insulin sensitivity, especially in children with type II. It is important to monitor hypertension among those children. ACE inhibitors should be considered for the treatment of hypertension in children as they have beneficial effects on slowing progression or preventing diabetic nephropathy (Rosenbloom et al., 2009).

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