ORIGINAL RESEARCH PAPER

Volume-7 | Issue-6 | June-2018 | PRINT ISSN No 2277 - 8179

INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

INCREASED LIPID PEROXIDATION IN NEPHROTIC SYNDROME

Medicine

Riska Habriel Ruslie* Department of Child Health, Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia*Corresponding Author

Oke Rina Ramayani Division of Nephrology, Department of Child Health, Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia

Rosmayanti Syafriani Siregar Division of Nephrology, Department of Child Health, Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia

Beatrix Siregar Division of Nephrology, Department of Child Health, Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia

ABSTRACT

Nephrotic syndrome (NS) is an immunoinflammatory disease in which podocyte injury is observed due to the accumulation of inflammatory mediators, that leads to massive proteinuria. Inflammation in NS promotes higher level of reactive oxygen species. Previous evidences suggests mitochondrial damage, increased lipid peroxidation, and low antioxidant level precede proteinuria. Increased level of lipid peroxidation negatively correlates with albumin serum. Furthermore, dyslipidemia in NS potentially worsen preexisting oxidative stres. In terms of NS management, antioxidant supplementation might be considered as adjuvant therapy to suppress lipid peroxidation.

KEYWORDS

nephrotic syndrome, lipid peroxidation, malondialdehyde, oxidative stress

Introduction

Nephrotic syndrome (NS) is a spectrum that includes a ray of clinical manifestations due to renal damage. Commonly found in children, this condition is the most frequent renal disorder reported within the age group. Manifestations of NS includes massive proteinuria (>40 mg/m2 body surface area/hour or random urine protein/creatinine ratio > 2 or dipstick ≥ 2+), hypoalbuminemia (≤ 2,5 g/dL), generalized edema, that may be accompanied by hypercholesterolemia.[1]

The principal cause of the development of NS is the increased permeability of glomerullar capillaries. This process leads to massive proteinuria and consequently hypoalbuminemia. In primary (idiopathic) NS, thinning of the podocytes processus was found. This finding implies the role of podocytes in the patophysiology of NS. Additionally, immune complex dysfunction was also found. This complex mediated by T cell, disrupts glomerular filtration barrier by releasing proinflammatory cytokines.[2]

Nonetheless, the pathogenesis of NS is still under debate. Clinical response of NS to systemic immunosuppressive agents favors the theory that NS is an inflammatory origin. The activation of proinflammatory cytokines disrupts podocytes causing massive proteinuria. This chronic proteinuria induces local cytokines release and leucocytes influx to glomerulus and to interstitial tissue leading to progressive tubulus dysfunction, renal fibrosis and glomerulosclerosis. Immunosuppresive therapy disrupts this cycle by inhibiting synthesis of cytokines as well as cytokine receptor blockage through activating NF-KB and JAK/STAT pathway. The proinflammatory cytokines build up in NS pathogenesis may manifest as an increased in serum level of the cytokines.[3]

Significant inflammation that takes place in NS pathogenesis can lead to the formation of reactive oxidative species. This accumulation may further deteriorates cell destruction, disrupt lipid metabolism and causes DNA damage. In previous animal study, the accumulation of free radicals was found, that suggests its role in renal injury specifically podocyte damage. Based on these findings, inflammation and accumulation of free radicals are thought to underlie the pathogenesis of NS.[4]

Free radicals have a rather short half time making it unfeasible to be measured clinically. The accompanying lipid damage can be measured through Malondialdehyde (MDA), which is the byproduct of lipid peroxidation. Thus, formation of free radicals is measured indirectly through lipid peroxidation.5 This current article is aimed to explain the increased level of lipid peroxidation in nephrotic syndrome.

Inflammatory response in nephrotic syndrome

a. Previous paradigm on the pathogenesis of idiopathic nephrotic syndrome (INS) Early study on the pathogenesis of INS was done by Shalhoub in 1974, called "Pathogenesis of lipoid nephrosis: a disorder of T-cell function". This study reported no significant difference between minimal lesion glomerulonephritis (GN) and primary segmented focal glomerulosclerosis. Around the time, both were thought as lipoid nephrosis that is identical to INS. Shalboub implied that INS is a T-cell dysfunction that leads to increased permeability due to plasma lymphocytes. This hypothesis was based on the absence of immune complex in glomeruli, immediate response to steroid therapy, association between INS and Hodgkin disease, and through observation that measles often leads to remission of NS. Thus, the associated massive proteinuria and hypoalbuminemia are thought due to the increased permeability of glomerular capillaries induced by T-cell mediated viral infection or allergen.[6]

One of the most fascinating evidence is probably the renal allograft. The preexisting NS was found absent when the renal with minimal lesion GN was transplanted to non-NS donor. In patients with minimal lesion GN there is a recurrent risk regardless being a transplant donor. Proinflamatory cytokines transfer through placenta also induces neonatal NS that may require apheresis, suggesting the role of circulating factors in minimal lesion GN.[6]

Based on this hypothesis of Shalhoub, studies have been directed to identify circulating factors released by T cell that increased glomerular permeabilty towards serum protein. Among the serum proteins identified, cytokines was found most potent. Cytokine is a small size protein (weight molecule of 8-80 kDa) that acts as a soluble autocrine or paracrine mediator. It is produced by both immune and non-immune cells. In relapse cases (mostly minimal lesion GN), increased of various serum or urine cytokines are found. This includes interleukin (IL)-2, IL-2 soluble receptor, interferon (IFN) -γ, IL-4, IL-12 , IL-18, tumor necrosis factor (TNF) -α, and vascular endothelial growth factor (VEGF). The main primary cytokine in inducing protein loss has not yet being identified, possibly due to broad immunogenetic variation within individuals.

The T cell population that deviates in INS has been under investigation, that includes Th2 dominance over Th1 activity in atopic persons. However, more rencent studies reported remission following B cell deprivation through monoclonal antibody or rituximab (anti-CD20 agent) that contradicts Shalhoub hypothesis, which focus on the T-cell dysfunction in INS pathogenesis.6

b. More recent theory of NS pathogenesis

A newer paradigm in INS pathogenesis has arised since the finding of Tryggvason et al (1998), which found that the mutation of NPHS1 (Nephrin Precursor Homo Sapiens 1) gene occurs in INS. This gene expresses podocyte nefrin (superfamily immunoglobulin protein). This study addressed more on the biology and the physiology of glomerulus and podocytes (glomerular visceral epithelial cells) that play a pivotal role in INS pathogenesis. Podocytes are differentiated from the outer cells of glomerular basal membrane. Podocytes act as a final barrier of urinary protein filtration by forming maintance podocyte foot processes (FPs) and slit diaphragms (SDs). SD is the main selective barrier in kidneys. The FPs contains contractile and dynamic apparatus that includes actin, myosin II, α-actinin-4, talin, vinculin, and synaptopodin. FPs bind to glomerular basal membrane through α3β1-integrin and dystroglycans. Knowledge on SD structure is based on genetic studies of familial NS, which revolves around SD proteins such as podocyne, nefrin, α-actinin-4, and transient receptor potential channel C6. Genes encoding these proteins can undergo mutations in inherited NS.6-8

Based on those findings, several hypothesis has been proposed that focused more on the role of podocyte and associated molecules in INS. The molecules thought to interplay includes proinflammatory cytokines, reactive oxygen species, NF-kB, hemopeksin, and CD80. Those molecules induce inflammation and cause podocyte damage.6 Cho et al (2003) found higher level of proinflammatory cytokines IL-8 and TNF- α in both urine and plasma in relapse patients compared to remission and control group.9 Ece et all (2004) also reported significantly elevated level of plasma IL-8 in relapse NS patients.[4]

All forms of NS showed podocyte disturbance, which raise the concern of its injury or damage being a major role in NS pathogenesis. In the last decade, genetic cause of podocyte injury has been directed towards SD molecules and FP dynamic modulator of actin. Several gene mutations vital in podocyte regulation have been reported that includes nefrin, podocin, CD2-Associated Protein (CD2AP) and α-actinin-4.6 Podocyte function is speciafically modulated thtough contractile fillaments of actin in FP. Damage to the podocytes might be due to reorganization of FP cytoskeleton of actin leading to thinning of FP and disrupt SD. Downregulation of podocyte may also contribute to progressive kidney failure, that may be induced by podocyte apoptosis, detachment from glomerulal basal membrane and/or inability to proliferate.[6]

CD80, also known as B7-1, is a transmembrane protein that acts as antigen presenting cell (APC) and promote signal co-stimulatory in T cell activation. Previous evidence showed expression of CD80 in response to podocyte stimulus, that leads to podocyte abnormality and proteinuria. This correlation stresses the importance of this molecule in NS pathogenesis as well as potential target therapy in treating proteinuria in NS.[8]

Reactive oxidative species (ROS) is a common term to represent several reactive molecules and free radicals derived from oxygen, such as superoxide anion, hydrogen peroxide, and hydroxil radicals. It is reported that ROS induced proteinuria and podocyte damage. Additionally, Akt (protein kinase B) is a major mediator in cell maintenance by preventing apoptosis. Akt exert its anti-apoptotic effecr though several target, such as pro-apoptotic Bcl-2 family, forkhead transcription factor and cyclic AMP response element-binding protein (CREB).6

Lipid peroxidation

Lipid is considered one of the most sensitive molecules to free radicals. This interaction induces lipid peroxidation. Lipid peroxidation is a reaction between free radicals with polyunsaturated fatty acid (PUFA).10 Lipid peroxidation continuously forms lipid free radicals (R-) that ensures ongoing reaction.

Lipid peroxidation typically undergoes three phases. It begins with the separation of one hydrogen atom within the methylene group (-CH2-) of PUFA by free radical. This leads to carbon radical formation within PUFA. This carbon radical can be stabilized through rearrangement of double binding that leads to the formation of conjugated dienes. This dienes when exposed to oxygen molecule, would create lipid peroxide radicals (LOO-). This molecule further deletes one hydrogen atom of another nearby lipid molecule to continuously form carbon radical thus the cycle loops.

Formation of lipid endoperoxyde within PUFA composed of at least 3 double binding promotes synthesis of malondialdehyde (MDA) as a byproduct. MDA is a highly reactive molecule that commonly used as a biological biomarker to measure the level of oxidative stress and free radicals.10,11

Lipid peroxidation in NS

Inflammatory reactions that occur in NS leads to higher level of ROS, especially superoxide anion (O2-) and hydrogen peroxide (H2O2). Proinflammatory cytokines such as TNF-α, IL-1β, and IFN gamma stimulates mitochondria and NADPH, resulting in superoxide anion. The resulting free radicals damage cell membranes that is high in PUFA, causing lipid peroxidation and consequently form MDA. The free radicals can potentially further activates or recruit proinflammatory cytokines. Both the ROS and proinflammatory cytokines are known to exert its damage on podocytes.

Free radicals may lead to advance renal injury causing NS to develop.12,13 Within kidneys, free radicals are formed in vascular cells, juxtaglomerular cells, tubulus cells, podocytes, mesangial cells and glomerulus.14 ROS derived from lipid peroxidation disrupt tubulus epithelial integrity and increase glomerular permeability to protein as well as distort normal glomerular hemodynamic.15 Functional disruption that underlies NS is the increase of glomerular filtration permeability due to previously mentioned free radicals.28 Previous evidence suggested mitochondrial damage, MDA accumulation, and downregulation of glutathione peroxidase precede proteinuria.[16]

Hypoalbuminemia and hyperlipidemia in NS independently associate with the increased cardiovascular risk possibly due to higher level of oxidative stress.19 Slight accumulation of lipid peroxide is enough to oxidase protein that leads to cell or tissue damage. Thus lipid peroxidation is considered to contribute in the progression of NS.15,20 Dysfunction of lipid metabolism is one of the clinical manifestation in NS. Individuals with NS has a higher risk of atherosclerosis and progressive renal insufficiency.14 Lipid is a target molecule of free radicals that is due to increased antioxidant consumption such as erythtocyte-SOD.[21]

Previous study showed significantly higher level of serum MDA ($p<0,001$) in NS patients (3,64 + 1,3) vs control (1,58 + 0,42). In NS, phagocytes infiltration was seen that also produce ROS.20 Balamurugan et al (2007) also reported higher level of MDA in NS group. Another study by Dwivedi et al (2009) and Begenik et al (2013) conducted in adult NS, also found higher level of MDA in NS group compared to control.23,24 The lower albumin level in NS is due to protein loss through increased glomerular permeability. The level of serum MDA was found to negatively correlate with serum albumin.

Within glomerulus, the activity of SOD scavenger was found declined. Erhythrocyte SOD activity was observed to diminish significantly in NS (1,07 + 0,5) vs control (1,88 + 0,9).20 SOD is an intracellular enzyme that disrupt free radicals by converting it to a less reactive form, H2O2. This molecule is further metabolized through catalase and glutathione peroxide. Thus SOD is considered vital in lessening the damaginf effect of oxidative stress. Diminished activity of erhythrocyte SOD is due to overconsumption following increased antioxidant formation and increased renal excretion in NS patients. 25-27 Thus, the balance between free radicals and antioxidants is impaired in NS. Lower level of albumin also contributes to the imbalance, since albumin is a main plasma antioxidant as well. Another antioxidant level such as ascorbic was also found significantly decreased in NS.[13]

Another study by Mao et al (2014) found significanlt higher level of MDA and lower vitamin C level as an antioxidant in NS patients compared to non-NS group. These findings reside even in remission.28 Study by Balamurugan et al (2003) also supports these findings, reporting lower level of ascorbic acid and GSH in NS patients.29 Bulucu et al (2000) reported lower SOD activity and higher MDA level in NS. Zachwieja et al (2003) also found lower antioxidant level and it associates with abnormal level of lipid.[31]

Ece et al (2004) found significantly elevated MDA level, reduced SOD and total antioxidant in relapse NS. Another study also found increased plasma MDA level and lower level of antioxidant in relapse NS compared to remission and control group.29,30 These findings can potentially direct the use of antioxidant in combination with

immunosuppressive agents to suppress lipid peroxidation as part of NS treatment.[4]

Summary

Nephrotic syndrome is a clinical spectrum composed of massive proteinuria (>40 mg/m2 body surface area/hour or protein/creatinine ration in random urine >2 or dipstick ≥ 2+), hypoalbumin of ≤ 2,5 g/dL, generalized edema, and hypercholesterolemia. NS is immunoinflammatory condition, in which accumulated inflammatory cytokines damage podocytes thus massive proteinuria develops. Inflammation in NS increases ROS formation that contributes to podocyte disruption. Thus, inflammation and elevated free radicals are thought to underlie the pathogenesis of NS. Previous evidence suggest mitochondrial damage, increased lipid peroxidation and diminished level of antioxidant precede proteinuria. It is also implied that serum MDA level negatively correlates with serum albumin level. Additionally, dyslipidemia found in NS can further intesify the oxidative stress. The importance of antioxidant in suppressing lipid peroxidation has been studied that warrants consideration as an adjunct in NS therapy.

References

1. Pais P, Avner ED. Nephrotic syndrome. In: Kliegman RM, Stanton BF, StGeme JW III, eds. Nelson Textbook of Pediatrics. 20th ed. Philadelphia: Elsevier; 2016. Chapter 527.
2. Wirya IW. Sindrom Nefrotik. Dalam: Buku Ajar Nefrologi: Ikatan Dokter Anak Indonesia; 2004.p. 383.
3. Camici M. The nephrotic syndrome is an immunoinflammatory disorder. Med Hypotheses. 2007;68(4):900-5.
4. Ece A, Atamer Y, Gurkan F. Anti-oxidant status in relation to lipoproteins, leptin and pro-inflammatory cytokines in children with steroid-sensitive nephrotic syndrome. Nephrology. 2004;9:366-73.
5. Arkhaesi N. Kadar malondialdehyde serum sebagai indikator prognosis keluaran pada sepsis neonatorum. Semarang: Departemen Ilmu Kesehatan Anak FK Undip; 2008.
6. Kaneko K. Molecular Mechanisms in the Pathogenesis of Idiopathic Nephrotic Syndrome. Tokyo: Springer Japan; 2016.
7. Yoo TH, Fornoni A. Nonimmunologic targets of immunosuppressive agents in podocytes. Kidney Res Clin Pract. 2015; 34(2):69-75.
8. Fogo AB. The Targeted Podocyte. J Clin Invest. 2011;121(6):2142-5.
9. Cho MH, Lee HS, Choe BH, et al. Interleukin-8 and tumor necrosis factor-alpha are increased in minimal change disease but do not alter albumin permeability. Am. J. Nephrol. 2003; 23:260–6.
10. Muliasari A. Konsentrasi lipid peroksida hati kelinci hiperlipidemia yang diberi senyawa hipolipidemik. Bogor: Program Studi Biokimia; 2009.
11. Dalle-Donne I, Rossi R, Colombo R, et al. Biomarkers of Oxidative Damage in Human Disease. Clin Chem. 2006;52:601–23.
12. Zachwieja J, Bobkowski W, Zaniew M, et al. Apoptosis and antioxidant defense in the nephrotic syndrome. Pediatr Nephrol. 2003;18:1116-21.
13. Dwivedi J, Sarkar PD. The study of oxidant and antioxidant status with homocysteine, total protein, and albumin in nephrotic syndrome. Int J Med Health Sci. 2014;3(1):18-21.
14. Dwivedil J, Sarkar PD. The study of lipid profile, LP (a) and electrolytes with oxidative stress, total protein and albumin in nephrotic syndrome. Int J Res Med Sci. 2014 Feb;2(1):62-6.
15. Ghodake SR, Suryakar AN. Role of reactive oxygen species in pathogenesis of nephrotic syndrome. Indian J Clin Biochem. 2010;25(1):82-5.
16. McBryde KD, Kershaw DB, Smoyer WE. Pediatric steroid-resistant nephrotic syndrome. Curr Probl Pediatr. 2001; 31: 275-307
17. Solin ML, Ahola H, Haltia A, et al. Lipid peroxidation in human proteinuric disease. Kidney Int. 2001;59:481-7
18. Sawant SU, Chandran S, Almeida AF, et al. Correlation between oxidative stress and thyroid function in patients with nephrotic syndrome. Int J Nephrol. 2011; Article ID 256420: 1-5.
19. Granqvist A, Nilsson UA, Ebefors K. Impaired glomerular and tubular antioxidative defense mechanism in nephrotic syndrome. Am J Physiol Renal Physiol. 2010; 299(4):F898-904.
20. Dogra G, Ward N, Croft KD, et al. Oxidant stress in nephrotic syndrome: comparison of F2-isoprostanes and plasma antioxidant potential. Nephrol Dial Transplant. 2001; 16: 1626-30.
21. Ghodake SR, Suryakar AN, Ankush RD, et al. Role of free radicals and antioxidant status in childhood nephrotic syndrome. Indian J Nephrol. 2011;21(1):37-40.
22. Balamurugan R, Selvaraj N, Bobby Z, et al. Increased glycated hemoglobin level in non-diabetic nephrotic children is associated with oxidative stress. Indian J Physiol Pharmacol. 2007;51(2):153-9.
23. Dwivedi J, Sarkar PD. Interrelationship of oxidative stress, homocysteine, lipoprotein(a), copper and zinc in nephrotic syndrome: recent advances: risk for cardiac diseases. Pharmacologyonline. 2009;2:605-5
24. Begenik H, Soyoral YU, Erkoc R, et al. Serum malondialdehyde levels, myeloperoxidase and catalase activities in patients with nephrotic syndrome. Redox Rep. 2013;18(3):107-12.
25. Goldstone A, Rastegar R, Shariftabrizi A, et al. Paradoxical dose and time- dependent regulation of superoxide dismutase and antioxidant capacity by vitamin E in rat. Clin Chim Acta. 2006; 265: 153-9.
26. Beltowski J, Jamroz-Wisniewska A, Wojcicka G, et al. Renal antioxidant enzymes and gluthathione redox status in leptin-induced hypertension. Mol Cell Biochem. 2008;319:163-74.
27. Tian J, Chen JH, Li Q, et al. Lipid peroxidation in IgA nephropathy and the effect of lipo - prostaglandin E1. J Nephrol. 2005; 18: 243-8.
28. Mao S, Zhang A, Huang S. Serum levels of malondialdehyde, vitamin C and E in idiopathic nephrotic syndrome: a meta-analysis. Ren Fail. 2014 Jul;36(6):994-9.
29. Balamurugan R, Bobby Z, Selvaraj N, et al. Increased protein glycation in non-diabetic pediatric nephrotic syndrome: possible role of lipid peroxidation. Clin Chim Acta. 2003;337(1-2):127-32.
30. Bulucu F, Vural A, Aydin A, et al. Oxidative stress status in adults with nephrotic syndrome. Clin Nephrol. 2000;53(3):169-73.
31. Zachwieja J, Bobkowski W, Dobrowolska-Zachwieja A, et al. Decreased antioxidant activity in hypercholesterolemic children with nephrotic syndrome. Medical Science Monitor. 2003; 9(6):235–9.
32. Mocan H, Aksoy A, Uydu HA, et al. Oxidative damage of erythrocyte membrane in nephrotic syndrome. Pediatr Nephrol. 1999;13:326–32.