European Journal of Applied Sciences 2 (2): 62-69, 2010
ISSN 2079-2077

Variations in the Enzyme Activity of Carbohydrate Metabolic Disorder on Cardiac Function

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Abstract: It is estimated that 70% to 80% of diabetic patients die of cardiovascular complications, such as ischemic heart disease, atherosclerosis, hypertension, arrhythmias, and congestive heart failure. All these complications seem to arise from the occurrence of oxidative stress and the development of calcium-handling abnormalities. In particular, the genetic machinery in both cardiac and vascular cells is altered in chronic diabetes. Therefore, a novel therapy needs to be designed for the treatment of diabetes-induced cardiovascular abnormalities. The present clinical study has shown that the abnormalities in cardiac functions. The concentration of various enzymes like SGPT, CPK and LDH were slightly elevated in diabetic patients compared to normal level, which were mainly originated from the liver and heart.

Key words: Serum glutamate pyruvate transaminase or alanine transaminase (SGPT or ALT) · Creatine phospho kinase(CPK) · Lactate dehydrogenase(LDH)

INTRODUCTION

Diabetics have greater prevalence of heart disease such as ischemic heart disease, hypertensive heart disease, cardiomyopathy and congestive heart failure [1-3]. The diabetic state shows many metabolic abnormalities, which adversely influence atherosclerosis causing coronary artery disease and peripheral vascular disease. On coronary angiography, diabetics often have multivessel CAD when compared to age and sex matched non-diabetics. Ischemic chest pain is blunted in DM. Myocardial ischemia or myocardial infarction may be associated with only mild symptoms or may be totally silent. Silent infarctions are more common in diabetics (39%) when compared to non-diabetics (22%) [4]. As regards clinical presentation of coronary artery disease in diabetics, it may present as stable angina, unstable angina or acute myocardial infarction. But the clinical features and course of heart disease in diabetes mellitus have some peculiarities. Patient may present with breathlessness as angina equivalent or acute dyspnoea due to left ventricular failure in acute myocardial infarction. In other cases of acute myocardial infarction, patient may present with arrhythmias or hypotension without chest pain. Hypertension is more common in diabetics especially in women than in non-diabetic patients. Diabetic nephropathy is more common in patients having hypertension and DM. Diabetic nephropathy is accompanied by a greater incidence(37%) of cardiovascular mortality as compared to the general population. This is a partly because of associated hypertension [5]. It may result from microangiopathy, metabolic changes or possibly both. Patient gets symptoms of left ventricular dysfunction. There are features of left ventricular failure presenting as dyspnoea on exertion or nocturnal dyspnoea. Acute myocardial infarction in presence of pre-existing diabetic CMP will lead to a morbid course. Clinically, heart is enlarged and usually third and fourth sounds are audible. Basal crepitations may be present [5, 6].

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History is not of much help in the diagnosis of myocardial infarction in diabetics. The patient may present with atypical symptoms like dyspnoea, fatigue, nausea, vomiting or confusion. These may be attributed to metabolic disturbances, leading to delay in diagnosis. Asymptomatic myocardial infarction is associated with increased cardiac morbidity and mortality related to delay in seeking medical opinion [7] compared diabetic and non-diabetic patients in whom acute myocardial infarction was associated with atypical symptoms. These patients were older than those with classic symptoms. Cardiogenic shock was noted in 35% patients with atypical presenting symptoms and the hospital mortality was 50%. Owing to autonomic neuropathy, diabetics have sinutachycardia. However, there is little variation of pulse rate with respiration (absence of sinus arrhythmia), decreased reflex bradycardia after Valsalva manoeuvre and decreased sympathetic response to titling and poor response to carotid pressure. Loss of parasympathetic activity may be more than loss of sympathetic activity. Clinically, this presents as orthostatic hypotension, painless myocardial infarction and cardio respiratory arrests [7, 8]. Autonomic neuropathy is associated with increased cardiovascular mortality. Upto 33% of deaths are sudden deaths. Since parasympathetic fibres are affected earlier, there is relative increase in sympathetic tone and these results in tachycardia and inappropriate coronary vasoconstriction leading to angina pectoris. Sympathetic fibres get damaged at least 5 years after parasympathetic fibres and this causes postural hypotension. Patients having autonomic neuropathy may have sudden painless death. Some of these may be due to arrhythmias secondary to silent myocardial infarction [8, 9].

Oral hypoglycaemic drugs (both sulphonylureas and biguanides) accelerate CAD, adversely affect myocardial function and facilitate heart disease in diabetics [4]. The atherosclerosis process in a diabetic is more commonly seen than in a non-diabetic. The risk factors for diabetic vascular disease are severity and duration of diabetes, age, genetic factors, smoking, hypertension, hyperlipidaemia and insulin resistance with compensatory hyperinsulinaemia. Patient suffers from claudication, nocturnal pain, rest pain in limbs, repeated infections of foot, skin atrophy, ulcerations and patchy areas of gangrene. Nocturnal pain is a form of ischemic neuritis that precedes rest pain [10]. Autonomic dysfunction is evident in both obesity and diabetes. In persons with diabetes, impaired cardiovascular autonomic activity is characterized by a reduction in parasympathetic tone with a relative increase in sympathetic activity and is specifically associated with a number of clinically significant manifestations including exercise intolerance, intraoperative cardiovascular lability, orthostatic hypotension, silent myocardial ischemia, and increased risk of mortality. This overview will examine the relationship of the autonomic nervous system in obesity and diabetes and explore the effect of weight loss on autonomic function [11]. Obesity is an important contributor to the risk of developing insulin resistance, diabetes, and heart disease. Alterations in tissue levels of malonyl-CoA have the potential to impact on the severity of a number of these disorders. This review will focus on the emerging role of malonyl-CoA as a key "metabolic effector" of both obesity and cardiac fatty acid oxidation. Both hypothalamic and cardiac studies have demonstrated that control of malonyl-CoA levels has an important impact on obesity and heart disease. Targeting enzymes that control malonyl-CoA levels may be an important therapeutic approach to treating heart disease and obesity [12].

Diabetes also induced global perturbations in the expression of genes regulating cardiac fatty acid metabolism, whose dysfunction is likely to play a key role in the promotion of oxidative stress, thereby contributing to the pathogenesis of diabetic myocardial disease. In particular, these data point to impaired regulation of mitochondrial beta-oxidation as central in the mechanisms that generate DCM pathogenesis. This study provides a comprehensive molecular snapshot of the processes leading to myocardial disease in diabetes [13]. Baroreceptors dysfunction is evident in diseases such as coronary artery disease, heart failure, arterial hypertension, diabetes mellitus and obesity. Blunted BRS provides prognostic information for cardiovascular diseases and possibly for diabetes, while its' prognostic information for obesity is not yet established. This review deals with the mechanisms affecting baroreflex function, the newer techniques of BRS estimation and the most recent insights of baroreflex function in the healthy population and in various diseases with emphasis on diabetes and obesity. In addition, the clinical implication of a reduced BRS in these disorders is discussed [14]. Increased urinary albumin excretion (UAE) has been shown to be associated with increased cardiovascular mortality in patients with type 2 diabetes [15]. The development of experimental type 2 diabetes mellitus in rats was accompanied by dysfunction of inhibitory and stimulatory heterotrimeric G-proteins, components of hormone-sensitive adenylate cyclase signal system. These changes reflect abnormal coupling between receptors and G-proteins in tissues of diabetic patients [16].

MATERIALS AND METHODS

The study included 10 patients in the age group between 45-65 yrs, treated at the Sooriyan Clinical Laboratories, Avadi in Chennai. All subjects had glucose level greater than 150mg/dl. The patients were monitor during a period of one month. All subjects gave informed consent to participate in this study. The venous blood samples were drawn for all the estimation. Blood samples from fasting subjects were collected. The Serum was separated and the following biochemical parameters were analyzed. Parameters analyzed include estimation of serum glutamate pyruvate transaminase or alanine transaminase (SGPT or ALT), creatine phospho kinase(CPK) and lactate dehydrogenase (LDH).

Serum Glutamate Pyruvate Transaminase or Alanine Transaminase (SGPT or ALT): The enzyme SGPT or ALT catalyzes the following reaction:

alanine + α-ketoglutarate ➔ oxaloacetate + pyruvic acid

Under controlled condition, the pyruvic acid is made to react with DNPH. The hydrazone is coupled to NaOH to give a brown color. The OD is measured using a green filter at 540 nm. Two test tubes labeled as test and blank are taken and to all the tubes 0.5 ml of GOT substrate is taken. The tubes are incubated at 37°C. in a water bath for few minutes. 0.1 ml of serum is added to the test and the tubes are incubated for 60 minutes at 37°C. Add 0.5 ml of DNPH reagent to both tubes, mix well and incubate at room temperature for 20 minutes. Add 5 ml of 0.4N NaOH to both the tubes and wait for 10 minutes. The OD is read using a green filter at 540 nm.

Creatine Phospho Kinase (CPK) (Hughe's Method): Creatine phosphate and ADP are used as substrate with Mg^{2+} and cysteine as activators. Barium hydroxide and zinc sulphate are used to precipitate proteins and to prevent hydrolysis of creatine phosphate, which takes place in acid solution. *p*-chloromercuribenzoate is added to complete the inactivation of the creatine kinase and to prevent interference of cysteine with the colour development. Measured into each of two tubes 0.2ml magnesium solution, 250µl creatine phosphate, 0.1ml cysteine and 0.1ml serum, mix and warm to 37°C in a water bath. To one (the test) add 250µl ADP, mix and incubate 30 minutes. Meanwhile add 250µl ADP to the blank followed at once by 0.5ml *p*-chloromercuribenzoate. At the end of the incubatio add 0.5ml P-chloromercuribenzoate to the test, then to both tubes add 0.5ml Barium hydroxide followed by 0.5ml zinc sulphate, shaking well after each addition. Centrifuge. To 1ml of supernatant add while shaking 2.5ml α-naphthal, 0.5ml dilute diacetyl and 6ml water, incuba at 37°C for an hour, mixing by inverting at 15minutes intervals. Then read at 520nm. Dilute the creatine standard 1 to 5 and put through 250µl of this instead of the ADP for the standard, and for the reagent blank 250µl of water instead of ADP completing both as described above.

Serum creatine kinase activity (U/L)

$$= \frac{\text{Reading of unknown (U) - Reading of blank (B)} \times 10^3 \times \text{creatine taken (µmol)}}{\text{Reading of standard (S)- Reading of reagent blank (RB)} \times \text{Incubation time (min)} \times \text{serum volume (ml)}}$$

$$\frac{(U-B)}{(S-RB)} \times \frac{10^3 \times 1.2 \times 0.25}{30 \times 0.1}$$

Lactate Dehydrogenase (LDH) (Wroblewski and LaDue Method): Lactate dehydrogenase (LDH) catalyses the reaction:

$$\text{lactate} + NAD^+ \leftrightarrow \text{pyruvate} + NADH + H^+$$

The optimum pH with pyruvate as substrate is 6.8 to 7.5 but with lactate is appreciably higher at 9 to 10. Measured 2.4ml phosphate buffer in to a spectrophotometer cuvette with 1cm light path, add 0.1ml serum and 0.1ml NADH. Mix and allow stand 20minutes at 25°C for any keto-acids in the serum to be reduced, then add 0.1ml pyruvate prewarmed to 25°C, mix, and moniter the rate of change in extinction at 340nm at this temperature.

Serum lactate dehydrogenase activity (U/L) =

$$\Delta E_{340}\ /\text{min} \times \frac{1000}{\text{Volume of serum used (ml)}} \times \frac{\text{volume of the cuvette (ml)}}{6.3}$$

$$= E340\ /\text{min} \times \frac{1000}{0.1} \times \frac{2.7}{6.3}$$

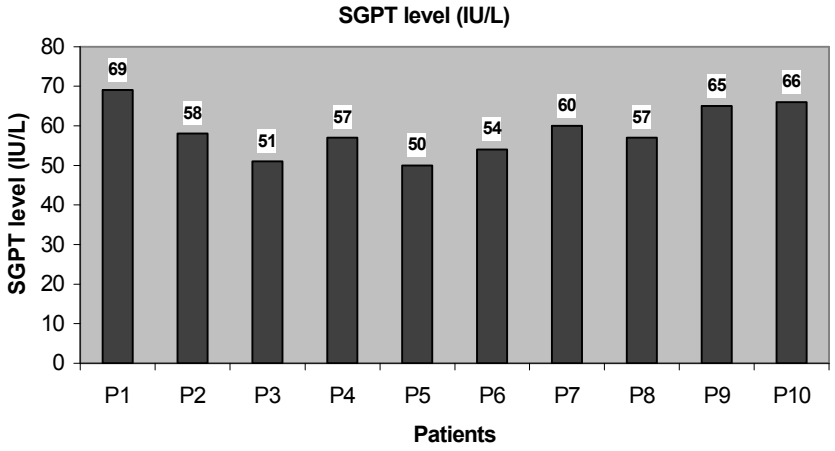
$$= \Delta E_{340}\ /\text{min} \times 4286$$

RESULTS AND DISCUSSION

The results obtained from the above mentioned parameters analyzed are listed below:

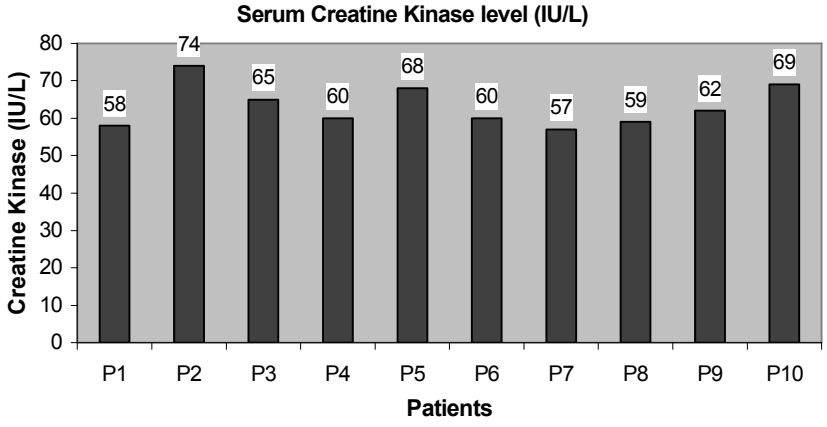
1.SGPT level (IU/L)

S. No.	Sex	Age	Body weight	SGPT level (IU/L)
P1	FM	47	68	69
P2	M	52	72	58
P3	M	54	64	51
P4	FM	48	68	57
P5	M	50	72	50
P6	M	62	72	54
P7	FM	68	74	60
P8	FM	68	64	57
P9	M	54	68	65
P10	M	63	72	66



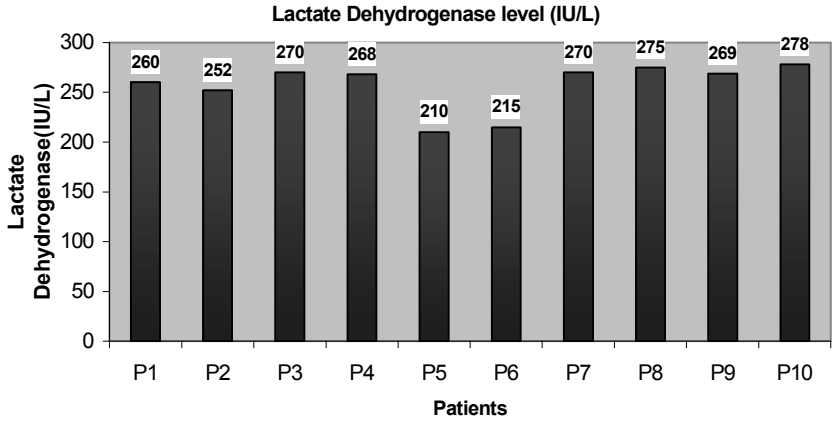
2. Creatine phospho kinase level (IU/L)

S. No.	Sex	Age	Body weight	SGPT level (IU/L)
P1	FM	47	68	58
P2	M	52	72	74
P3	M	54	64	65
P4	FM	48	68	60
P5	M	50	72	68
P6	M	62	72	60
P7	FM	68	74	57
P8	FM	68	64	59
P9	M	54	68	62
P10	M	63	72	69



3. Lactate dehydrogenase level (IU/L)

S. No.	Sex	Age	Body weight	SGPT level (IU/L)
P1	FM	47	68	260
P2	M	52	72	252
P3	M	54	64	270
P4	FM	48	68	268
P5	M	50	72	210
P6	M	62	72	215
P7	FM	68	74	270
P8	FM	68	64	275
P9	M	54	68	269
P10	M	63	72	278



Benedict's Test: Benedict's test was done to identify the presence of urine sugar present in diabetic patients. It is a routine test done for the diagnosis of urine sugar and rarely for certain body fluids and some chemical solution. Urine sample was taken in a separate test tube and the test was carried out. 5ml benedict's reagent was taken in a test tube and 9drops of test sample was added and heated till boiling in the bunsen flame and cool the tube and the colour change was noted and results were recorded.

S. No.	Sex	Age	Body weight	Result
P1	FM	47	68	Present++++
P2	M	52	72	Present++++
P3	M	54	64	Present+++
P4	FM	48	68	Present++++
P5	M	50	72	Present++
P6	M	62	72	Present++
P7	FM	68	74	Present+++
P8	FM	68	64	Present+++
P9	M	54	68	Present++++
P10	M	63	72	Present++++

Hyperglycemia occurs commonly in acutely and critically ill patients and has been associated with adverse clinical consequences. An emerging body of literature describes the beneficial effects of intensive glycemic monitoring and treatment (tight glycemic control, or "TGC"). This manuscript reviews the experience of a cohort of 5365 non-cardiac surgery patients admitted to the adult intensive care unit of a university-affiliated community hospital before and after implementation of TGC(17). Free fatty acids are the preferred substrate for the myocardium. However, under conditions of ischemia, glucose becomes the primary myocardial energy source. Its metabolism avoids the toxic end-products of free fatty acids, which include oxygen free radicals [18]. Diabetes is an established major factor of poor prognosis after an acute coronary syndrome. Recent studies have addressed the impact of abnormal glucose metabolism at the acute phase in patients without known diabetes. It has been found that abnormal glycemia regulation is more common than normal regulation in patients presenting with acute coronary syndrome, whatever the method used to evaluate blood glucose metabolism. Recent findings also

argue for a direct deleterious effect of hyperglycemia on myocardium [19]. The renin-angiotensin system (RAS) inhibition decreases cardiovascular and renal morbidity and mortality and the incidence of new onset type 2 diabetes [20]. The activation of the renin-angiotensin system plays an important role in diabetes-induced changes in SL and SR membranes as well as cardiac function [21]. The use of echocardiography as a screening tool in the asymptomatic diabetic population is problematic. Biomarkers of cardiac dysfunction have been proposed for diagnosis. The role of biomarkers in the diagnosis of this condition and proposed a diagnostic algorithm that may be useful for the assessment of asymptomatic patients with diabetes [22].

A global epidemic of type 2 diabetes exists and in the near future it may be closely associated with an epidemic of cardiovascular disease. Overwhelming evidence exists for the linear association between worsening glycaemic control and increased risk for coronary heart disease. Brief episodes of cardiac ischemia render the heart more resistant to subsequent ischemic events; this phenomenon is called ischemic preconditioning [23]. Accumulation of cellular damage with advancing age leads to atherothrombosis and associated cardiovascular disease. Two chief questions that remain unanswered are whether telomere shortening is cause or consequence of cardiovascular disease, and whether therapies targeting the telomere may find application in treating these disorders. Given that most research to date has focused on the role of telomerase, it is also of up most importance to investigate whether alterations in additional telomere-associated proteins may contribute to the pathogenesis of cardiovascular disease [24]. Patients with diabetes and hypertension have a higher incidence of coronary artery disease than do patients with diabetes or hypertension alone. The former patients also show impaired systolic and diastolic function and have more severe left ventricular hypertrophy as documented by echocardiography and at autopsy. Strict control of arterial pressure and glycemia may prevent or even ameliorate heart disease in patients with hypertension and diabetes [25]. Cardiovascular complications are the most common causes of morbidity and mortality in diabetic patients. Coronary atherosclerosis is enhanced in diabetics, whereas myocardial infarction represents 20% of deaths of diabetic subjects. Furthermore, re-infarction and heart failure are more common in the diabetics. Mechanistically, parasympathetic cardiac nerve dysfunction, expressed as increased resting heart rate and decreased respiratory variation in heart rate, is more frequent than the sympathetic cardiac nerve dysfunction expressed as a decrease in the heart rate rise during standing [26].

The aim of the study was to investigate the influence of various degrees of disorder of carbohydrate metabolism on cardiac function. Subjects were selected according to the degree of blood glucose level, age and sex and insulin levels. Disorders of carbohydrate metabolism are present when glucose level greater than 200mg/dl. Since patients included in this study all had greater glucose level. A female at the age of 47 whose body weight is 68 has the glucose level of 360mg/dl. A male at the age of 52 whose body weight is 72 has the glucose level of 338mg/dl. As such experiment has been made to 10 patients and the result was also the same. The liver helps maintain normal blood glucose concentration in the fasting and postprandial states. Loss of insulin effect on the liver leads to glycogenolysis and an increased breakdown of lipids especially triglycerides for hepatic glucose production. Abnormalities of triglyceride storage and lipolysis in insulin-sensitive tissues such as the liver are an early manifestation of conditions characterized by insulin resistance and are detectable earlier than fasting hyperglycemia. The precise genetic, environmental, and metabolic factors and sequence of events that lead to the underlying insulin resistance, however, is not fully understood. Clinical studies have shown that the cardiac function decreases. The serum enzymes concentration of SGPT, LDH and CPK are elevated in diabetic patients compared to normal level, which are mainly originate from the heart. It was found that the above enzyme levels are moderately increased in severe diabetic patients. It is also hypothesized that elevation in SGPT, a transaminase enzyme whose gene transcription is suppressed by insulin, could indicate impairment in insulin signaling rather than purely hepatocyte and cardiac injury. LDH is a specific marker that is known to rise in patients with type 2 diabetes. In epidemiological studies, it has a positive association with alcohol intake, cigarette smoking, coronary heart disease, BMI, systolic blood pressure, serum triglyceride, heart rate, uric acid, and hematocrit. It has an inverse association with physical activity level. Because LDH increases in diabetes and increases as BMI increases, it has been proposed as principal marker of cardiac dysfunction. A female at the age of 47 whose body weight is 68 has the insulin level of 29 mIU/ml. A male at the age of 52 whose body weight is 72 has the insulin level of 28

mIU/ml. As such experiment has been made to 10 patients and the result was also the same. A female at the age of 47 whose body weight is 68 has the SGPT level of 69 IU/L. A male at the age of 52 whose body weight is 72 has the SGPT level of 58 IU/L. As such experiment has been made to 10 patients and the result was also the same. A female at the age of 47 whose body weight is 68 has the LDH level of 260 IU/L. A male at the age of 52 whose body weight is 72 has the LDH level of 252 IU/L. As such experiment has been made to 10 patients and the result was also the same. Glycosylated haemoglobin, triglyceride, total cholesterol and urinary glucose levels are moderately elevated in both male and female diabetic patients compared to non-diabetics. The HDL cholesterol level was moderately decreased in both male and female diabetic patients compared to non-diabetics. Those patients who have high blood glucose levels have only small amount of HDL-Cholesterol. The above result gives the reason for elevated serum triglyceride and total cholesterol levels.

ACKNOWLEDGEMENT

Authors thank sincerely the Dr. Vel R. Rangarajan, Chairman, Dr. Sakunthala Rangarajan, Vice-Chairman, VELTECH Group of Educational Institutions and Dr. K. Siddappa Naidu, Principal, VELTECH MULTITECH Dr.Rangarajan Dr.Sakunthala Engineering College, Chennai – 600 062 for their unremitting encouragement and valuable advices.

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