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The Role of Pentoxifylline in Diabetic Nephropathy: A Case Control Study

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Abstract

Background: Diabetic nephropathy is a major diabetic complication and a frequent cause of morbidity and mortality in diabetic patients. Early identification and proper management of diabetic nephropathy is essential to improve outcome in those patients. The standard mode of treatment includes strict diabetic control together with protein saving angiotensin converting enzyme inhibitor (captopril). Recently, the xanthine derivative Pentoxifylline has been proposed as an efficient adjuvant therapy to treat diabetic nephropathy.

Aim: To evaluate the role of Pentoxifylline as an adjuvant therapy to treat diabetic nephropathy.

Patients and methods: The present case control study included 100 diabetic patients with diabetic nephropathy evidenced by proteinuria. They were classified into two groups; the first group included 50 patients who were treated using standard diabetic control serving as a control group and angiotensin converting enzyme inhibitor (captopril) whereas the second group received in addition Pentoxifylline to serve as a study group.

Results: Pentoxifylline resulted in more significant reduction in proteinuria and more significant rise in GFR when used as an adjuvant treatment than captopril alone. Three months after starting treatment mean proteinuria was 207.78 ±163.22 versus 324.12 ±203.05, in study and control groups, respectively (P=0.002); mean GFR was 87.00 ±14.98 versus 78.78 ±13.46 in study and control groups, respectively (P=0.005).

Conclusion: Pentoxifylline is an efficient adjuvant therapy to treat diabetic nephropathy.

Key words: Diabetic nephropathy, Pentoxifylline, prteinuria

INTRODUCTION

The syndrome of diabetic renal disorder or diabetic nephropathy (DN) is known to be characterized by the existence of glomerular injury caused by DM, abnormal albumin quantities in urine and reduced glomerular filtration rate (GFR). Diabetes is not a single disorder and it may be due to auto-immune destruction of pancreatic beta cells (type 1 DM), combine insulin resistance and relative deficiency of insulin (type 2) or could be due to other conditions like endocrine abnormalities and exocrine pancreatic lesions. (1) The high incidence of diabetes made it the cause number one of "end-stage renal disease (ESRD)" globally. For instance, diabetes was at the top of the list of causes behind ESRD in Mexico, Malaysia and Singapore during the period from 2009 to 2011. Some countries with high incidence of ESRD include United States, Philippines, Hong Kong, Korea, New Zealand and Japan [1]. The frequency of diabetes related ESRD gets higher with increasing age. The rates of ESRD caused by diabetes, in 2011, in the US were "44, 266, and 584 per million for the age groups 20–44, 45–64, and 65–74 years, respectively". In addition, same results were observed in the study named (AusDiab) that included 11,247 Australian diabetic patients [2].

It is important to realize that diabetic patients may or may not develop DN and the progression of disease in those who develop DN is not the same depending on a list of risk factors. The major risks that can be modified include hyperglycemia, hypertension and dyslipidemia.

Data obtained from the Steno Diabetes Center, Joslin Diabetes Center and AusDiab researches, in addition, strongly consider smoking as a strong risk factor for diabetic nephropathy [3, 4]. On the other hand, the major risks that cannot be modified include race genetic makeup, and age. The is higher chance for acquisition of DN when there is a strong family history of DN. [5] Mexican Americans, Pima Indians and African Americans racial groups are also at higher risk [6]. Some authors proposed that men had higher risk of DN than women [7].

Hidden nephropathy is the first detection of little but abnormal quantities of albumin in urine, known as "microalbuminuria (persistent albuminuria at level 30–299 mg/24 hours)". Macroalbuminuria or overt nephropathy "(persistent albuminuria at level ≥300 mg/24 hours)" occurs following long period in type 1 diabetes; however, it may be seen simultaneously with diagnosis of type 2 diabetes. Diabetic Patients who develop macroalbuminuria are at higher risk of getting ESRD. Type of diabetes is strongly implicated in determining the natural history of DN [7].

When type 1 diabetes left untreated, around 80 percent of patients with persistent microalbuminuria develop rise in albumin excretion by a fraction of (10%–20%) each year which will be followed by overt nephropathy later on within 10 to 15 years. When overt nephropathy is developed, the glomerular filtration rate gets down at a rate of 2 to 20 mL/minute/year and is then followed by ESRD in 50 percent of patients 10 years later and in 75 percent 20 years later [8]. Micro-anatomical changes may be detected within 2–8 years, in the form of mesangial expansion and thickening of glomerular basement membrane, after diabetes onset and before the onset of albuminuria and decline in GFR [9].

Late diagnosis of type 2 diabetes is associated with more frequent detection of DN. The AusDiab study of Australian diabetic patients described that albuminuria is frequent among those with established diabetes, is found earlier than the time of diabetes onset, and gets more frequent in association with more impaired tolerance for glucose [2]. Around 20 to 40 percent of patients with type 2 DM with microalbuminuria develop overt nephropathy; and approximately 20 percent will have ESRD following the acquisition of overt nephropathy. [8, 10]

In order to delay the progression of DN, the following measures should be taken: sufficient control of hemodynamic and metabolic derangements. Practically speaking, this involves sufficient blood glucose reduction and hypertension control. Efficient glycemic control is successful in decreasing microvascular diabetic adverse outcomes [1].

"ACE inhibitors" are well known for their successful potential in slowing progression of disease in patients with type 1 and type 2 DM. During the 1990s, captopril showed the potential of ACE inhibitors in decreasing the albuminuria progression and reduction in kidney function in patients with type 1 DM, with or without lowering of blood pressure [11-13].

"Pentoxifylline is a methylxanthine-derived phosphodiesterase inhibitor" that blocks the receptor for adenosine and reduces viscosity of blood. In addition, it possesses immunomodulatory and anti-inflammatory effects, and reduces urine and serum TNF-α in patients with diabetes who have DN [1]. Despite the substantial amount of literatures supporting the idea of Pentoxifylline usefulness in DN, sufficient controversy exist that justify the conductance of the present study.

PATIENTS AND METHODS

The present case control study included 100 diabetic patients with diabetic nephropathy evidenced by proteinuria. They were classified into two groups; the first group included 50 patients who were treated using standard diabetic control serving as a control group and angiotensin converting enzyme inhibitor (captopril) whereas the second group received in addition Pentoxifylline to serve as a study group. Initial assessment included measurement of glomerular filtration rate and proteinuria and then they were followed up for 3 months following which re-assessment of measurement of glomerular filtration rate and proteinuria has been carried out. The study was carried out in Al-Diwaniyah teaching hospital, Al-Diwaniyah province/ Iraq throughout the period extending from January 2017 to April 2017.

Statistical analysis

Data were analyzed using Statistical Package for Social Sciences (SPSS version 23). Categorical variables were presented as number and percentage whereas numeric data were presented as mean and standard deviation. Chi-Square test was used to study association between categorical variables whereas independent sample t-test was used to study differences in means of numeric variables. P-value for significant level was considered at ≤ 0.05 and for highly significant level at ≤ 0.01.

RESULTS

Mean age of control group was insignificantly different from that of study group, 54.50 ±9.09 versus 53.53 ±8.42, respectively, (P= 0.584). on the other hand, no significant difference was found in distribution of patients in both groups according to gender (P=0.418). Mean duration of diabetes mellitus in control group was 5.91 ±4.23 years and it showed insignificant difference from that of study group, 5.73 ±3.76 years (P= 0.827), as shown in table 1.

Before starting treatment, there was insignificant difference in mean proteinuria between study and control group 458.80 ±176.92 versus 458.70 ±193.54 (P= 0.998). Different modes of treatment in both groups succeeded in reducing proteinuria; however the reduction was more significant in the study group, 207.78 ±163.22 versus 324.12 ±203.05 (P=0.002), as shown in table 2.

Before starting treatment, there was insignificant difference in mean glomerular filtration rate (GFR) between study and control group 75.98 ±12.07 versus 75.54 ±12.27 (P= 0.858). Different modes of treatment in both groups succeeded in increasing GFR; however the increment was more significant in the study group, 87.00 ±14.98 versus 78.78 ±13.46 (P=0.005), as shown in table 2.

DISCUSSION

The present study showed that addition of pentoxyfilline produced more significant reno-protective effect than captopril alone by reducing proteinuria and increasing GFR to more significant levels.

It was found that pentoxifylline had similar potential to captopril in decreasing albuminuria and in keeping serum creatinine; better that placebo in these potentials when seventeen randomized trials (including 991 patients) were analyzed using Cochrane meta-analysis; unfortunately, the included studies were of small sample sizes, of inadequate methods and included no information regarding mortality or ESRD [14].

Table 1: Demographic characteristics of control and study groups

Characteristic	Control group	Study group	P
Age (mean ± SD years)	54.50 ±9.09	53.53 ±8.42	0.584*
Male /Female (number of cases)	27/23	31/19	0.418†
Duration of DM (mean ± SD years)	5.91 ±4.23	5.73 ±3.76	0.827*

*Student t-test; † Chi-Square test

Table 2: Proteinuria and GFR in control and study groups before and after treatment

Characteristic	Control group	Study group	P
Proteinuria before treatment	458.70 ±193.54	458.80 ±176.92	0.998
Proteinuria after treatment	324.12 ±203.05	207.78 ±163.22	0.002*
GFR before treatment (mean ± SD ml/minute)	75.54 ±12.27	75.98 ±12.07	0.858
GFR after treatment (mean ± SD ml/minute)	78.78 ±13.46	87.00 ±14.98	0.005*

*significant at <0.05.

Beside this meta-analysis, several studies have evaluated the role of adding pentoxifylline to Rennin-Angiotensin System (RAS) blockers and the finding were supportive to the previous assumption of pentoxifylline beneficial role in reducing proteinuria. Roozbeh et al. conducted a study that included 74 type 2 DM patients (with overt proteinuria) who were divided into two groups for who either captoprialone or combine captopri and pentoxifylline (400 mg per day) were given; the group received combined treatment reported greater reduction in proteinuria beside reduction in blood pressure by a modest fraction [15]. in another study carried out by Oliaei et al., 50 patients with type 2 DM and overt proteinuria who were also divided into two groups referring to the agents used to reduce proteinuria (RAS inhibition versus pentoxifylline); the results showed greater decline in proteinuria but similar creatinine clearance [16]. Ghorbani et al included 100 patients with type 2 DM (with proteinuria) "randomized to pentoxifylline 400 mg/day or placebo for 6 months". Either groups received enalapril and losartan in combination. Following six months, pentoxifylline therapy was accompanied by less proteinuria and greater creatinine clearance [17]. All these studies are in accordance with the findings of the present study.

Proteinuria is an essential indicator of ESRD in patients with DN. [18]. Decreasing proteinuria is successful in retarding the progression of chronic kidney disorder, in addition to reducing cardiovascular complications [19, 20].

The mechanisms behind the proteinuria reduction by pentoxifylline is still unclear, however some postulation may be considered. The first possible way is adenosine 2 receptors blocking that modify GFR and the kidney function of atrial natriuretic factor [19, 21]. The second possible effect is the the hemorheologic action of pentoxifylline that induces beneficial alterations in flow of blood by enhancing fluidity of blood in the peritubular venous plexus and decreasing "low-molecular-weight proteins overload" into the proximal tubule, effects that decrease the pressure inside glomeruli [20]. The third way, pentoxifylline reduces inflammatory reaction inside kidney through its anti-TNF-α effects [22, 23].

In conclusion, Pentoxifylline is an efficient adjuvant therapy to treat diabetic nephropathy.

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