



Evaluation of Urinary Monocyte Chemotactic Protein -I in Childhood Nephrotic Syndrome

Thesis

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Pediatrics

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وَعَلَّمَكَ مَا لَمْ تَكُنْ
تَعْلَمُ وَكَانَ فَضْلُ اللَّهِ
عَلَيْكَ عَظِيمًا

صدق الله العظيم

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تقييم البروتين الأول المسئول عن
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في بول الأطفال المصابين بالمتلازمة
النفروزيه

رسالة توطئة للحصول على درجة الماجستير في طب الأطفال

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SUMMARY

This study was conducted on 90 pediatric subjects including 70 patients with nephrotic syndrome following up at the Pediatric Nephrology Clinic, Children's Hospital, Ain Shams University, and 20 age and sex matched controls.

The aim of this study was to compare the levels of the urinary MCP-1 in patients with steroid resistant and sensitive nephrotic syndrome in both remission and relapse in the hope of finding a correlation between urinary MCP-1 level and the nature and severity of the disease.

All patients were evaluated by clinical assessment, clinical examination, routine laboratory investigations and uMCP-1 was measured using ELISA technique.

Our results revealed that nephrotic patients in relapse had the highest level of uMCP-1 followed by patients in remission then the control subjects.

We found that no correlation between uMCP-1 and the age of onset of the disease, its duration and the type of treatment among nephrotic patients in remission or in relapse.

There were positive correlations between uMCP-1 on one

hand. and urinary protein/creatinine ratio and serum cholesterol on the other hand. Also, there were a negative correlation between uMCP-1 and serum albumin among the nephrotic patients in remission and in relapse.

The differences in the level of uMCP-1 between the patients with FRNS, SRNS, SDNS and SSNS in remission or in relapse were insignificant.

In conclusion we found that uMCP-1 to be of value only in the diagnosis of childhood nephritic syndrome and the subsequent relapses, but of very little prognostic value as it's levels were increased in conditions where proteinuria existed but was not significantly elevated in a specific category of NS (according to steroid response).

REFERENCES

- **Al-Akash S and Al-Makdama A (2005):** Mycophenolate mofetil in children with steroid-dependent and/or frequently relapsing nephrotic syndrome. *Ann Saudi Med*; 25(5):380-384.
- **Al-Saran K, Mirza K, Al-Ghanam G and Abdelkarim M (2006):** Experience with levamisole in frequently relapsing, steroid-dependent nephrotic syndrome. *Pediatr Nephrol* ; 21 (2):201-205.
- **Anochie I, Eke F and Okpere A (2006):** Childhood nephrotic syndrome: change in pattern and response to steroids. *J Natl MedAssoc*; 98(12):1977-1981.
- **Appel G (2006):** Improved outcomes in nephrotic syndrome. *Clev. Clin. J. Med*; 73(2):161-167.
- **Arun S, Bhatnagar S, Menon S, Saini S, Hari P and Bagga A (2009):** Efficacy of zinc supplements in reducing relapses in steroid-sensitive nephrotic syndrome. *Pediatr Nephrol*; 4. [Epub ahead of print]
- **Bagga A (2008):** Management of Steroid Sensitive nephrotic syndrome. *Indian Pediatr*; 45:203-214.
- **Bakhtawar KM, Min KT, FemkeW, Nic JG, Jan-Leendert PB, Liffert V, et al., (2008):** High Absolute Risks and Predictors of Venous and Arterial Thromboembolic Events in Patients With Nephrotic Syndrome. *Circulation*; 117:224-230.

- Bakkaloglu SA, Soylemezoglu O, Necla Buyan, Tohru Funahashi, Atilla H. Elhan, Harun Peru, et al.,(2005):** High serum adiponectin levels during steroid-responsive nephrotic syndrome relapse. *Pediatric Nephrology*; 20 (4):474-477.

- Balakumar P, Arora MK, Reddy J and Singh M (2009):** Pathophysiology of Diabetic Nephropathy. Involvement of Multifaceted Signalling Mechanism. *J Cardiovasc Pharmacol*; 54:2.

- Banba N, Nakamura T, Matsumura M, Kuroda H, Hattori Y and Kasai K (2000):** Possible relationship of monocytes chemoattractant protein-1 with diabetic nephropathy. *Kidney Int*; 58:684-690.

- Barnett AH (2001):** The role of angiotensin II receptor antagonist in the management of diabetes. *Blood Press*; 10: 21-26.

- Barrat B and Clark J. (1994):** The management of idiopathic nephrotic syndrome in children. *Pediatr Drugs*; 5(5):335-349.

- Barrat M and Clark G. (1999):** Steroid responsive nephrotic syndrome. In: Barrat M, Anver E and Harmer W (eds.). *Pediatric nephrology*, 4th ed. Baltimore, Lippincott, Williams & Wilkins: 731-747.

- **Barrat TM and Clark G. (2009):** Steroid responsive nephrotic syndrome. In: Johathan W and Waverly (Eds.). Pediatric nephrology. Williams & Wilkins. USA, Baltimore, Philadelphia. 4th ed.:767-781.

- **Boekhoudt GH, Guo Z, Beresford GW and Boss JM (2003):** Communication between NF-kappa B and Sp1 controls histone acetylation within the proximal promoter of the 90onocytes chemoattractant protein 1 gene. J Immunol; 170:4139-47.

- **Broyer M, Meyrier A, Niaudet P and Habib M (1998):** Minimal change and focal segmental glomerulosclerosis. In: Davison AM, Grunfeld JB, Kerr D, Ritz E and Winearls CG(eds). Oxford Textbook of Clinical Nephrology. 2nd ed. Oxford Univesity Press, Oxford, New York; 36:493-523.

- **Charo I, Myers S, Herman A, Franci C, Connolly A and Coughlin S (1994):** Molecular cloning and functional expression of two monocyte chemoattractant protein receptors reveals alternative splicing of the carboxyl- terminal tails. Cell Bio; 91:2752-2756.

- **Chemli J and Harbi A (2009):** Treatment of steroid-resistant idiopathic nephrotic syndrome. Arch Pediatr; 16(3):260-268.

- **Cho MH, Hong EH, Lee TH and Ko CW (2007):** Pathophysiology of minimal change nephrotic syndrome and focal segmental glomerulosclerosis. Nephrology (Carlton); 12 (3): 11-14.

- Cho MH, Lee HS, Choe BH, Kwon SH, Chung KY, Koo JH, et al., (2003):** Interleukin-8 and tumor necrosis factor-alpha are increased in minimal change disease but do not alter albumin permeability. *Am J Nephrol* 23:260 –266

- Conductier G, Blondeau N, Guyon A, Nahon JL, and Rovère C (2010):** The role of monocyte chemoattractant protein MCP1/CCL2 in neuroinflammatory diseases. *Journal of Neuroimmunology*; 475086: 1- 8.

- Czupryniak A, Kałużyńska A, Tkaczyk M, Półtorak-Krawczyk A, Ostrowski B, Wiecek B, et al., (2006):** Assessment of the peripheral circulation in children with nephrotic syndrome treated with cyclosporin A. *Przegl Lek.*;63 Suppl 3:214-216

- Dahinden C, Geiser T, Brunner T, von Tscharner V, Caput D, Ferrara P, et al. (1994):** Monocyte chemotactic protein 3 is a most effective basophil- and eosinophils activating chemokine. *J Exp Med*; 179:751-756.

- Deshman SL, Kremlev S, Amini S and Sawaya BE (2009):** Chemoattractant protein 1 (MCP-1): An Overview. *J interferon cytokine Res*; 29: 313-326.

- Deshpande PV and Griffiths M (2005):** Pulmonary thrombosis in steroid-sensitive nephrotic syndrome. *Pediatr Nephrol.* ; 20(5):665-669.

- Eardley KS, Zehnder D, Quinkler M, Lepenies J, Bates RL, Savage CO, et al.,(2006):** The relationship between albuminuria, MCP-1/CCL2 and interstitial macrophages in chronic kidney disease. *International Society of Nephrology*; 69: 1189–1197.

- Eddy AA and Giachelli CM (1995):** Renal expression of genes that promote interstitial inflammation and fibrosis in rats with protein-overload proteinuria. *Kidney International*; 47: 1546-57.

- Eddy AA and Symons JM (2003):** Nephrotic syndrome in childhood. *Lancet*; 362(9384):629-639.

- Eddy AA, Warren SJ, Liu E and Mcculloch L (1996):** Expression and function of monocyte chemoattractant protein-1 in experimental nephrotic syndrome. *Clinical immunology and immunopathology*; 78(2): 140–151.

- El-Husseini A, El-Basuony F, Mahmoud I, Sheashaa H, Sabry A, Hassan R, et al., (2005):** Long-term effects of cyclosporine in children with idiopathic nephrotic syndrome: a single-centre experience. *Nephrol Dial Transplant*; 20(11):2433-2438.

- Farid FA, Abdel- Baki, A. and El-Nahrawi, H (1999):** Urinary type IV collagen in children with nephrotic syndrome. *Egypt. Ped.*, 16(13): 389-400.

- Farid FA, El-Hakim I, Osman M, et al. (1998):** Correlation between excretion of proteins and Ca^{++} in 24 hours urine in a random urine sample in nephrotic children. *Egypt. Ped.*, 15(7): 740-765.

- Farid FA, Mohamed AA, Afify HM, and Rizk MM (2008):** Serum and urine leptin concentration in children with nephrotic syndrome. *Egyptian J Pediatr.*; 25(4): 675-686.

- Farid FA, Reda S, El-Tehewy M, Nadia M, Ali AG. Adel K.et al., (1997):** The pattern of nephrotic syndrome among Egyptian children. *The Egyptian J Pediatr*; 14(1-2):71.

- Farid FA, Reda SM, El-Awady HM, El-Said HM, and Yousef FM (2005):** new concept in management of childhood nephrotic syndrome through inhibition of hypercoagulation. *Egyptian J Pediatr*; 22(1):33-50.

- Feber J, Al-Matrafi J, Farhadi E, Vaillancourt R and Wolfish N (2009):** Prednisone dosing per body weight or body surface area in children with nephrotic syndrome-is it equivalent?

- Fluss J, Geary D, and deVeber G (2006):** Cerebral sinovenous thrombosis and idiopathic nephrotic syndrome in childhood: report of four new cases and review of the literature. *Eur J Pediatr.*; 165(10): 709 –716.

- Frank C, Herrmann M, Fernandez S, Dirnecker D, Boswald I, Kolows W, et al (2000)** : Dominant T cells in idiopathic nephrotic syndrome of childhood. *Kidney Int*; 57: 510-517.

- Frassinetti CP, Bezerra DS, De Sousa BF, Costa OC and Kubrusly M, Evangelista JB (2005)**: Treatment of steroid-resistant nephrotic syndrome with cyclosporine: study of 17 cases and a literature review. *Nephrol.*; 18(6):711-720.

- Gbadegesin R and Smoyer WE (2008)**: Nephrotic Syndrome: Denis F. Geary, Franz Schaefer: *Comprehensive Pediatric Nephrology*, Mosby, Philadelphia, First Edition, 12: 205-218.

- Grewal IS, Rutledge BJ, Fiorillo JA, Grewal IS, Rutledge BJ, Fiorillo JA, et al., (1997)**: Transgenic Monocyte Chemoattractant Protein-1(MCP-1) in pancreatic islets produces monocytes-rich insulitis without diabetes. Abrogation by a second transgene expressing systemic MCP-1. *J Immunol* 159:401-408.

- Hafeez F, Ahmed TM and Samina U (2006)**: Levamisole in steroid dependent and frequently relapsing nephrotic syndrome. *J Coll Physicians Surg Pak.*; 16(1):35-37.

- Hashimura Y, Nozu K, Kanegane H, Miyawaki T, Hayakawa A, Yoshikawa N, et al., (2009)**: Minimal change nephrotic syndrome associated with immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome. *Pediatr Nephrol.* 2009 Feb 3. [Epub ahead of print].

- **Hodson EM, Craig JC and Willis NS (2005):** Evidence-based management of steroid-sensitive nephrotic syndrome. *Pediatr Nephrol*; 20(11): 1523-1530.

- **Horuk R, Colby X D, Schall T and Neote K (1993):** The human erythrocyte inflammatory peptide (chemokine) receptor: biochemical characterization, solubilization and development of a binding assay for the soluble receptor. *Biochemistry* 32:5733-573.

- **Ibrahim S and Rashed L (2008):** Correlation of urinary onocytes chemoattractant protein-1 with other parameters of renal injury in type 2 diabetes mellitus. *Saudi J Kid Dis Transpl*; 19:911–17.

- **Iyengar AA, Kamath N, Vasudevan A, and PhadkeKD (2011):** Urinary indices during relapse of childhood nephrotic syndrome. *Indian J Nephrol*; 21(3): 172–176.

- **Iglesias J and Levine JS (2001):** Albuminuria and renal injury – beware of proteins bearing gifts. *Nephrol Dial Transplant*; 16:215-218.

- **Jia T, Serbina NV, Brandl K, Zhong MX, Leiner IM, Charo IF, et al. (2008):** Additive roles for MCP-1 and MCP-3 in CCR2-mediated recruitment of inflammatory monocytes during *Listeria monocytogenes* infection. *J Immunol*; 180:6846-53.

- **Jiang Y, Beller D, Frendl G and Graves D (1992):** Monocyte chemoattractant protein-1 regulates adhesion molecule expression and cytokine production in human monocytes. *J Immunol*; 148:2423-2428.

- **Jiang Y, Valente AJ, Williamson MI, Zhang L and Graves DT (1990):** Post-translational modification of a monocyte-specific chemoattractant synthesized by glioma osteosarcoma and vascular smooth muscle cells. *J Biol Chem* 265:18318-18321.

- **Kerlin BA, Blatt NB, Fuh B, Zhao S, Lehman A, Blanchong C, et al.,(2009):** Epidemiology and Risk Factors for Thromboembolic Complications of Childhood Nephrotic Syndrome: A Midwest Pediatric Nephrology Consortium (MWPNC) Study. *J Pediatr*. 2009 Apr 23. [Epub ahead of print].

- **Kietkajornkul C, Klinklom A and Kirawittaya T (2008):** Pericardial effusion in childhood nephrotic syndrome. *J Med Assoc Thai*; 91(3): 35-40.

- **Kim MJ and Frederick WK (2011):** Urinary monocyte chemoattractant protein-1 in renal disease. *Clinica Chimica Acta*; 12375:1-9.

- **Klein M, Henschkoski J, Yu Z and Vogt B (2004)** Edema and the nephrotic syndrome. *Ther Umsch*; 61(11):655-660.

- **Korbet SM (2002):** Percutaneous renal biopsy. *Semin Nephrol*; 22:254–267.