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IMPLICATIONS OF PHYSICAL ACTIVITY ON THE MARKERS OF RENAL DAMAGE AMONG TYPE 2 DIABETIC SUBJECTS

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ABSTRACT

Diabetes mellitus is the fast spreading epidemic of the 21st century and mortality rate is high among the physically inactive middle and old aged people. Diabetic Nephropathy is the leading cause of End Stage Renal Disease and affects approximately 40% of Type 2 Diabetic patients and most of the patients entering dialysis are diabetic. In the present study the impact of physical activity on the markers of renal damage among young, middle and older aged diabetic subjects, living in semi urban area Thanjavur town, Tamil Nadu has been investigated. For the present study, the male subjects of 35-45, 46-55 and 56-65 years were selected. The activity of analyzed biomarkers of renal damage was found to be significantly elevated in elderly diabetic persons when compared to the physically active diabetic subjects. Increased blood urea production in diabetes may be accounted for by enhanced catabolism of both liver and plasma proteins. Uric acid is a strong and an independent risk factor for diabetes. Hyperglycemia induced elevated levels of plasma urea and creatinine are considered as significant markers of renal dysfunction. However the present study indicated that the Groups which are active physically and regularly doing exercise particularly walking has reduced renal damage markers nearly to the normal Group. There is a positive and significant correlation obtained between lifestyle modified people and diabetic control.

KEYWORDS: diabetes, liver enzymes, physical activity, walking.

INTRODUCTION

Diabetes mellitus is a clinically and genetically heterogeneous group of disorders characterized by abnormally high levels of glucose in the blood (hyperglycemia). It is the most common endocrine disease, characterized by metabolic abnormalities and long term complications involving the eyes, kidneys, nerves and blood vessels. Several distinct types of Diabetes mellitus exist and are caused by a complex interaction of genetics and environmental factors. The two broad categories of Diabetes mellitus are designated type 1 and type 2. Type 1 diabetes is the result of complete or near total insulin deficiency. Type 2 Diabetes mellitus is a heterogeneous group of disorders characterized by variable degrees of insulin resistance, impaired insulin secretion, and increased glucose production.[1] Lifestyle management is a fundamental aspect of diabetes care and includes diabetes self-management education and support, medical nutrition therapy (MNT), physical activity, smoking cessation counseling, and psychosocial care.

Physical inactivity is an independent risk factor for diabetes in Indians. Researchers looking at levels of physical activity among South Asians noted some awareness of its importance but a lack of putting it into practice.[2] The reasons included cultural norms, social expectations, time constraints and health problems. It has also been reported that healthcare professionals perceive South Asians as holding fatalistic beliefs surrounding their health status and are reluctant to provide lifestyle advice because of poor cultural and religious understanding, thus exacerbating the problem.[3] For decades exercise has been considered a cornerstone of diabetes management, along with diet and medication. However, high-quality evidence on the importance of exercise and fitness in diabetes was lacking until recent years.

Urea, uric acid, and creatinine are the parameters to diagnose functioning of the kidney. Changes in serum creatinine concentration more reliably reflect changes in GFR than do changes in serum urea concentrations.[4] Creatinine is formed spontaneously at a constant rate from creatinine, and blood concentrations depend almost solely upon GFR. Urea formation is influenced by a number of factors such as liver function, protein intake, and rate of protein catabolism.[5] Biologically, uric acid plays an important role in worsening of insulin resistance in animal models by inhibiting the bioavailability of nitric oxide, which is essential for insulin-stimulated glucose uptake.[6]

Consequently, this study aims to evaluate the kidney function among diabetes patients compared to non-diabetic control group. Serum urea, uric acid and creatinine are most widely

accepted parameters to assess renal status in susceptible diabetic and hypertensive subjects. They can be used as disease biomarkers which not only reflect renal function but are also associated with various extra renal conditions. It has therefore been suggested that these renal damage markers may be useful for assessing overall health status.

Keeping the above factors in mind, Thanjavur area has been selected for the present study. It comes in the category of semi urban area. Recent reports have pointed out that the actual causes of death among the diabetic subjects are usage of tobacco, physical inactivity, malnutrition and excessive use of alcohol. In the present study the impact of life style intervention, physical activity on the renal damage markers among young, middle and old aged diabetic subjects, living in Thanjavur town, Tamil Nadu has been investigated.

MATERIALS AND METHODS

For the present study, only the male subjects were selected. The age groups selected were 35-45, 46-55and 56-65 years and categorized as young, middle and old aged diabetic subjects. All the human volunteers were issued with a questionnaire to determine the eligibility for participation in the study. The questions elicited vital information on age, body weight, height, exercise, habits, health status, smoking habit, alcohol intake and the use of dietary supplements. Physically active diabetic subjects with the habit of walking for at least 30 min/ day or 2 days once were included for the investigation. Written informed consent was obtained from all the participants of the study after providing sufficient explanation for participation in the study.

The blood was collected by venous arm puncture after an overnight fasting. The puncher site was then cleaned with an antiseptic spirit and tourniquet was placed around the upper arm, i.e. 4 inches above the intended puncture site to obstruct the return of venous blood to heart and to distend the vein. A needle was inserted into the vein and blood was collected using a syringe. During the procedure, the tourniquet was removed and samples of blood were collected into clean labeled capped tubes for estimation of various parameters. Plasma and serum were separated by centrifugation at 1300 x g for 15min and stored at 4^0C until analysis for renal damage biomarkers.

The blood pressure was measured by the method described by Brar and Ramesh.[7] The Systoloic (first korotkov phase) and diastolic (fifth korotkov phase) blood pressure was

measured with a standard mercury Sphygmomanometer on the left arm after at least 10 minutes of rest. Mean values were determined from two independent measurements.

The data collected in the present study were carefully categorized, segregated and statistically analyzed. The values are expressed as Mean ± Standard Deviation. Further, the values were analyzed by one way analysis of variance (ANOVA) using SPSS for windows and the levels of significances were noted.

RESULTS

Urea

Table 1 show that the level of urea for control group was 22.88±1.81. However, physically active walking subjects, showed near normal value between 20 and 23±0.95. Further, the statistical analysis showed that the levels of urea among the different age groups were significantly elevated ($P<0.01$) compared to the normal subjects. Physically active walking subjects showed significantly low levels of urea among different age groups of diabetics compared to the normal subjects.

Uric Acid

The results of the biochemical analysis of uric acid in the blood serum are given in Table 2. The mean value of uric acid was very low in the control Group (3.50±0.35) while highest mean value was noticed in Group 2, particularly in the elderly. However, all 3 categories of physically active walking subjects showed significantly low level of uric acid compared to the other groups. Physically active young diabetics were found to have a significantly low level of uric acid compared to the diabetic subjects of other age groups.

Creatinine

Table 3 depicts the levels of creatinine among different age groups of diabetic subjects with / without lifestyle interventions. It can be inferred from the table, that the mean values of creatinine levels were significantly high among the diabetic subjects. The lowest mean value was recorded in the control and physically active walking subjects (0.9 to 1.0). Physically active walking diabetics were depicted to have near normal values.

Systolic Blood Pressure (SBP)

The levels of Systolic Blood Pressure in different groups of diabetic subjects and control are shown in Table 4. The highest blood pressure was recorded in the diabetic subjects. However,

the diabetics having regular exercise of walking showed normal blood pressure (119.10±2.25). Young diabetics having the habit of walking recorded a significantly low SBP level compared to diabetic subjects of other age groups.

Diastolic Blood Pressure (DBP)

The Diastolic Blood Pressure (DBP) level is given in the Table 5. Diabetics subjects revealed significantly high (P<0.01) DBP level compared to normal. Diabetics revealed significantly high DBP with normal irrespective of age. Diabetic subjects with the habit of walking were found to have a significantly declined (P<0.01) DBP levels, among diabetic subjects.

Correlation Analysis

The relationship between the markers of renal damage urea, uric acid, SBP, DBP was significantly positive (P<0.01) while serum creatinine also showed significantly positive correlation with other parameters at 0.05 level (Table 6).

Table 1. Effect of physical activity on urea levels among young, middle and old diabetic subjects

Groups	Age Groups	N	Mean±SD	F-value	P Value
Normal	Control	20	22.85±1.81		
Diabetic subjects	young	16	26.00±1.55	26.77	0.001 (0.01)
	middle	20	27.05±1.32		
	old	14	27.57±2.38		
Physically active diabetic subjects	young	16	20.83±0.75	4.56	0.001 (0.01)
	middle	17	21.71±0.76		
	old	12	23.00±0.95		

Table 2. Effect of physical activity on uric acid levels among young, middle and old diabetic subjects

Groups	Age Groups	N	Mean±SD	F-value	P Value
Normal	Control	20	3.50±0.35		
Diabetic subjects	young	16	5.23±0.59	123.47	0.001 (0.01)
	middle	20	5.80±0.39		
	old	14	5.61±0.27		
Physically active diabetic subjects	young	16	3.70±0.57	17.42	0.001 (0.01)
	middle	17	4.00±0.60		
	old	12	4.64±0.40		

Table 3. Effect of physical activity on creatinine levels among young middle and old diabetic subjects

Groups	Age Groups	N	Mean±SD	F-value	P Value
Normal	Control	20	0.8±1.99		
Diabetic subjects	young	16	1.04±2.20	17.4	0.001 (0.01)
	middle	20	1.01±0.19		
	old	14	1.30±0.17		
Physically active diabetic subjects	young	16	0.87±0.04	0.39	0.763 (NS)
	middle	17	0.94±0.03		
	old	12	0.96±0.08		

Table 4. Effect of physical activity on SBP levels among young middle and old diabetic subjects

Groups	Age Groups	N	Mean±SD	F-value	P Value
Normal	Control	20	119.10±2.25		
Diabetic subjects	young	16	143.44±6.76	63.65	0.001 (0.01)
	middle	20	142.25±7.52		
	old	14	145.71±9.38		
Physically active diabetic subjects	young	16	121.67±3.20	55.10	0.001 (0.01)
	middle	17	131.29±1.89		
	old	12	130.75±4.09		

Table 5. Effect of physical activity on DBP levels among young, middle and old diabetic subjects

Groups	Age Groups	N	Mean±SD	F-value	P Value
Normal	Control	20	79.10±1.97		
Diabetic subjects	young	16	88.44±2.10	74.21	0.001 (0.01)
	middle	20	87.75±2.84		
	old	14	88.50±2.10		
Physically active diabetic subjects	young	16	81.17±2.01	17.32	0.001 (0.01)
	middle	17	83.86±2.67		
	old	12	84.25±2.26		

Table 6. Correlation between markers of renal damage among diabetic subjects with different lifestyle interventions

	Urea	Uric acid	Creatinine	SBP	DBP
Urea		0.712**	0.495*	0.520**	0.381**
Uric acid	0.712**		0.463*	0.686**	0.555**
Creatinine	0.495*	0.463*		0.443*	0.418*
SBP	0.520**	0.686**	0.443*		0.686**
DBP	0.381**	0.555**	0.418*	0.686**	

** Correlation is significant at the 0.01 level * Correlation is significant at the 0.05 level

DISCUSSION

Diabetic nephropathy is a chronic microvascular complication in uncontrolled Diabetes mellitus. In renal impairment, classical markers (urea and creatinine) become abnormal, characterized with glomerular changes like thickening of basement membrane and accumulation of matrix material in the mesangium. The renal markers such as urea, uric acid, creatinine, systolic blood pressure and diastolic blood pressure showed that in the age group 5 particularly among aged people, smoking and alcohol consumption did the worst. Increased blood urea production in diabetes may be accounted for by enhanced catabolism of both liver and plasma proteins.[8]

Creatinine is a waste product that is normally filtered from the blood and excreted with the urine. Higher creatinine levels in diabetic patients may be related to disturbance of kidney function.[9] In addition, the observed increases in urea and creatinine may be explained on the basis of glomerular hyper-filtration due to increase creatinine clearing from blood.[10] Although serum creatinine is a more sensitive index kidney function compared urea level. This is because creatinine fulfills most of the requirements for a perfect filtration marker.[11]

Reports by Fry and Farrington[12] showed that raised plasma creatinine and urea levels in diabetic patient indicated a pre-renal problem such as volume depletion. Investigations suggested that high creatinine levels noted in diabetic patients might be due to impaired function of the nephrons. Increased serum creatinine and blood urea levels recorded in Type 1 and Type 2 DM patients could be attributed to a fall in the filtering capacity of the kidney thus leading to accumulation of waste products within the system. Although serum creatinine and blood urea tests can expose the patient's renal function, serum creatinine is a more sensitive indicator, as many extrarenal conditions such as dehydration, can increase urea levels. However, serum creatinine levels alter very little except in renal dysfunction.[13]

Amartey et al[14] who observed that hyperglycemia induced elevated levels of plasma urea and creatinine which are considered as significant markers of renal dysfunction.

Kuwabara,[15] which supports the recent observation, that serum uric acid is a potential risk factor for diabetic patients particularly with hypertension, stroke, and cardiovascular diseases. Dehgham et al[16] suggests high uric acid levels as a novel risk factor for T2DM. Prevalence of hyperuricemia is associated with cardiovascular risk factors in the developing countries. Serum uric acid is positively associated with serum glucose among diabetic subjects aged 55 years and older. Dehgham et al[16] on a population based study suggests uric acid as strong and an independent risk factor for diabetes. Serum uric acid has been shown to be associated with oxidative stress[17], which may be related to the development of diabetes. Biologically, uric acid plays an important role in worsening of insulin resistance in animal models by inhibiting the bioavailability of nitric oxide, which is essential for insulin-stimulated glucose uptake.

Van Buren and Toto[18] reports stated that increased blood pressure accelerates the course of diabetic renal disease. Blood pressure with the diabetes may be increased because of reduced bioavailability of nitric oxide, secondary to oxidative stress, increased sodium reabsorption secondary to increased angiotensinogen production by adipocytes and increased vasoconstrictive effects of fatty acids and other adipokines. In the present study the diabetic subjects showed elevated levels of SBP and DBP compared to the normal subjects.

McFarlane et al[19] stated that diabetes and hypertension are widely acknowledged risk factor for kidney damage. Elevated blood glucose and related microvascular disease are associated with slow but progressive damage to the kidneys. In a diabetic kidney, there are increased perfusion and GFR, and probable increase in intraglomerular capillary pressure. T2DM also causes growth of the kidney and enlargement of the glomeruli, which are then susceptible to damage. There is modification of glomerular components (basement membrane) particularly resulting from non-enzymatic glycation and the accumulation of advanced glycation end products. These combined mechanism result in pathologic changes in the glomerular structure.

However the present study indicated that the groups which are active physically and regularly doing exercise particularly walking has reduced renal damage markers nearly to the normal Group. There is a positive and significant correlation obtained between lifestyle modified

people and diabetic control. The mechanism by which physical activity lowers blood pressure includes reduction of oxidative stress and amelioration of insulin resistance. Insulin resistance impairs NO synthesis and may contribute to develop blood pressure elevation. Diabetes decreases NO bioavailability because of either insulin deficiency or defective insulin signaling (insulin resistance) in endothelial cells. Hyperglycemia is shown to acutely inhibt the production of NO in arterial endothelial cells.

Normally over 75% of blood glucose is cleared into skeletal muscle by insulin and insulin resistance in muscle is the primary defect leading to diabetes. The major mechanism by which physical activity decreases the risk for diabetes is by improvement in insulin sensitivity. Exercise may ameliorate insulin resistance by direct effects on muscle, such as enhancing insulin receptor autophosphorylation and increasing GLUT - 4 content, and glucose transport phosphorylation by reducing visceral obesity, which is associated with a reduction in free fatty acid levels, and by improvements of insulin stimulated limb blood flow.[20]

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