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The Impact of Exercise Training on Biomarkers, Altered Renin-Angiotensin-Aldosterone System (RAAS) in Diabetic Nephropathy Individuals

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ABSTRACT

Objective: Diabetes mellitus is a major cause of metabolic and systemic diseases contributing mainly for kidney and cardiovascular anomalies all around the world. To manage such untoward outcomes, in addition to medications, the present study aims to assess productive effects of exercise on Renin-Angiotensin-Aldosterone System (RAAS), biomarkers, related albuminuria, estimated glomerular filtration rate (eGFR) and clinical factors.

Methods: A prospective, cohort-controlled experiment was conducted. Confirmed cases (n = 150) either gender of diabetes with underlying chronic kidney disease (CKD) and diabetic nephropathy (DN) with aged 35-45 were selected, divided into 3 groups each with no exercise, 3 months and 6-month exercise, respectively. Exercise regiments were prescribed and blood was collected at the end of each periodic end. Blood was analyzed for Renin, Angiotensin II, biomarkers, parathyroid hormone (PTH), lactate, insulin and fasting glucose according to standard procedures on Roche Cobas c503, e801, e411, Snibe X800 and NOVA PHOX plus.

Results: Statistically analyzed data exhibited potentiating effects of exercise. Renin, Aldosterone, PTH and PCO2, predicated significance betterment only after 6 months of exercise whereas Angiotensin II, Lactate, PCO2, PO2, Urine albumin and glomerular filtration rate (GFR) exhibited moderate to marked/highly significant changes both after 3 months and after 6 months of exercise.

Conclusion: It has been concluded, in addition to all traditional treatments and medications, long term exercise does have benefits in the betterment of diabetic patients with underlying DN and thus be encouraged to be part of every treatment plans based on individuals' specifications.

Keywords: *Chronic kidney disease, Diabetic Nephropathy, End stage renal disease, Glomerular filtration rate, Renin Angiotensin Aldosterone system.*

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1. INTRODUCTION

Diabetes is a primary global cause of end-stage renal disease (ESRD), which is the final stage of kidney disease. Nearly one in three adults with diabetes will develop chronic kidney disease (CKD) and this increasing[1, 2]. Diabetic nephropathy (DN) is a chronic disease characterized by progressive elevated blood pressure, elevated urinary albumin excretion and cardiovascular risk, as well as decreased glomerular filtration rate (GFR) and progressive decline to ESRD [3]. According to available data, the mortality associated with DN is nearly 30 times greater than that of diabetic patients without renal damage [4]. For this reason, nephrologists, endocrinologist, diabetologist, and general physician are evaluating ways to intervene, in the early stages of DN, to prolong its decline to ESRD.

It has been reported and found within the literature that management of the patient with DN can be classified into four main components: management of cardiovascular risk, management of glycemia, management of blood pressure and oxidative stress, and management of the renin–angiotensin system (RAS) [5], all of which are drug-management directed. These

methods all can help manage DN. However, in recent years, in conjunction with drug interventions, exercise, and specifically aerobic exercises such as fast walking or jogging, is thoroughly accepted as a viable management option to prevent and treat cardiovascular disease and therefore is beneficial for slowing the progression of DN [6]. Furthermore, studies have shown that moderate exercise (at least two times a week) has some association with a decreased risk of unfavorable renal outcomes, including a lower incidence of albuminuria [7]. Earlier studies suggested exercise may help to slow the progression of DN [8]. Additionally, studies have examined the effects of various levels of exercise on DN and found that moderate-intensity exercise provided the most benefit to patients with DN.

The reasoning behind the physiological basis of end-stage renal disease (ESRD), metabolic derangements in diabetes nephropathy (DN) and chronic kidney disease (CKD), and increased oxidative stress, collectively diminish nitric oxide (NO) production that may interfere with vasodilation. However, in a hyperglycemic state, stimulation of the local renin-angiotensin system (RAS) will increase angiotensin II and Renin levels that lead to constriction of the efferent arteriole. To shield the glomerular filtration rate, dilation of the afferent arteriole occurs. The afferent dilation and efferent constriction leads to significant increase in intra-glomerular pressures leading to increased GFR, injury to the glomerulus, and proteinuria [9-11].

Present study described the estimation of Renin, Angiotensin II, biomarkers (urea, creatinine, PTH, PCO_2, PO_2) and metabolic parameters (insulin, fasting glucose, lactate) in diabetic patients with co-morbid of diabetic nephropathy, and prescribed exercise regiments for a period of a total of 6 months. The aim is to assess its productive effects on renin-angiotensin-aldosterone system, biomarkers, related albuminuria, eGFR and clinical factors.

2. METHODS

The study was designed and carried out in a series of prospective, cohort-controlled experiments for the period of 3 and 6 months. The study was approved by the institutional bioethical committee. (Ref # IBC KU-368-B/2023) Inclusion criteria for the study group were the following, males or females, aged-35-45 years, 150 confirmed cases of diabetes with underlying CKD and DN with hypertension, albuminuria, nonsmoking, with no surgical interventions or none of the ailments such as cardiac, pulmonary, or neurological. Patients were divided into 3 groups each with n = 50 patients. Group A no exercise, Group B 3 months after exercise and Group C 6 month after exercise. Exclusion criteria were the following: <35 and greater than 45, patients with surgical interventions, with comorbid and having prescribed medications related to diseases other than diabetes and CKD. Fasting blood was collected at zero day (1st Start day of exercise and/or study), end of 3 months (90th day). 6 months (180th day) and processed as per analytical protocols.

Laboratory studies, were performed on fully automated (Roche Cobas c503, e801, e411 and Snibe X800 analyzers using standard techniques. Renin, Angiotension II and aldosterone were performed on Snibe[12], whereas urea, creatinine, lactate, urine albumin were performed on Roche Cobas c503, c501 and parathyroid hormone (PTH) were performed on Cobas e801 by the methods documented earlier [13,14]. PCO_2 and $PO_2$was analyzed on NOVA pHox Arterial blood gas analyzer (NOVA Bio-medical, USA) whereas eGFR was calculated as per MDRD calculator.

Exercise regiments were prescribed as follows, non-high intensity weight-baring exercise with a moderate exercise period of 30 min. The exercise period included the following: warm-up (3–5 min) of aerobic movement exercise of range of motion joints: Shoulder flexion and extension (10 times on both shoulders), wrist flexion and extension (up to 10 repetitions on each forearm), and ankle flexion and extension (10 times on each joint); the main activity stage (20–30 minutes) consisted of cycle ergometer exercise with desired level of 12-13 on the rate of perceived exertion scale (RPE);treadmill walking and cool down (3–5 min) as in the warm-up aerobic movements.

Statistical analysis was performed using Statistical Package for Social Sciences (SPSS) version 27, with statistics from each group (A, B and C) (Pre exercise, 3 months, 6 months post exercise) being compared with one another using one-way ANOVA where Groups B and C were treated as independent samples (the different periods 3 and 6 months apart) with Tukey's HSD (honestly significant difference) to facilitate pair wise comparisons of data within the ANOVA study. The F statistic indicates whether there are overall differences between the data means. The Tukey HSD test tells which of the means, if any, are significantly different (from e.g. no months = treatment 1 (T1) vs 3 months post exercise treatment 2 (T2).

3. RESULTS

Present study was designed and carried out in a series of prospective, cohort-controlled experiments for the period of 3 and 6 months. The study groups were the male and females, aged-35-45 years, 150 confirmed cases of diabetes with underlying CKD and DN with hypertension, albuminuria, nonsmoking, with no surgical interventions or any ailment such as cardiac, pulmonary, or neurological. Patients were divided into 3 groups each with n = 50 patients. Group A before exercise, Group

B 3 months after exercise and Group C 6 month after exercise. All hormone and biomarker parameters were statistically compared with each other for zero, 3 and 6 months. Parametric data of Renin, aldosterone, Angiotensin II, PTH, urea, creatinine, lactate, urine albumin, PCO_2, PO_2 and eGFR are provided in Table 1 and 2. Statistical analysis showed variable, moderate to significant changes in bio-metabolic levels over the period of 3 and 6 months of exercise. Data depicted remediable influence of exercise on diabetic patients with nephropathy conditions, more prominently at 6 months as compared to 3 months' time duration. Urea and creatinine analysis showed non-significant potentiation of exercise on both parameters, whereas insulin and fasting glucose showed marked significant correctness both at 3 and 6 months after exercise (Table 03). Remedial status of Renin, Angiotensin II and aldosterone, in addition to biomarkers, metabolic component, and oxidative blood gases status has also been statistically analyzed via Tukey's HSD (honestly significant difference) procedure that facilitates pairwise comparisons within ANOVA data. Tukey's HSD test allows determining between which of the various pairs of means - if any of them - there is a significant difference (e.g zero months = treatment 1 (T1) vs 3 months treatment 2 (T2) and so on). Analyzed data have been summarized in Table 12. In case of Renin, Aldosterone, PTH and PCO_2, data predicated significance betterment only after 6 months of exercise whereas fasting glucose and insulin, Angiotensin II, Lactate, PCO_2, PO_2, Urine albumin and GFR exhibited moderate to marked/highly significant changes and potentiated responsiveness both after 3 months and after 6 months of exercise (Table 03)

Table 1: Fundamental statistics of blood Renin, Angiotensin and Aldosterone levels at zero months, 3 months and 6 months in diabetic patients with renal modification and nephropathy.

Parameters	Zero day	3 months	6 months
Renin mU/L	208.76	187.4	170.28
Angiotensin pg/ml	83.32	74.00	65.24
Aldosterone pg/ml	267.44	225.4	205.24

Table 2. Blood urea, creatinine, glucose, insulin, PTH, lactate, PCO_2, PO_2 and urine albumin and eGFR parameters of diabetic patients with underlying nephropathy and renal diseases at baseline and after 3 and 6 months of exercise.

Parameters	Zero day	3 months	6 months
Urea mg/dl	124.24	107.8	95.42
Creatinine mg/dl	5.05	4.87	3.81
Glucose Fasting mg/dl	115.28	100.92	88.54
Insulin Fasting mg/dl	21.04	16.96	13.44
PTH pg/ml	317.72	253.74	230.26
Lactate mg/dl	14.74	16.38	12.00
PCO_2 mmHg	44.72	44.81	37.00
PO_2 mmHg	78.54	82.08	87.64
Urine albumin mg/g	126.1	97.82	73.6
eGFR ml/min per1.73 m^2	60.34	68.20	77.23

Table 03: Data showing level of significance of components of RAAS, metabolic, oxidative stress and urine-nephrotic systems at zero, 3 months and 6 months of exercise.

	Data analysis of effects of periodic exercise treatment (T1 = zero month, T2 = 3 months and T3 = 6 months) with $P < 0.05$ and Q depicts significant or non-significant result			
Parameters	**T1: T2**	**T1:T3**	**T2:T3**	**Outcome**
Renin	Q = 2.33 (p = .22811)	Q = 3.84 (p = .02029)	Q = 1.50 (p = .53863)	T1:T3 moderately significant
Angiotensin II	Q = 6.55 (*p* = .00002)	Q = 12.70 (p = .00000)	Q = 6.16 (p = .00007)	All three modules showed high significance
Aldosterone	Q = 2.78 (p = .12529)	Q = 4.12 (p = .01143)	Q = 1.35 (p = .60845)	T1:T3 is slightly significant
Urea	Q = 1.66 (p = .47072)	Q = 2.96 (p = .09471)	Q = 1.30 (p = .62882)	Non-significant
Creatinine	Q = 1.14 (p = .70159)	Q = 3.03 (p = .08498)	Q = 1.89 (p = .37606)	Non-significant

Glucose-fasting	Q = 12.52 (p = .00000)	Q = 23.32 (p = .00000)	Q = 10.80 (p = .00000)	All three modules showed high significance
Insulin-Fasting	Q = 8.87 (p = .00000)	Q = 16.66 (p = .00000)	Q = 7.79 (p = .00000)	All three modules showed high significance
PTH	Q = 2.85 (p = .11204)	Q = 3.72 (p = .02521)	Q = 0.87 (p = .81052)	T1:T3 is slightly significant
Lactate	Q = 4.85 (p = .00224)	Q = 8.11 (p = .00000)	Q = 12.96 (p = .00000)	All three modules showed high significance
PCO_2	Q = 0.23 (p = .98582)	Q = 29.29 (p = .00000)	Q = 29.52 (p = .00000)	T1:T3 and T2:T3 highly significant
PO_2	Q = 7.65 (p = .00000)	Q = 19.67 (p = .00000)	Q = 12.02 (p = .00000)	All three modules showed high significance
Urine albumin	Q = 22.07 (p = .00000)	Q = 40.84 (p = .00000)	Q = 18.77 (p = .00000)	All three modules showed high significance
eGFR	Q = 9.12 (p = .00000)	Q = 19.63 (p = .00000)	Q = 10.52 (p = .00000)	All three modules showed high significance

4. DISCUSSION

In present study we have assessed Renin, Angiotensin II, aldosterone and other metabolic parameters in diabetic patients with co-morbid of diabetic nephropathy to evaluate correlation with RAAS. These diabetic patients were, in addition to regular medical treatment modalities, also prescribed exercise regiments for a period of 3 and 6 months. The aim is to assess the productive effects of exercise in diabetic nephropathy patients on renin-angiotensin-aldosterone system and biomarkers such as urea and creatinine. Result exhibited moderate to considerable decline or normalization of altered levels of Renin, Angiotensin II, aldosterone, fasting glucose and insulin, lactate, PO_2, PCO_2, urine albumin and eGFR level during the period of 3 as well as 6 months of exercise suggesting that exercise does induce reduction in untoward metabolic and/or physiological effects, oxidative stress and cellular damages.Potentiated beneficial effects were manifested by regularization of RAAS, PCO_2 and PO_2, increase in glomerulo-filtration rate, decrease urinary albumin and other metabolic and regulatory components, thus exhibiting that long term regular exercise does collar and combat any pertaining untoward clinical conditions, such as underlying diabetic nephropathy in diabetic patients.

To understand the system that contributes nephropathy in diabetic patients, it is imperative to shed light on RAAS. The RAAS is present throughout the body and fulfills an important function in the control of water, electrolyte balance, and blood pressure to maintain blood flow homeostasis. There are two axes of the RAAS, a presser axis and a depressor axis. In the presser axis, renin converts angiotensinogen to angiotensin I (Ang I), which is subsequently converted to angiotensin II (Ang II) by angiotensin converting enzyme (ACE). Ang II is the most important effector of the presser axis and acts by binding to the Ang II type 1 receptor (AT1R) to cause vasoconstriction, enhance renal water and sodium reabsorption, and induce release of aldosterone [15,16]. Under the pathophysiology of diabetic kidney disease (DKD), activation of the pressor axis via RAAS signaling is sustained and exaggerated, resulting in elevated intraglomerular pressure and glomerular hypertension. Sustained activation of Ang II increases reactive oxygen species (ROS) levels, promotes extracellular matrix (ECM) accumulation, and stimulates mesangial cells to produce more transforming growth factor-β1 (TGF-β1). These changes contribute to glomerulosclerosis and fibrosis [19]. Research on aerobic exercise in diabetic mice, with and without metformin, has demonstrated that the urine expression level of ACE2 in diabetic mice was reduced during the second week of the study and continued to decline throughout week ten. Exercise, in comparison to the sedentary group, increased the expression level of ACE2 in the glomeruli of diabetic mice [19]. The etiology of diabetic kidney disease(DKD) is layered and complex. Specifically, genetic and epigenetic regulation is involved in the development of DKD at the molecular level. Changes in gene expression are significantly related to epigenetic changes (DNA methylation, histone changes, and non-coding RNA activity) relating to the signaling pathways of inflammation and fibrosis[19,20]. These molecular processes are modified via oxidative stress and AGEs, which develop from hyperglycemia and may further advance the disease pathogenesis of DKD. At the cellular level, mitochondrial dysfunction, altered metabolism, and excess ROS are all important contributions to DKD [21,22].

Numerous human studies have indicated that physical activity can slow the progression of DN.
A meta-analysis [7] assessing 38,991 individuals showed that physical activity increased the GFR and decreased the UACR in people with diabetes, thereby suggesting an enlivened physical activity has the potential to reduce albuminuria and the risk of DN development. In another study, kidney outcomes were assessed in 19,664 diabetic and 11,648 non-diabetic individuals over a follow-up of 56 months [6, 24]. According to self-reported data on physical activity, individuals' physical

activity 2-6 times a week had a 43% lower relative risk of adverse kidney outcomes than sedentary individuals, and individuals engaging in physical activity daily, had a 44% lower relative risk. Similarly, a cohort study confirmed that higher cardiorespiratory fitness was associated with decreased predictive risk for mortality in individuals with chronic kidney disease (CKD) [20]. Earlier studies showed that exercise training improved insulin sensitivity in insulin-resistance subjects as well, perhaps this is due to increased expression and activity levels of proteins regulating glucose metabolism, insulinscription, and increased lipolysis in muscle. It is also suggested that involvement in exercise may increase cardiorespiratory fitness [25]. A randomized controlled trial carried out in 99 individuals, with a mean GFR of 33 mL/min/1.73 m2, of which 59% had diabetes and 29% had coronary artery disease demonstrated that long-term exercise training improves cardiorespiratory fitness in patients with chronic kidney disease (CKD) [25] similarly to what we found in our study, indicating that exercise training is associated with improved GFR and lower levels of albuminuria [25]. Similar findings were found in a more recent study of patients with albuminuria, where each individual factor indicated differences between the two groups (lower or normalized for the exercise group versus control group) in levels of HemoglobinA1c (HbA1c), fasting plasma glucose (FPG) and triglycerides (TG) (24), which emphasizes health care professionals to encourage their patients to sustain regular exercise. We have also noticed gradual normalization or decline of Renin, Angio-II and Aldo concentration in addition to alterations in levels of PTH, fasting insulin and glucose, urea, creatinine, urine albumin and lactate insinuating that in our study cohort, a similar mechanism might have been activated due to regimental exercise over a period of 3 and 6 months, resulting in betterment of RAAS and biomarker status.

It has also been observed that patients with DN experience greater mortality compared with CKD patients not having diabetes. A cohort study of 1,024,977 patients with CKD (128,505 with diabetes) found mortality risks to be 1.2 to 1.9 times greater for participants with diabetes compared with participants without diabetes [10]. Therefore, those that would be considered active or undergoing physical activity appear to receive benefits of physical activity on kidney health which appears to be particularly effective for individuals with diabetes [6]. In regard to the progression of the DN various studies have shown an inverse relationship regarding exercise levels (active versus sedentary) and frequency of exercise (less frequent - more intense).We have seen more marked changes in RAAS components, some biomarkers and metabolic component at 6 months' time as compared to 3 months of exercise, advocating aforementioned rationale. However productive potentiated responsiveness was also at appreciated significant level for potent metabolic biomarkers such as insulin, lactate and glucose. Additionally, a 10-year follow-up study in which 2180 patients with type 1 diabetes were included has shown a lower risk of DN progression associated with exercise, particularly when occurring at high frequency and intensity [11].

5. CONCLUSION

Present study described the potentiated beneficial responsiveness of 3 and 6 months exercise in diabetic individuals with co-morbid of diabetic nephropathy. To assess the effects, Renin, Angiotensin II, aldosterone, biomarkers (urea, creatinine, PTH, PCO_2, PO_2), metabolic parameters (insulin, fasting glucose, and lactate), urine albuminuria and eGFR were analyzed in blood at zero, 3 and 6 months' time. Potentiated beneficial effects were manifested by regularization of RAAS, PCO_2 and PO_2, increase in glomerulo-filtration rate, decrease urinary albumin and other metabolic and regulatory components, thus exhibiting that long term regular exercise does corrects and combat any pertaining untoward clinical conditions, such as underlying diabetic nephropathy in diabetic patients.

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Disclosure
None to declare.

Conflict of Interest
None to declare.

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