Effect of Exercise on Urinary Excretion of Some Indicators of Diabetic Nephropathy in Type I Diabetic Children

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ABSTRACT

Diabetic nephropathy is the leading cause of chronic renal failure. Microalbuminuria is considered to be the earliest marker of glomerular lesions in diabetics. Hence, it seems of clinical importance to study what would predict the development of microalbuminuria in diabetic patients with normoalbuminuria. It has been reported that increased urinary transferrin excretion rates were found in normoalbuminuric type 1diabetic patients. The use of physical exercise as a provocative test to detect early signs of diabetic renal disease not recognizable in the resting condition was suggested. Fifty patients with type 1 diabetes mellitus with mean age of 13 years and mean disease duration of 7 years were evaluated. Baseline blood pressure, random blood glucose, creatinin clearance, urinary micro-albumin and transferrin were determined. Patients and controls were subjected to standardized moderate exercise after water loading on treadmill for 20 minutes, after which urinary excretions of microalbumin and transferrin were re-evaluated using ELISA technique. We found that moderate intensity exercise have resulted in significant elevation of both systolic and diastolic blood pressure, urinary excretion of microalbumin (mean=64±111.4µg/min) and transferrin (2.24±6.57µg/min, p=0.024) in patients with type 1 diabetes as well as matched control subjects (mean=22.48±15.47µg/min for microalbumin and 0.08±0.069µg/min for transferrin). Yet, the effect of exercise was more evident in diabetics who displayed significantly higher post-exercise urinary protein levels. We recommend the use of exercise test as a simple non-invasive one that can be easily applied in clinics to uncover diabetic nephropathy in uncomplicated diabetic patients at risk.

INTRODUCTION

Diabetes is a metabolic disorder of multiple causes characterized by chronic hyperglycemia and disorders of carbohydrate, fat and protein metabolism. Results from defects in insulin secretion (type 1), insulin action (type 2), or combination of these factors *(www.emedicin.com,2006).*

Nephropathy is the deterioration of the kidneys. The final stage of nephropathy is called end-stage renal disease, or ESRD *(www.healthwise.com, 2006).*

Diabetic nephropathy is the leading cause of chronic renal failure in the United States and other Western societies. It is also one of the most significant long-term complications in terms of morbidity and mortality for individual patients with diabetes. Diabetes is responsible for 30-40% of all end-

stage renal disease (ESRD) cases in the United States. Although both type 1 diabetes mellitus (insulin-dependent diabetes mellitus [IDDM]) and type 2 diabetes mellitus (non-insulin-dependent diabetes mellitus [NIDDM]) lead to ESRD, type 1 is more likely to lead to ESRD *(www.umm.edu.2006)*.

There is good evidence that early treatment delays or prevents the onset of diabetic nephropathy or diabetic kidney disease *(www.emedicin.com, 2006)*.

Microalbuminuria (MA) is an important early marker of risk for diabetic renal disease and if persistent, it is considered to be the earliest marker of glomerular lesions in patients with diabetes mellitus, thus indicating an early stage of diabetic nephropathy *(Bognetti et al, 1997)*.

In children, as in adults, the development of MA appears to be related to glycemic control and duration of diabetes *(www.emedicin.com,2006)*.

Exercise induces hemodynamic and hormonal changes, which are able to provoke an increase in renal protein excretion even in some normal subjects. Exercise capacity may be limited in patients with diabetes but the reason for this is unclear. Physical activity may increase the glomerular leakage of albumin in diabetic patients with normal UAER at rest (*Cesarini et al, 1996)*.

The use of physical exercise as a provocative test to detect early signs of diabetic renal disease not recognizable in the resting condition was suggested by some authors *(Bognetti et al, 1997)*.

Urinary excretion of transferrin and albumin was studied in patients with type I diabetes mellitus by (*O"Donell et al, 1991)* where a significant elevation of urinary transferrin excretion rate was found. Moreover, all diabetic patients with elevated albumin excretion rates had elevated transferrin excretion rates.

A significant correlation between the indices of proximal renal tubular function and the urinary excretion of transferrin but not with albumin excretion was reported. This discrepancy in urinary excretion of transferrin and albumin may reflect impaired proximal renal tubular reabsorption of transferrin and/or altered glomerular basement membrane selectively for the two proteins *(Martin et al, 1992)*.

In this context, measuring transferrin excretion was proved to be a more sensitive parameter than albumin in studies using urinary protein excretion as a response to a provocative exercise challenge *(Konen et al, 1993)*.

Aim of the study

The aim of this study is to investigate the effect of a standardized exercise on the urinary excretion of some indicators of diabetic nephropathy in type 1 diabetic children and adolescent without any clinical signs of nephropathy.

PATIENTS AND METHODS

Patients

The present study included 50 type 1 diabetic children and adolescents recruited from the regular attendants of the Diabetes Specialized Clinic, Children's Hospital, Ain Shams University according to the following criteria:

- 5 years disease duration and more.
- Age less than 18 years.
- Normal blood pressure for age and sex and normal urinary albumin excretion.
- Normal fundus examination.

Twenty one age and sex-matched healthy children belonging to same

socioeconomic standard were included in the study as controls. They were selected from siblings of patients attending Pediatrics Out patients Clinic, Ain Shams University.

Methods

All patients were subjected to the following:

1) History taking: A structured questionnaire was planned to fulfill the following data:
   A. Demographic data; name, age, sex, socio-economic class.
   B. Disease duration.
   C. Insulin therapy; type, dose and frequency.
   D. History suggestive of acute metabolic complications:
   - History suggestive of hypoglycemic attacks (sweating, headache, blurring of vision, tremors, convulsions and coma).
   - History suggestive of hyperglycemia (polyuria, polyphagia, polydypsia, loss of weight, coma due to diabetic ketoacidosis.
   - Files were revised for the number of hospital admission due to these attacks during the last year prior to the study to exclude those with brittle diabetes or poorly controlled.

   E. History suggestive of chronic diabetic complications:
   - Ocular manifestations: persistent blurring of vision flashes of light.
   - Renal manifestations: polyuria, oligouria, dysuria, loin pain and haematuia.
   - Peripheral neuropathy manifestations: tingling, numbness, parathesia, impaired or loss of sensations.
   - Symptoms of autonomic neuropathy as palpitation and postural hypotension.
   - Gastrointestinal manifestations: dysphagia, heartburn, anorexia, or gastric fullness.
   - Skin manifestations: recurrent pyogenic infections, fungal infections.
   - Files were revised for the presence of documented retinopathy or motility disorders.

   F. Age at menarche in girls.

2) Examination:

Thorough clinical examination with particular emphasis on:
   A. Anthropometric measures; weight (in kg.) and height (in cm.) were plotted against percentiles for age and sex according to Egyptian growth charts (Ghaly and Salah Eldin, 2002).
   B. Sexual maturity rating according to Tanner's classification, 1962.
   C. Blood pressure measurements (recumbent and in response to standing).
   D. Full neurological examination to detect evidence of peripheral neuropathy.
   E. For autonomic neuropathy; heart rate variation during breathing and blood pressure response to standing were evaluated.
   F. Routine direct ophthalmological examination annually performed for those patients ≥5years disease duration.

3) Laboratory investigations:

Base line:
   A. Random blood sugar.
   B. Glycated hemoglobin (HbA1c).
   C. Complete urine analysis to exclude any case with urinary tract infection or proteinuria.
   D. Timed Corrected Creatinine clearance.
   E. Urinary microalbumin was measured by using ORGENTEC

DIAGNOSTEKA GmbH, Immunometric Enzyme Immunoassay for the quantitative determination of micro-albumin in urine.

F. Urinary transferrin was measured by using The DIAMED EUROGEN Transferrin ELISA kits, enzyme immunoassay for the quantitative determination of human transferrin in plasma, human serum and other biological fluids.

4) Exercise Protocol:
   A. Each patient and control was submitted to individual physical examination on the day before the exercise test for the standardization of exercise load at moderate intensity. Intensity of exercise was determined by utilizing the heart rate reserve (HRR), an indicator of VO2 reserve, which refers to the maximum oxygen uptake reserve, an indicator of the difference between maximum oxygen consumption and oxygen consumption at rest.
   B. Moderate exercise was defined by reaching an HRR of 50% during exercise on a treadmill according to the following formula: HRR = [(HRR max -HR rest) (0.5)] +HR rest
   C. HR max was calculated using the formula 220 – age (Lane et al, 2004).
   D. On the morning of the exercise test, diabetic subjects had their usual insulin injections and a standard breakfast with normal content of proteins and sodium.
   E. Patients and controls were allowed to drink one liter of tap water and to rest in the sitting position for at least 15 min.
   F. Immediately before the test the subjects were asked to urinate, (Samples were stored at -20 for later analysis of microalbumin and transferrin).
   G. Exercise test lasted for 20 min on treadmill.
   H. Midtime and post-exercise blood pressure and heart rate were checked to ensure their previously set level.
   I. A second urine sample (post exercise) was obtained and samples were stored at -20o for later analysis of microalbumin and transferrin).

RESULTS

The work included 50 patients with type 1 diabetes mellitus, 25 males and 25 females recruited from the regular attendants of the Diabetes Clinic, Children's Hospital, Ain Shams University. Their ages ranged from 8-17 (13±2.79) years, and disease duration 5 to 14 years (6.98±2.13) years, compared to 21 healthy subjects age- and sex-matched and belonging to same socioeconomic standard, comparison between both groups showed a non-significant difference as regards age and sex.

Table (1): Height and Weight percentiles in Diabetic Patients and Control Group.

Variable		Diabetic patients	Controls	t-test	p-value
		n=50	N=21	-4.82	0.001
Height PC for age and sex	Mean	45.38	72.71		
	SD	31.07	16.47		
Weight PC for age and sex	Mean	51.44	79.04	-5.97	0.001
	SD	28.78	10.08		

PC: Percentile

A significant difference was found between diabetic patients and healthy control subjects regarding height and weight percentiles.

Table (2): Pubertal Staging in Diabetics and Control Group.

Pubertal Staging	Diabetic patients		Controls		Chi-Square Test	P- value
	n=50		n=21			
	No	%	No	%		
Pre-pubertal	24	48	10	47.6	0.001	0.999
pubertal	19	38	8	38.1		
Post-pubertal	7	14	3	14.3		

There was no significant difference between diabetic patients and healthy subjects as regards pubertal staging. None had delayed puberty.

Table (3): Base line (Pre-exercise) Random Blood Sugar in Diabetic Patients and Control Group.

Blood Sugar (mg/dl)	Diabetic patients	Controls	t-test	p-value
	n=50	n=21		
Mean	130.8	121.2	0.901	0.242
SD	46.17	21.62		

There was no significant difference between diabetic patients and control healthy subjects with respect to basal blood sugar.

Table (4): HbA1c in Diabetic Patients and Control Group.

Glycosylated hemoglobin %	Diabetic patients	Controls	t-test	p-value
	n=50	n=21		
Mean	8.05	5.5	11.5	0.001
SD	1.36	0.50		

Diabetic patients have had higher mean HbA1c. In view of metabolic control, 27 patients (54%) were poorly controlled (HbA1c >7.6%).

Table (5): Creatinine Clearance, (ml/min/1.73) in Diabetic Patients and Control Group.

Creatinin Clearance, (ml/min/1.73)	Diabetic patients	Controls	t-test	p-value
	n=50	n=21		
Mean	164.01	157.66	0.280	0.780
SD	93.21	69.93		

The two groups were comparable in mean creatinine clearance.

Table (6): Comparison between Basal Systolic and Diastolic blood pressure percentile in diabetic patients and control subjects.

Variable	Diabetics n=50		Controls n=21		t-test	P-value
	Mean	SD	Mean	SD		
Systolic	84.7	8.17	59.05	13.47	6.1	0.001
Diastolic	81.1	12.47	58.33	12.08	6	0.001

Diabetic patients had higher mean systolic and diastolic BP, although none was hypertensive (above 95th percentile).

Table (7): Comparison between Mid time exercise systolic and diastolic blood pressure percentile in patients and control subjects.

Variable	Diabetics N=50		Controls n=21		t-test	P-value
	Mean	SD	Mean	SD		
Mid time Systolic	91.7	6.02	87.6	6.45	2.55	0.013
Mid time Diastolic	90.7	8.39	79.04	12.71	3.86	0.001

There was a significant difference between diabetic patients and control healthy subjects regards mid time exercise systolic and diastolic blood pressure percentile.

Table (8): Comparison between pre- and post-exercise blood pressure percentile in diabetic patients.

Variable	Pre-exercise		Post-exercise		Z test	P-value
	Mean	SD	Mean	SD		
Systolic percentile	84.7	8.17	92.2	4.97	-4.819	0.001
Diastolic percentile	81.1	12.47	87.6	6.45	-3.993	0.001

After exercise, both systolic and diastolic BP rose significantly and 54%of diabetic patients were above the 95th percentile for systolic and 40% were above 95th percentile for diastolic.

Table (9): Comparison between pre-and post-exercise blood pressure percentile in control subjects.

Variable	Pre-exercise		Post-exercise		Z test	P-value
	Mean	SD	Mean	SD		
Systolic percentile	59.05	13.47	87.62	6.45	-3.972	0.001
Diastolic percentile	58.33	12.08	79.05	12.7	-3.57	0.001

There was a significant difference between pre- and post-exercise systolic and diastolic blood pressure percentile in healthy subjects. None was hypertensive post exercise.

Table (10): Pre–exercise urinary microalbumin (µg/min) In Diabetic Patients and Control Group.

Urinary microalbumin (µg/min)	Diabetic patients n=50	Controls n=21	t-test	p-value
Mean	11.19	3.87	4.64	0.001
SD	10.26	2.84		

Diabetic patients have had higher mean urinary microalbumin, but none was microalbuminuric (figure 1).

Table (11): Post–exercise urinary microalbumin (µg/min) In Diabetic Patients and Control Group.

Urinary microalbumin (µg/min)	Diabetic patients n=50	Controls N=21	t-test	p-value
Mean	64.12	22.48	2.58	.013
SD	111.43	15.47		

There was a significant difference between diabetic patients and control healthy subjects regards post-exercise urinary microalbumin excretion (figure 1).

Table (12): Comparison between pre- and post- exercise microalbumin excretion rate (µg/min) in diabetic patients and control subjects.

		Mean	SD	t-test	P-value
Diabetics n=50	Pre	11.19	10.26	-3.49	0.001
	Post	64.12	111.4		
Controls n=21	Pre	3.87	2.8	-5.68	0.001
	Post	22.5	15.5		

Post exercise, microalbumin excretion rate increased significantly in both diabetic patients and control subjects. Of 50 diabetics, 30 (60%) turned microalbuminuric (20-200µg/min) and 3 (6%) were macroalbminuric (>200µg/min) versus 9/21 (33%) and none in the control group, respectively (figure 1).

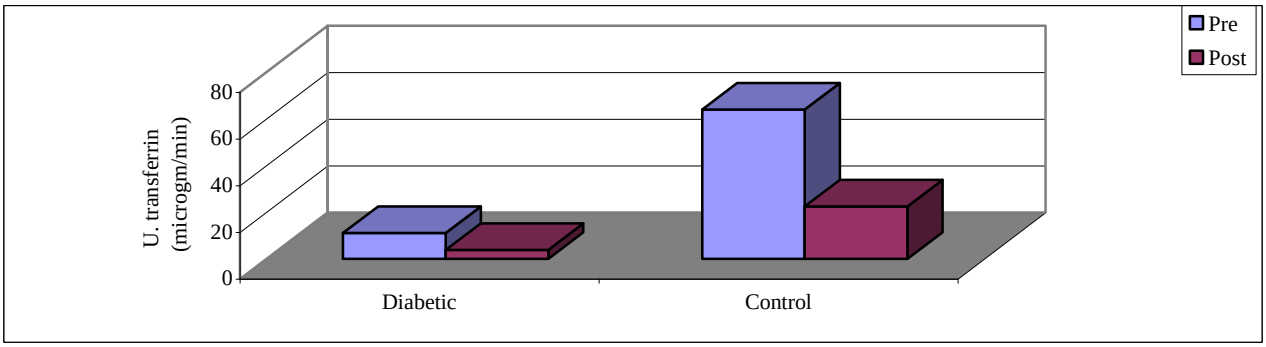

Fig. (1): Pre- and post-exercise urinary microalbumin excretion in diabetic & control patients (after exclusion of the highest value; 722.2µg/min in the diabetic group).

Table (13): Pre–exercise urinary transferrin In Diabetic Patients and Control Group.

Urinary transferrin (µg/min)	Diabetic patients	Control	t-test	p-value
	n=50	n=21	2.45	0.018
Mean	0.177	0.008		
SD	0.486	0.004		

The table shows that there was a significant difference between diabetic patients and control healthy subjects regards basal, pre-exercise urinary transferrin excretion (figure 2).

Table (14): Post–exercise urinary transferrin in Diabetic Patients and Control Group.

Urinary transferrin (µg/min)	Diabetic patients	Control	t-test	p-value
	n=50	N=21	2.32	0.024
Mean	2.24	0.08		
SD	6.57	0.069		

Post-exercise, mean urinary transferring was significantly higher in diabetics. According to calculated cutoff value (0.22µg/min), 24 patients out of 50 (48%) had elevated urinary transferrin excretion rate and were considered transferrinuric (figure 2).

Table (15): Comparison between pre- and post- exercise transferrin excretion rate (TER) in diabetic patients and control subjects.

		Mean	SD	t-test	P-value
Diabetics n=50	pre	0.177	.486	-2.35	0.023
	post	2.24	6.57		
Controls n=21	pre	0.008	0.004	-4.9	0.001
	post	0.08	0.069		

Exercise was associated with excretion of significant amounts of transferrin in both groups (figure 2).

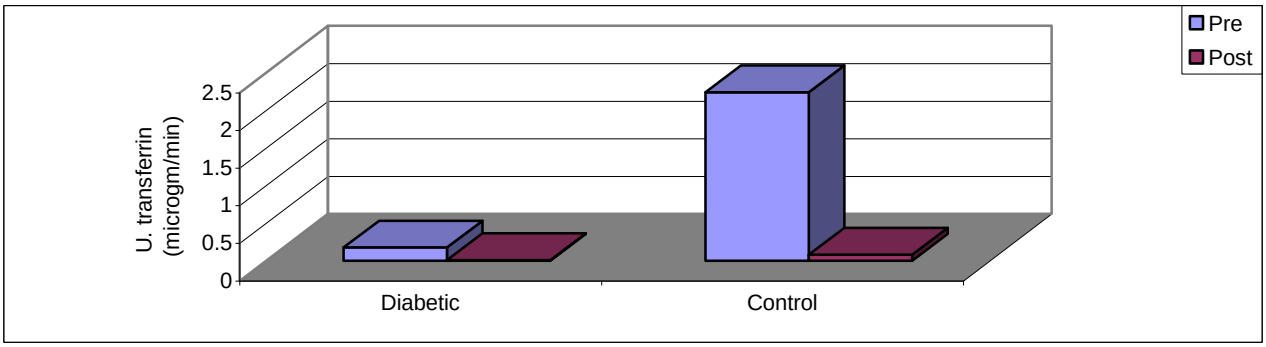

Fig. (2): Shows pre- and post-exercise urinary transferrin excretion in diabetic & control patients (after exclusion of the highest value which was 41.667 µg/min in the diabetic group).

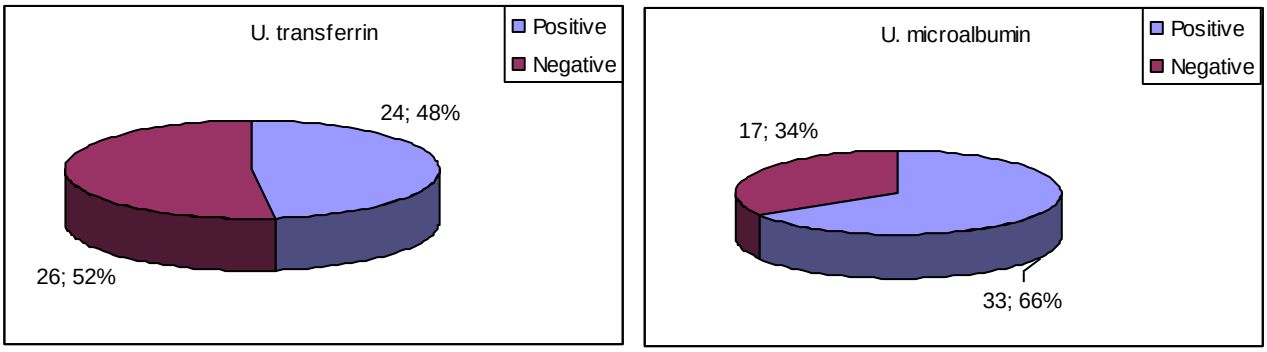

Fig. (3): Frequency of post-exercise urinary microalbumin and transferrin excretion in diabetic patients.

DISCUSSION

Diabetic nephropathy is the main cause of increased morbidity and mortality in patient with IDDM, denotes a clinical condition characterized by persistent proteinuria, decline in renal glomerular functions, hypertension and progression to end stage renal disease. It is becoming a major cause of chronic renal failure necessitating dialysis. Therefore, it is important in managing DM to detect DN as early as possible and prevent its development (Marshall, 2004).

The presence of diabetes may be interpreted as a condition of risk for the development of nephropathy, since approximately one third of the patients with IDDM will develop this long term complication. Among these patients, renal disease has been identified as the most important cause for increased mortality. This fact justifies the search for risk markers in an attempt to prevent or at least postpone its development (ADA, 2005).

Microalbuminuria is the hallmark for incipient diabetic nephropathy, early intervention at this stage may retard the progression into end stage renal failure (Nordwall, 2006).

Long standing IDDM in patients with normal AER is still at risk of developing clinically significant nephropathy. It is therefore important to identify markers of increased nephropathy risk among these patients (Caramori et al., 2003).

Up to 40% of patients with IDDM develop clinical proteinuria predicting an irreversible decline of kidney functions .Persistent microalbuminuria is considered to be the earliest marker of glomerular lesion, thus indicating an early stage of diabetic nephropathy. Urinary albumin excretion can be increased by physical activity in normal subjects and the use of physical exercise as a provocative test to detect early signs of diabetic renal disease not recognizable in resting condition was suggested by some authors. The test of exercise-induced albuminuria may be employed to identify normoalbuminuric IDDM patients at risk of developing albuminuria without repeated testing (O'Brien et al, 1995 and Dahlquist et al., 2001).

The aforementioned data stimulated us to plan our study on type 1 diabetic patients for early detection of DN, aiming to testing for urinary predictors of DN, comparing the response to standardized exercise of diabetic children with matched normal subjects and to defining the risk factors early in the course of type 1 DM including disease duration, hypertension and degree of glycemic control.

Urinary tract infections were excluded by complete urine analysis for patients and controls to avoid misleading proteinuria due to infections as reported by ADA position statement 2004, that UTI can cause transient elevations in urinary proteins excretion. For this reason, it is considered necessary to rule out UTI before assessment proteins in urine to avoid falsely elevated results (ADA, 2004).

Baseline (pre-exercise) blood pressure, random blood glucose, serum and urinary creatinine, creatinine clearance, urinary micro-albumin and urinary transferrin were determined.

Patients and controls were subjected to standardized moderate exercise (determined by utilizing the heart rate reserve) on treadmill for 20 minutes, after which urinary excretions of microalbumin and transferring were re-evaluated.

Our study demonstrated a significant lower height and weight percentiles in diabetics as compared to control subjects (45.38±31 vs 72.7±16.5, p-value =0.001 for height percentile; and 51.44±28.8 vs 79±10, p-value = 0.001 for weight percentile).

Similarly, Aziz, 2000 demonstrated that final adult height was lower in type 1 diabetics than target genetic height (mid-paternal height) and Egyptian type 1 IDDM patients were under weight. Abdel Hamid, 2004 reported that stunted growth was found to be significantly more frequent in microalbuminuric diabetic children than normoalbuminuric ones.

Weight loss despite eating a lot to relieve their constant hunger in patients with type 1diabetes, sometimes occurs rapidly. That's because the body cells are deprived of glucose and energy as glucose is lost into urine. Without the energy glucose supplies, cells die at an increased rate before they can divide and replace themselves. Muscle tissues and fat stores shrink, and body weight declines (www.health libraryCNN.com).

In the current study, baseline (pre-exercise) systolic blood pressure percentiles in patients and control group showed a significant difference (mean=84.7±8.17 in patients vs 59±13.5 in controls, p-value=0.001). The same was true for diastolic blood pressure percentiles (mean = 81.1±12.47, and 58±12.1 for patients and controls respectively, p-value=0.001). However both systolic and diastolic blood pressure in both groups was still within normal range, indicating that none was hypertensive (above the 95th percentile).

This runs in parallel with Hassan, 1994 who reported that both systolic and diastolic blood pressure were significantly higher in diabetic patients than control group but still within normal range.

Similar results were found by Pietrzak et al., 2003 who suggested that elevated systemic blood pressure is one of the most important risk factor of diabetic nephropathy. They found that 24-hour automatic blood pressure monitoring is useful for early detection of increased blood pressure in diabetic children and adolescents. The patients with elevated both systolic and diastolic blood pressures had more frequently glomerular hyperfiltration. The persons with elevated only diastolic blood pressure had the lowest glomerular filtration and filtration fraction.

In the current study, exercise was associated with significant elevation of both systolic and diastolic mean blood pressure percentiles in the immediate post-exercise period in each of the two studied groups. A significant percentage of diabetics were hypertensive after exercise; 54% for systolic and 40% for diastolic blood pressure. On the other side, none of the control subjects was hypertensive.

Our findings are in agreement with Cesarini et al., 1996 who found that systolic blood pressure was significantly increased in both diabetics and controls after timed exercise period. Similarly, Galassetti et al., 2002 reported exercise-induced elevations in heart rate, systolic, diastolic and mean arterial pressure in fifteen patients with type 1 DM during 90 min of euglycemic exercise at 50% of the maximum rate of O2 consumption.

On the other hand, Lane et al., 2004 found that mean blood pressure did not differ in diabetic patients submitted to either moderate or intense protocol of exercise.

As regards mean corrected creatinine clearance expressing mean glomerular filtration rate (GFR; ml/min/1.73), diabetic patients and controls were comparable (mean =164±93 vs 157.7±69.9; p=0.78). This is expected as our cohort was normotensive and normoalbuminuric.

A similar finding was reported by Caramori et al, 1999 who found that in a large cross-sectional study, there was no reduction in GFR among normoalbuminuric normotensive type 1 diabetics.

In the current study, the baseline (pre-exercise) urinary microalbumin excretion rate was significantly higher in diabetic patients than control group (mean =11.9 ± 10.26 vs 3.87 ± 2.84 µg/min, p= 0.001). If expressed as urinary microalbumin/creatinine we observed the same finding (mean =27.9 ±26.6 vs 8.89 ± 9µg/mg creatinine, p = 0.001).

A similar finding was reported by Narita et al, 2004 who demonstrated that excretion rates of all small-sized plasma proteins, as transferrin, IgG, ceruloplasmin and α1-microglobulin were increased in parallel in normoalbuminuric diabetic patients and their increased urinary excretion may equally have a predictive value of the future development of microalbuminuria. This is clinically very important because additional methods for early prediction of diabetic nephropathy are mandatory.

We disagree with Cesarini et al., 1996 who evaluated the responses of blood pressure and UAE to standardized exercise in normotensive, normoalbuminuric type 1 DM patients comparing them with normal subjects. At baseline, the albumin/creatinine was comparable in the two groups. Also Bognetti et al., 1994 reported that there was no significant difference in AER between diabetic patients and healthy control group.

In the present study, when the level of microalbumin excretion at baseline was compared to post-exercise one, it was higher in each group immediately after the end of exercise; mean 11.19±10.26µg/min pre-exercise vs 64±111.4µg/min post-exercise, p=0.001 in diabetics and mean 3.87±2.8µg/min pre-exercise vs 22.5±15.5µg/min post-exercise, p=0.001 in control subjects.

Ala-Houhala 1990 studied the effects of exercise on glomerular permeability at rest and after exercise. Exercise significantly reduced the glomerular filtration rate (GFR) and the renal plasma flow and markedly increased the filtration fraction (FF) in both diabetics and controls. The fractional clearances of albumin and IgG increased significantly during exercise in diabetics. Exercise also significantly increased the fractional clearance of albumin in healthy controls with significant difference between the two groups.

The physiological mechanisms responsible for exercise proteinuria in healthy subjects are not completely understood although several factors have been identified. An increased quantity of protein in the urine may be due to an increased filtration of plasma protein through the renal glomerulus and into the renal tubule. This is termed "glomerular

proteinuria", with albumin comprising the greatest proportion of excreted proteins (albuminuria). Glomerular proteinuria regularly occurs in response to exercise.Although an increased renal FF and alteration in glomerular capillary wall charge-selectivity were observed in both healthy and IDDM patients (www.health libraryCNN.com).

Exercise may uncover a covert renal lesion which despite the presence of normal albumin excretion rate may lead to the later development of microalbuminuria (O'Brien et al., 1995).

In diabetes, there may be altered glomerular basement membrane charges which may facilitate the passage of charged macromolecules as transferrin and albumin which have a relatively similar molecular mass of 76.500. There is a variable protienuric response to exercise observed in diabetic patients with normal renal functions and normal protein excretion in urine. A subset of those IDDM patients respond abnormally to exercise stress with increase albumin or other proteins excretion to levels compatible with microalbuminuria, so recent studies identify those subset as normoalbuminuric diabetic patients at risk of nephropathy (Lane et al., 2004).

Our study demonstrated the evidence of glomerular dysfunction by another indicator protein, transferrin. The baseline (pre-exercise), urinary transferrin excretion rate was significantly elevated (mean 0.177±0.486µg/min in diabetics than controls (mean 0.008±0.004µg/min, p = 0.018). When results are expressed as urinary transferrin/creatinine, a similar difference was detected (mean = 374.3 ± 801.2 vs 18.16 ± 10.2 ng/mg creatinine in patients and controls respectively, p= 0.003).

Al-Hemaisy, 1999 reported that the behavior of urinary transferrin was found to be similar to albumin in many aspects. Also 70% of diabetic patients had elevated urinary transferrin while urinary albumin was still in the normal range, resulting in a sensitivity of 100% and specificity of 57.5%. Transferrin excretion correlated as well with albumin excretion, both correlated positively with disease duration and glycated hemoglobin (the two major risk factors for diabetic nephropathy).

In the current study we found that there was a positive significant correlation between pre-excersie microalbuminuria and pre-excersie transferrinuria in diabetics (r=0.437, p=0.002), which was not significant in control group (r=0.114, p=0.621).

Similar to our findings, urinary microalbumin and transferrin determined in diabetic patients with normal renal function, were found to be highly correlated (r= 0.902, p<0.001). However, a low titer of transferrinuria was observed, (25.5%) among the patients with microalbuminuria. Determination of transferrinuria did not appear to be superior to the determination of microalbuminuria in early diabetic nephropathy (Kawanish et al., 1995).

Our study compared transferrin excretion rate pre- and post-exercise in type 1 DM patients who showed a significant rise in transferrin excretion rate after exercise (mean= 0.177± 0.476µg/min pre-exercise vs 2.24±6.57µg/min post-exercise, p=0.023). Similarly, exercise was associated with significant increase in urinary transferring excretion in control subjects (mean=0.008±0.004 pre-exercise vs 0.08±0.069 post-exercise, p=0.001).

It is noteworthy mentioning that our diabetic patients displayed higher post-exercise urinary albumin and transferrin

excretion than control subjects, i.e. exercise induced loss of excessive amounts of proteins in urine of subjects studied, but the effect was more pronounced in type 1 diabetics.

Konen et al., 1993 reported similar results. They compared urinary transferrin and albumin excretion in patients with insulin dependent diabetes mellitus (non microalbuminuric) and non diabetic controls before and after a standardized exercise challenge of only moderate intensity for 20 min. Both groups were similar for age and sex. After exercise, both urinary albumin and transferrin excretion increased in diabetics in comparison to controls. They reported that measuring transferrin excretion may be a more sensitive parameter than albumin in studies using urinary protein excretion as a response to a provocative exercise challenge.

Kruger et al, 1996 studied albumin and transferrin excretion during exercise in diabetic children without signs of nephropathy to investigate proteinuria under these conditions. Patients with insulin-dependent diabetes mellitus and healthy children undertook a bicycle exercise test. Albuminuria was calculated as the albumin excretion rate (AER) and albumin-to-creatinine ratio before and after exercise. No significant difference in metabolic control (HbA1c) was detected between the diabetic groups. There was no increase in AER in the healthy children after exercise. Before exercise, the diabetic groups had an AER similar to controls. Diabetics with disease duration of more than 5 years had a significant increase in albuminuria, of these patients, 43% also had a measurable urinary excretion of transferrin, indicating structural glomerular damage. There was no correlation between albuminuria and parameters of metabolic control or renal function. They conclude that in diabetic children an exercise test unveil albuminuria in certain patients, while their AER may be normal at rest.

In the current study, control group showed significant positive correlations between urinary microalbumin excretion post exercise and diastolic blood pressure (r=0.460 and p=0.036), pre-exercise urinary microalbumin (r=0.548 and p=0.01) and post-exercise urinary transferrin excretion (r=0.542 and p=0.011), whereas such correlations between post-exercise urinary microalbumin excretion and HbA1c (r=-0.233 and p=0.309), systolic blood pressure and pre-exercise urinary transferrin excretion (r=0.287 and p=0.2) were not statistically significant. Meanwhile, diabetic patients showed a positive significant correlation between immediate post-exercise urinary microalbumin excretion and systolic blood pressure percentile (r=0.504 and p=0.000), diastolic blood pressure percentile (r=0.390 and p=0.005), level of urinary transferrin excretion pre-exercise (r=0.310 and p=0.028), and also a positive highly significant correlation with post-exercise urinary transferrin excretion level (r=0.504 and p=0.000). But negative significant correlation between immediate post-exercise urinary microalbumin excretion with age (r=-0.473 and p=0.001) and HbA1c(r=-0.355 and p=0.011)were found.

Similar to our results Sufliarska, et al, 1998 demonstrated there was a significant correlation between HbA1c, systolic and diastolic blood pressure and the amount of urinary excretion of albumin ($p < 0.001$).

A similar finding was found by Bognetti et al, 1994 who reported that pre and post-exercise UAE in diabetics was positively correlated to HbA1c (r =0.293, P= <0.05).

From the course of the study we can conclude that moderate intensity exercise have resulted in significant elevation of both systolic and diastolic blood pressure, urinary

excretion of albumin and transferrin in patients with type 1 diabetes as well as matched control subjects. Yet, the effect of exercise was more evident in diabetics who displayed significantly higher post-exercise urinary protein levels. The degree of metabolic control reflected by HbA1c correlated with post-exercise urinary albumin and transferrin excretion.

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الملخص العربي

تأثير التمارين الرياضية علي الإفراز البولي لبعض مؤشرات اعتلال الكلي في مرضي النوع الأول من البول السكري في الأطفال

اعتلال الكلي في مرضي البول السكري يعتبر سبب رئيسي للإصابة بالفشل الكلوي المزمن في المجتمعات الغربية ويعتبر أيضا من أهم المضاعفات المزمنة لمرض البول السكري . اعتلال الكلي في مرضي البول السكري تم تعريفه علي أنه زيادة مستمرة في إفراز الألبومين بالبول > 300 مجم \ اليوم أو > 200 ميكرو جرام \ الدقيقة (في حالة عدم وجود أمراض أخري بالكلي) وانخفاض في معدل تنقية الكلي للدم مع حدوث ارتفاع بضغط الدم. وقد ثبت وجود خمس مراحل لحدوث الاعتلال الكلوي في مرضي البول السكر ووجد أن التشخيص المبكر والتدخل العلاجي المبكر ذو أهمية قصوي في منع تطور الإصابة إلي الفشل الكلوي . وقد تم اختيار 50 مريضا ومريضه بالبول السكري النوع الأول من عيادة السكر التابعة لمستشفي الأطفال بجامعة عين شمس بمتوسط عمر 13 سنة وتراوحت مدة الإصابة بمرض السكر بينهم بمتوسط 7 سنوات وتمت مقارنة النتائج للمرضي بنتائج مجموعة متناسبة من حيث السن والجنس مكونة من 21 طفل من الأطفال الأصحاء . وقد تم أخذ تاريخ مرضي كامل وعمل فحص إكلينيكي شامل لجميع الأفراد المرضي والأصحاء وعمل تحاليل معملية لقياس نسبة السكر العشوائي بالدم ، كرياتنين بالدم والبول، نسبة تنقية الكرياتنين ونسبة الألبومين المجهري والترانسفرين بالبول مع الأخذ بالاعتبار عمل تحليل بول كامل لاستبعاد وجود أي عدوي بمجري البول. وخضع جميع الأفراد تحت البحث إلي اختبار رياضي مقنن علي جهاز المشاية الرياضية لمدة 20 دقيقة بعد شرب لتر ماء والجلوس لمدة 15 دقيقة ثم أخذ عينة بول قبل وبعد التمرين الرياضي مباشرة لقياس نسبة الألبومين المجهري و الترانسفرين في الحالتين . وقد لاحظنا أن قياسات ضغط الدم في أطفال البول السكري قبل التمرين الرياضي أعلي من غيرهم ولكن القياسات لم تصل إلي حد الإصابة بارتفاع ضغط الدم (>95 % بالنسبة للسن والجنس) إلا بعد أداء التمرين الرياضي إذ ارتفعت دلالات الضغط العلوي لدي 54% منهم ودلالات الضغط السفلي لدي 40% من المرضي إلى أكثر من 95% للسن والجنس وهذا لم يحدث في الأطفال الأصحاء. أما بالنسبة لدرجة تنقية الكلي للكرياتنين فلم يلاحظ فرق واضح إحصائيا بين مرضي البول السكري وغيرهم لأن المرضي تحت الدراسة تم اختيارهم باعتبار أن قياسات ضغط الدم وإفراز الألبومين بالبول طبيعية. وقد أوضحت النتائج وجود ارتفاع واضح في نسبة الألبومين المجهري في بول الأطفال مرضي السكر قبل التمرين الرياضي مقارنة بالأطفال الأصحاء وأيضا بعد التمرين الرياضي عند مقارنته بالأطفال غير المصابين. كذلك ظهر اختلاف إحصائي واضح بين نسبة الألبومين المجهري في بول الأطفال مرضي السكر قبل وبعد التمرين الرياضي 66% من المرضي ظهر لديهم بروتينات بالبول منهم 60% ألبومين مجهري و6% ألبومين .