Pentoxifylline Therapy in Idiopathic Membranous Nephropathy


The Departments of Internal Medicine and Clinical Pathology, Faculty of Medicine, Cairo University

Abstract

Idiopathic membranous nephropathy is the most common form of nephrotic syndrome in adults. The immune-mediated glomerular injury in membranous nephropathy is associated with increased production of tumor necrosis factor alpha (TNF-α) which play a contributory role.

This study aimed to explore the role of pentoxifylline therapy on the level of tumor necrosis factor alpha (TNF-α) in idiopathic membranous nephropathy.

Results: 20 patients and 10 control subjects were chosen and divided into 3 groups. Group 1: 10 membranous nephropathy patients received pentoxifyllin. Group 2: 10 membranous nephropathy patients without pentoxifyllin. Group (3): Control group. We exclude secondary MN and patients with severe MN in the form of impaired renal functions, severe hypertension or heavy proteinuria >8gm/24 hours. It was found that urinary and serum TNF-alpha levels before treatment were higher in the study group (1.5350) and (1.080) respectively than in the control group (0.20) and (0.225). p-value <0.001 (Table 2).

After 3 months of treatment with pentoxifylline there was improvement of urinary and serum TNF-α levels in group (I) p-value=0.007 and 0.005 respectively. It also showed significant reduction in 24 hours urinary proteins level from (4.48) before treatment to (1.10) after 3 months treatment p-value 0.005. On the otherhand the levels serum TNF-α in group (II) show no statistically sig differences (0.92) to (1.40) p-value 0.721 with improvement of 24h urinary proteins with p-value 0.005. There was no statistical difference between group I and II 3 months after treatment as regarding both urinary and serum TNF-α, p-value >0.05.

There was statistically sig differences in both serum and urinary TNF-alpha in the studied groups before and 3 months after treatment with p-value 0.021, 0.001 respectively. But serum level of TNF- alpha was higher after the treatment.

We found that 24 urinary proteins were positively correlated with urinary TNF-α (r=0.443 -p-value 0.05), but was not sig correlated to serum TNF-α (r=0.324 -p 0.164).

Conclusion: We concluded that TNF-α is high in patients with idiopathic membranous nephropathy, and we found that pentoxifylline has a beneficial effect in patients with idiopathic membranous nephropathy in lowering 24h urinary protein and urinary TNF-alpha.

Key Words: Idiopathic membranous nephropathy – TNF-alpha.

Introduction

MEMBRANOUS nephropathy (MN) is the most common causes of the nephritic syndrome in non diabetic adults [1].

The characteristic histologic lesion is diffuse thickening of glomerular basement membrane throughout all glomeruli in absence of significant hyper cellularity. With diffuse granular pattern of IgG and C3 in immune florescence staining [2].

Idiopathic (MN) is an immune mediated diseases involving deposition of immunoglobulin (IgG) and complement components in the subepithelial layers of glomerular basement membrane, immune complex and complement activation lead to functional insufficiency of the glomerulus and proteinuria and impairment of filtration barrier [3].

TNF-α is a cytokine involved in systemic inflammation and is a member of a group of cytokines that stimulate acute phase reaction. The primary red of TNF is regulation of immune cells and to induce inflammation, over production of TNF-α have been implicated in variety of human diseases [4].

Striking glomerular capillary wall and visceral glomerular epithelial cell TNF-α protein staining was observed in all cases of (MN) and TNF- α urinary concentration was significantly increased in patients with (MN) and with crescentic (GN). The expression of TNF-α by glomerular epithelial cells exclusively in biopsies showing a membranous morphology. Strongly suggests that TNF- α has a role in the pathogenesis of membranous nephropathy [5].
Pentoxifylline is a methylxanthine that improves perfusion in the impaired microcirculation. It demonstrated a potent inhibitory effect on cell proliferation, inflammation of messangeal cells and renal fibroblasts [6]. It also suppresses the increased expression of TNF-α in rats and it suppresses intra cellular adhesion molecules. All this was associated with reno-protective effect through reduction of proteinuria [7].

**Subjects and Methods**

The study included 20 patients with idiopathic (MN) and 10 normal control subjects. They were divided into 3 groups:

° Group (1): 10 patient with idiopathic membranous nephropathy, they received pentoxityllin (Trental) 1200mg/day with anti hypertensive, antiproteinuric agents (captopril 12.5/8h) and ARBS (valuable 40mg once day) with adequate blood pressure controls.

° Group (2): 10 patients with (MN) they received the same anti hypertensives, anti proteinuric agent and lipid lowering agents but without pentoxifylline.

° Group (3): 10 normal healthy subjects.

All were subjected to:

• Full history and clinical examination.

• CBC, liver function tests.

• Kidney function tests.

GFR estimation by using modification of Diet in renal disease study equation (MDRD) in order to classify CKD according to CKD staging system:

° Group I: Include 6 patients (stage I) normal GFR >90ml/min 1.73m² 3 patients (stage II) (GFR between 60-89ml/min/1.73), and 1 patient (stage II) (GFR between 30-59ml/min/1073m²).

° Group II: Include 6 patients (stage I) 4 patients (stage II).

• Serum albumin in g/dl.

• Serum cholesterol and triglycerids (mg/dl).

• 24h urinary proteins.

• Tests to exclude secondary (MV) as:

• HBV, HCV, ANA, C3 levels.

• Abdominal U/s, chest X-ray.

• Renal biopsy (Light microscopy) was done to diagnose membranous nephropathy.

• TNF-α in blood and urine before in the starting treatment and 3 months after treatment for group I, II using Elisa procedure.

**Results**

The study was carried out to evaluate the effect of pentoxifyllin therapy in idiopathic membranous nephropathy.

Clinical and laboratory findings of 20 Egyptian patients with (MN) and a matched 10 control healthy subjects.

The results show no statistical significant difference in laboratory parameters between groups I & II before treatment.

There was highly significant different between patient groups and control group as regarding urinary TNF-α (1.5350), (0.20) p-value <0.01 there was significant statistically difference (1.080), (0.225) with p-value <0.01 (1.080), (0.225) with p-value <0.001 in serum TNF-α between studied group (I, II) and control group.

The results also showed improvement in the levels of 24h urinary proteins, serum albumin, serum cholesterol, urinary TNF-α and serum TNF-α after 3 months of treatment in group (I) and all were statistically significant (p-value 0.001).

In group II all parameter showed improvement of 24th urinary protein, serum albumin, serum cholesterol, urinary TNF-α with statically significant difference (p-value) (<0.005) but serum TNF-α was higher after treatment but this was not statistical significant (p-value=0.721).

There was no statistically significant difference in laboratory parameter between group I & II after 3 monts a treatment p-value (>0.05).

• The laboratory parameters (24h urinary protein, serum albumin, serum cholesterol, urinary TNF-α and serum TNF-α. In both group I & II before and 3 months after treatment shows statistically significant difference p-value <0.05 but serum TNF-α was higher after treatment.

• 24h urinary proteins was +vely correlated with urinary TNF-α. In both groups I and II (r=0.443 – p-value=0.05). But not correlated to serum TNF-α.

• Also serum cholesterol level was +vely correlated with urinary TNF-α and it was significant (r=0.0464 –p-value=0.039) but was not statistically significant correlated with serum TNF-α (r=0.131 p= 0.179).
<table>
<thead>
<tr>
<th>Parameters</th>
<th>Group 1 Median (range)</th>
<th>Group 2 Median (range)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GFR (ml/min/1.7m²)</td>
<td>99 (55.3-186.6)</td>
<td>106.059 (65.3-167.1)</td>
<td>0.796 (NS)</td>
</tr>
<tr>
<td>24h urinary proteins (g/d)</td>
<td>4.48 (1.50-7.00)</td>
<td>3.50 (1.50-6.00)</td>
<td>0.211 (NS)</td>
</tr>
<tr>
<td>Serum albumin (mg/dl)</td>
<td>1.7 (1.20-2.80)</td>
<td>2.05 (1.20-2.50)</td>
<td>0.288 (NS)</td>
</tr>
<tr>
<td>Serum cholesterol (mg/dl)</td>
<td>439 (340-658)</td>
<td>347.50 (220-650)</td>
<td>0.054 (NS)</td>
</tr>
<tr>
<td>Urinary TNFα (pg/ml)</td>
<td>1.6350 (0.50-4.20)</td>
<td>1.275 (0.36-3.90)</td>
<td>0.473 (NS)</td>
</tr>
<tr>
<td>Serum TNFα (pg/ml)</td>
<td>1.600 (0.20-9.50)</td>
<td>0.925 (0.60-5.40)</td>
<td>0.273 (NS)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Study groups Mean (range)</th>
<th>Control group Mean (range)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary TNFα (pg/ml)</td>
<td>1.5350 (0.36-4.2)</td>
<td>0.20 (0.04-0.42)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum TNFα (pg/ml)</td>
<td>1.080 (0.2-9.5)</td>
<td>0.225 (0.005-0.330)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Before treatment</th>
<th>3 Months after treatment</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>24h urinary proteins (g/d)</td>
<td>4.48 (1.50-7.00)</td>
<td>1.1 (0.70-2.50)</td>
<td>0.005</td>
</tr>
<tr>
<td>Serum albumin (mg/dl)</td>
<td>1.70 (1.20-2.80)</td>
<td>2.80 (2.20-3.60)</td>
<td>0.005</td>
</tr>
<tr>
<td>Serum cholesterol (mg/dl)</td>
<td>439 (340-658)</td>
<td>300 (260-490)</td>
<td>0.005</td>
</tr>
<tr>
<td>Urinary TNFα (pg/ml)</td>
<td>1.635 (0.50-4.20)</td>
<td>0.65 (0.2-1.63)</td>
<td>0.007</td>
</tr>
<tr>
<td>Serum TNFα (pg/ml)</td>
<td>1.600 (0.20-9.50)</td>
<td>0.88 (0.16-4.20)</td>
<td>0.005</td>
</tr>
</tbody>
</table>

The immune-mediated glomerular injury in (MN) is associated with increased production of TNFα which may play a contributory role [9].

It is suggested that pentoxifylline reduce the production of TNFα and it was evaluated in several studies.

Discussion

Idiopathic (MN) is the most common form of nephritic syndrome in adults. The disease shows a benign or indolent course in the majority of patients [8].
There was a highly significant difference between the level of urinary TNFα in the studied groups and the control group (1.5350) and (0.20) respectively (p-value <0.001).

Also there was a highly significant difference in the level of serum TNFα between patients groups and control group (1.0800) and (0.225) respectively (p-value <0.001).

This finding is in consistent with James [9] who found a similar increase in urinary TNFα in patients with idiopathic membranous nephropathy, but he did not observe a corresponding increase in serum TNFα.

In our study, we found that in group 1 the level of 24 hour urinary proteins was significantly lower after treatment (4.48) to (1. 1) p-value=0.005. Also serum cholesterol was significantly lower (p-value =0.005). Also urinary and serum TNFα shows statistically significant lower value (p-value=0.007 and 0.005 respectively).

In group 2, there was statistically significant lowering of 24 hour urinary proteins p-value=0.005. Also there was statistically significant lowering of cholesterol and urinary TNFα p-value=0.005, 0.028 respectively. While there was elevation of serum TNFα after treatment 0.925 to 1.4 but this was not statistically significant (p-value 0.721). This comes in consistence with Stocke et al. [10] who proved that patients treated with angiotensin converting enzyme had significant lower serum TNFα but they did not asses urinary TNFα.

In our study, we also found that there was +ve correlation between urinary TNFα and 24 hour urinary proteins (r=0.443 – p-value=0.05). But not significantly correlated with serum TNFα (r=0.324 – p-value=0.164) and this is in consistent with Ducloix et al., [6] who found that the higher the protenurea the higher the urinary TNFα. And this may point the value of TNFα estimation in assessment of disease severity.

Regarding TNFα there was tendency towards lower urinary TNFα in group 1 (0.65) pg/ml, (0.7) pg/ml in group 2 but this was not statistically significant p-value=0.62.

Also there was tendency towards lower serum TNFα in group 1 (0.88) versus (1.4) in group 2 but this was not statistically significant p-value 0.762.

So, in group 1 patients who received pentoxifyllin had more lower 24h urinary proteins, urinary TNFα and serum TNFα.

Conclusion:

We conclude that TNF α is high in patients with idiopathic MN and it is correlated with the disease severity. Pentoxifylline has a beneficial effect in patients with MN in lowering urinary TNFα and 24h urinary proteins.

Recommendations:

Further studies to evaluate the beneficial role of pentoxifylline in idiopathic MN on long term treatment.

References


