MYOCARDIAL PERFORMANCE INDEX IN PEDIATRIC PATIENTS WITH TYPE 1 DIABETES

Thesis

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By

Sanaa Omer Mohamed Gamma
(M.B;B.Ch)

Under the supervision of:

Prof. Dr. Shereen Abdelghaffar
Professor of Pediatrics
Faculty of Medicine, Cairo University

Prof .Dr. Amira Esmat
Assist. Professor of Pediatrics
Faculty of Medicine, Cairo University

Prof .Dr. Rasha Ammar
Assist. Professor of Pediatrics
Faculty of Medicine, Cairo University

Faculty of Medicine
Cairo University
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ABSTRACT

Background: Cardiovascular disease is the most common cause of death in patients with diabetes mellitus (DM).

Aim of work: **To** evaluate whether myocardial performance index detects a subclinical impairment of left ventricular systolic and diastolic function in patients with of type 1 diabetes, without coronary artery disease, with or without hypertension. Furthermore, to evaluate whether myocardial performance index and some echocardiographic parameters relate to the metabolic control.

Patients and methods : Sixty patients with type 1 diabetes mellitus of varying diabetic duration and 25 age and sex matched healthy controls were studied. All participants had no structural cardiac abnormality. All subjects underwent standard and Doppler echocardiography for the assessment of the Doppler-derived myocardial performance index and cardiac dimensions. In all diabetic patients, a glycated haemoglobin test was also performed.

Results: Differences were observed in blood pressure, BMI, and conventional echocardiographic parameters comparing diabetic patients and the controls ($p = 0.000$). Myocardial performance index was significantly higher in diabetic patients, compared to controls, and was higher in males than females and in diabetic patients more than 3years duration than those less than 3yrs duration. Myocardial performance index significantly correlated to glycated haemoglobin ($r=0.46$, $p = 0.003$). Concerning cardiac dimensions, diabetic group showed statistically significant increased LA dimensions ($p = 0.033$), increased septal hypertrophy ($p = 0.010$), increased LVPW dimensions ($p = 0.003$), increased LVEDD ($p = 0.000$), significant lower systolic function in the form of lower EF % ($p = 0.000$), and lower FS ($p = 0.000$). EF was statistically significantly lower in females than in males ($p = 0.020$). Females had higher LVPW and LVEDD than males ($p = 0.028$, 0.000 respectively), Diabetic patients with duration more than or equal to 3yrs shows statistical significant higher Aortic, left atrial and PA dimensions more than diabetics with less than 3yrs duration. The cardiac dimensions were correlated to the glycoslated hemoglobin in its different levels but the resulted no statistical significance.

Conclusion: An early affection of left ventricular performance was shown by myocardial performance index in patients with type 1 diabetes without coronary artery disease, independent of the presence of hypertension. This index can provide a feasible tool to detect pre-clinical diabetic cardiomyopathy.

Key Word: Diabetic cardiomyopathy, LV function

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List of Abbreviations

ACE	Angiotensin-converting enzyme
AGEs	Advanced glycosylation end-product
AHA	American Heart Association
AHA	American heart association
AngII	Angiotensin II
ANS	Autonomic nervous system
AO	Aorta
ATP	Adenosine triphosphate
BMI	Body mass index
BNB	B-natruetic peptide
BP	Blood pressure
CA 2+	Calcium
CAD	Coranary artery Disease
cAMp	Cyclic Adenosine monophosphate
CAN	Cardiac autonomic neuropathy
CDC	Centers for Disease Control and Prevention
CHF	Congestive Heart Faliure
CIMT	Combined intema media thickness
CMR	Cardiac magnetic resonance
CVD	Cardiovascular disease
2D	Two-dimensional
DC	Diabetic cardiomyopathy
DCCT	Diabetes control and complication trial
DEMPU	Diabetes, Endocrine and Metabolic pediatric unit
Diastolic BP	Diastolic Blood Pressure
DKA	Diabetic ketoacidosis
DM	Diabetes mellitus
DMD	Diabetic myocardial disease
DMD	Diabetic myocardial disease
DPN	Diabetic peripheral Neuropathy
DRR	Diastolic relaxation rate

DRRe	Diastolic relaxation rate during the first third of diastole
DRRt	Diastolic relaxation rate during the whole diastole.
ECM	Extracellular matrix
EF	Ejection fraction
FFA	Free Fatty Acids
FPG	Fasting blood glucose
FS	Fraction Shortening
GADA	Glutamic acid decarboxylase Antibodies
GDM	Gestational diabetes mellitus
GLUT-4	Glucose transporter 4
HbA1C	Glycosylated haemoglobin
HDL	high density lipoprotein
HF	Heart Failure
HLA	Human leukocyte antigen
^{1}H-MRS	^{1}H-magnetic resonance spectroscopy
IA-2	Insulinoma-associated antigen-2
IAA	Insulin autoantibodies
ICA	Islet cell antibodies
ICT	Isovolumetric contraction time
IDDM	Insulin dependant diabetes mellitus
IGF-I	Insulin -like growth factor-1
IMT	Intima-media thickness
IRS	Insulin resistance syndrome
IVRT	Isovolumetric relaxation time
IVS	Inter ventricular septum
LA	Left atrium
LV	Left Ventricle
LVEDD	Left ventricle end diastolic dimeter
LVESD	Left ventricle end systolic dimeter
LVET	Left ventricular ejection time
LVL	Left ventricular hypertrophy
LVPW	Left ventricular posterior wall
MDI	Multiple daily insulin injection

MI	Myocardial Infarction
MODY	Maturity onset diabetes of the young
MPI	Myocardial Performance Index
mRNA	Messenger Ribo nucleic acid
NEFAs	Nonesterified fatty acids
NIDDM	Non-insulin-dependent diabetes mellitus
OGTT	Oral glucose tolerance test
PA	Pulmonary artery
PAS	Periodic acid-Schiff
PEP	Pre-ejection period
PER	Peak ejection rate
PFR	Peak filling rate
^{31}P-MRS	Phosphorus-31-nuclear MR spectroscopy
ROS	Reactive oxygen species
RV	Right ventricle
SD	Standard deviation
SERCA2a	Sarcoplasmic reticulum calcium
SPSS	Statistical package for the social science
T1DM	Type 1 diabetes mellitus
MR	Magnetic resonance
TD	Tissue Doppler
T-PER1	Time from the start of systole to PER
T-PFR2	Time from end-systole to PFR
WHO	World health organization

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INTRODUCTION

Evidence has been accumulating for the presence of myocardial dysfunction in patients with type 1 diabetes mellitus (T1DM) in the absence of ischemic, valvular, or hypertensive heart disease which may be partially responsible for the increased risk of congestive heart failure among T1DM patients. There is growing evidence to support the existence of diabetic cardiomyopathy as a distinct clinical entity that may lead to heart failure independent of coronary artery disease or hypertension (**Boudina et al., 2007).**

Diabetic cardiomyopathy is a distinct primary disease process, independent of coronary artery disease, which leads to heart failure in diabetic patients. Epidemiological and clinical trial data have confirmed the greater incidence and prevalence of heart failure in diabetes. Novel echocardiographic and MR (magnetic resonance) techniques have enabled a more accurate means of phenotyping diabetic cardiomyopathy **(Omar et al., 2009).**

Incidence of DC independent of AH and CHD still remains the subject of much controversy, though, its etiology remains unclear. It is generally accepted that the most important mechanisms of DC are probably metabolic disturbances, microangiopathy, myocardial fibrosis and CAN **(Francis, 2001).**

The prevalence of cardiomyopathy has been reported in type1, as well as type2 diabetes, suggesting that the metabolic consequences of hyperglycemia rather than the type of diabetes lead to diabetic cardiomyopathy (**Poirier et al., 2001**).

Because diabetic cardiomyopathy is gradual in onset, its manifestations may be masked by compensatory mechanisms for many years. The ability to detect early changes in diabetic cardiomyopathy, using non-invasive tests, is therefore, vital to define the natural history of diabetic cardiomyopathy and to determine long-term strategies (**Poirier et al., 2001).**

AIM OF WORK

The aim of the present study is:

- To detect any Echocardiographic findings suggestive of alteration in cardiac function in children with type 1 diabetes.
- To correlate cardiac indices with different demographic, anthropometric, and clinical data (age, sex, duration of diabetes, Body Mass Index and blood pressure) as well as laboratory data (glycoslated hemoglobin in diabetic group).
- To assess whether children and adolescents with type1 diabetes have early echocardiographic signs of subclinical cardiac dysfunction and whether sex, state of metabolic control, and diabetes duration are of influence.

TYPE 1 DIABETES

Diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction, and failure of various organs, especially the eyes, kidneys, nerves, heart, and blood vessels ***(American Diabetes Association, 2009).***

Hyperglycemia is the land mark of this metabolic syndrome and is the parameter most closely monitored to make diagnosis and to judge therapy. The vast majority of cases of diabetes fall into two broad etiopathogenetic categories. In type 1 diabetes, the cause is an absolute deficiency of insulin secretion. Individuals at increased risk of developing this type of diabetes can often be identified by serological evidence of an autoimmune pathologic process occurring in the pancreatic islets and by genetic markers. In type 2 diabetes, the cause is a combination of resistance to insulin action and an inadequate compensatory insulin secretory response ***(The Expert Committee on the diagnosis and classification of DM, 2009).***

Classification of diabetes

Diabetes is not a single entity, but rather a heterogeneous group of disorders in which there are distinct genetic patterns as well as other etiologic and pathophysiologic mechanisms that lead to impairment of glucose tolerance ***(ISPAD, 2009)***

A classification of diabetes is presented in table (1).

Table (1): Etiologic Classification of Diabetes Mellitus.

I. Type 1 diabetes (fl-cell destruction, usually leading to absolute insulin deficiency).
A. Immune mediated.
B. Idiopathic.
II. Type 2 diabetes (may range from predominantly insulin resistance "with relative insulin deficiency to a predominantly secretary defect with or without insulin resistance).
III. Other specific types:
A. Genetic defects of ft-cell **function:**
1. Chromosome 12, HNF-1 a (MODY3).
2. Chromosome 7, glucokinase (MODY2).
3. Chromosome 20, HNF-4-α (MODY1).
4. Chromosome 13, Insulin promoter factor-1 (IPF-1; MODY4).
5. Chromosome 17, HNF-I β(MODY5).
6. Chromosome 2, Neuro Dl (MODY6).
7. Mitochondrial DNA.
8. Others.
B. Genetic defects **in insulin** action:
1. Type A insulin resistance.
2. Leprechaunism.
3. Rabson-Mendenhall syndrome.
4. Lipoatrophic diabetes
5. Others
C. Diseases of the exocrine pancreas:
1. Pancreatitis
2. Trauma/pancreatectomy
3. Neoplasia
4. Cystic fibrosis
5. Hemochromatosis
6. Fibrocalculous pancreatopathy
7. Others
D. Endocrinopathies:
1. Acromegaly
2. Cushing's syndrome
3. Glucagonoma
4. Pheochromocytoma
5. Hyperthyroidism
6. Somatostatinoma
7. Aldosteronoma. •
8. Others
E. Drug- or chemical-induced:
1. Vacor
2. Pentamidine
3. Nicotinic acid

4. Glucocorticoids
5. Thyroid hormone
6. Diazoxide
7. β-adrenergic agonists
8. Thiazides
9. Dilantin
10. a-Interferon
11. Others

F. Infections:

1. Congenital rubella
2. Cytomegalovirus
3. Others

G. Uncommon forms of immune-mediated diabetes:

1. "Stiff-man" syndrome
2. Anti-insulin receptor antibodies
3. Others

H. Other genetic syndromes sometimes associated with diabetes:

1. Down's syndrome
2. Turner's syndrome
3. Wolfram's syndrome
4. Friedreich's ataxiax
5. Huntington's chorea,
6. Laurence-Moon-Biedl syndrome
7. Myotonic dystrophy
8. Porphyria
9. Prader-willi syndrome
10. Others

IV. Gestational diabetes mellitus (GDM).

HNF: Hepatocyte nuclear factor

MODY: Maturity onset diabetes of the young