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ORIGINAL ARTICLE

Hyperinsulinemia in pediatric patients with chronic kidney disease: the role of tumor necrosis factor-α

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Abstract We sought to determine the prevalence of hyperinsulinemia and insulin resistance in pediatric patients with chronic kidney disease (CKD) stages 2–4. Data were collected on 43 subjects, aged 6–21 years with mean glomerular filtration rate (GFR)=47 ml/min per 1.73 m^2 body surface area. Patients were grouped by body mass index (BMI) as either non-lean (>85th percentile) or lean (≤85th percentile). Fourteen (33%) subjects had hyperinsulinemia, and seven (16%) had elevated homeostasis model assessment of insulin resistance (HOMA-IR). Non-lean subjects had a higher serum insulin level (21.0 μU/ml vs 13.4 μU/ml, $P<0.0001$) and HOMA-IR (4.9 vs 3.2, $P<0.001$) than lean subjects had. The prevalence of hyperinsulinemia was higher in non-lean patients (40%) than in lean patients (29%) but was not statistically significant. High HOMA-IR was present in six (40%) non-lean subjects and in one lean subject ($P<0.001$). Correlation analysis demonstrated that serum insulin level was significantly associated with BMI, leptin and tumor necrosis factor (TNF)-α. Stepwise regression determined that increased BMI ($P=0.003$) and TNF-α ($P=0.01$) independently predicted higher insulin level in the whole cohort. Separate analysis for lean subjects showed no significant associations between serum insulin level and BMI; TNF-α was the only independent predictor of serum insulin ($\beta=1.11$, $P=0.01$). We conclude that hyperinsulinemia and insulin resistance are frequent in pediatric CKD. In lean patients inflammation appears to be an important determinant of serum insulin level.

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Keywords TNF-α · Children · Pediatric · Chronic kidney disease · Hyperinsulinemia · Insulin resistance

Abbreviations

CV	cardiovascular
CKD	chronic kidney disease
GFR	glomerular filtration rate
TNF-α	tumor necrosis factor-α
hsCRP	high-sensitivity C-reactive protein
IL	interleukin
BMI	body mass index
SBP	systolic blood pressure
DBP	diastolic blood pressure
HOMA-IR	homeostasis model assessment of insulin resistance
NFκB	nuclear factor κB
IRS-1	insulin receptor substrate-1

Introduction

Hyperinsulinemia and insulin resistance are well-known entities which convey elevated risk for cardiovascular morbidity and mortality in the general population. Recent studies of adults with chronic kidney disease (CKD) have shown that insulin resistance and hyperinsulinemia are already present in patients with mild renal insufficiency and are independently associated with cardiovascular events [1–4]. Hyperinsulinemia and insulin resistance have been described in small studies of adolescents on maintenance dialysis or with severe renal failure [5–10]. However, there has been no prior published research describing insulin levels and insulin resistance in children with mild-to-

moderate chronic renal insufficiency. The goals of this study, therefore, were to: (1) describe serum insulin levels and homeostasis model assessment of insulin resistance (HOMA-IR) in a cohort of children and adolescents with CKD stages 2–4, (2) estimate the cross-sectional association of these parameters with other potential cardiovascular (CV) markers such as lipids, adipokines and inflammation, and (3) define the association of kidney dysfunction and adiposity with insulin and HOMA-IR levels.

Methods

Forty-three subjects, ages 6 years to 21 years old with CKD stages 2–4 (measured glomerular filtration rate 16–87 ml/min per 1.73 m^2 body surface area) were recruited. The Institutional Review Board of Cincinnati Children's Hospital Medical Center approved the study, and informed consent was obtained for each study patient. At the time of evaluation, demographic and anthropomorphic information was recorded, including age, race, gender, height, weight, and blood pressure. Cause of renal disease was obtained from review of medical records. CKD staging was based on glomerular filtration rate (GFR) measurement by a single injection of Ioversol (Optiray 350, Mallinckrodt, St Louis, Missouri, USA). Iodine in timed blood samples was measured by X-ray fluorescence analysis (Renalyzer PRX90, Diatron AB, Sweden), and GFR was calculated from the slope of the iodine disappearance curve [11]. The sampling times were determined from the estimated GFR (eGFR) obtained by the Schwartz formula [12]. For subjects with eGFR > 60 ml/min per 1.73 m^2, blood samples were obtained at 150 min, 195 min, and 240 min after Ioversol injection, for those with eGFR of 30–60 ml/min per 1.73 m^2, blood samples were obtained at 150 min, 240 min, and 300 min after Ioversol injection, and for those with eGFR of <30 ml/min per 1.73 m^2 samples were obtained at 180 min, 270 min, and 360 min after Ioversol injection.

After the patient had fasted for 12 h, serum was collected in the morning of the GFR study. Insulin levels were measured by a radio-immunoassay (Linco Laboratories, USA) [13]. Hyperinsulinemia was defined as a serum insulin level above the 95th percentiles established by Weiss et al. [13]. The homeostasis model assessment of insulin resistance (HOMA-IR) was used as a measure of insulin resistance. We calculated HOMA-IR by dividing the product of serum insulin (in micro-units per milliliter) and glucose (in millimoles per milliliter) by a factor of 22.5. Insulin resistance was defined as HOMA-IR >4.39 (upper 2.5 percentiles or >2 SDs above mean HOMA-IR for normal-weight children) [14].

Lincoplex multianalyte kits were utilized for determination of serum homocysteine, adipokines (leptin, adiponectin, resistin), inflammatory cytokines [interleukin (IL)-6, tumor necrosis factor (TNF)-α, high-sensitivity C-reactive protein (hsCRP)] and apolipoprotein fractions (ApoA1, ApoA2, ApoB, ApoC, ApoE). Weight categories based on body mass index (BMI) were established as obese, >97th percentile for age and gender, overweight, between the 85th percentile and the 97th percentile, or lean, less than the 85 percentile.

Statistical analysis Values are presented as the mean ± SD. A two-sample *t*-test or the Mann–Whitney rank-sum test was used to compare continuous variables. Categorical variables were compared using the chi-square test or Fisher's exact test. The associations between variables were assessed by Pearson correlations. Stepwise forward multiple regression analysis was performed to assess independent predictors of serum insulin. Variables with $P<0.15$ from univariate analyses were entered in the regression analysis. The SAS 9.1 statistical package was used in the analysis. $P\leq0.05$ was considered statistically significant.

Results

Among the cohort of 43 children, 28 (65%) were male and 40 (93%) were white. Three children were African–American. The main causes of CKD were renal dysplasia/obstructive uropathy (66%) and glomerular and cystic diseases (34%). Almost half of the children (46%) were taking antihypertensive medications. Of those on medications, all were taking angiotensin-converting enzyme inhibitors or angiotensin receptor blocker. Fourteen patients were taking these medications as anti-proteinuric agents. The mean duration of CKD was 8.8±5.6 years. No patients had suffered from CKD for less than 1 year. Mean GFR was 47.4±21.1 ml/min per 1.73 m^2 body surface area, with range of 16–87 ml/min per 1.73 m^2. Twelve (28%) patients had CKD stage 2, 19 (44%) stage 3, and 12 (28%) stage 4. There were 28 (65%) lean (BMI < 85th percentile) and 15 (35%) non-lean (BMI ≥ 85th percentile) subjects. Four subjects were obese, with BMIs>97th percentile.

The mean serum insulin level for the cohort was 15.9± 14.5 μU/ml (range 2.0–86.7 μU/ml), and the mean HOMA-IR was 3.7±3.2 (range 0.34–17.5). Fourteen (33%) subjects had hyperinsulinemia, and seven (16%) had insulin resistance (HOMA-IR>4.39). None of the subjects had a serum glucose level >110 mg/dl.

In a univariate analysis (Table 1), serum insulin levels were significantly associated with BMI, leptin and TNF-α. There was no significant relationship between insulin and GFR or between insulin and age. Stepwise multivariate regression determined that only increased BMI (β=1.19,

Table 1 Pearson correlation analysis of anthropometric and biochemical markers

Variable	Insulin	Adiponectin	Age	BMI	GFR	Leptin	TNF-α
Insulin							
R	1.0	0.06	0.14	0.33	−0.04	0.05	0.33
P		0.67	0.35	0.04	0.75	0.29	0.04
Adiponectin							
R		1.0	−0.27	0.005	−0.24	−0.35	0.23
P			0.08	−0.42	0.11	0.01	0.13
Age							
R			1.0	0.38	−0.31	0.17	−0.03
P				0.01	0.04	0.28	0.87
BMI							
R				1.0	0.05	0.73	−0.11
P					0.72	<0.0001	0.46
GFR							
R					1.0	0.01	−0.19
P						0.94	0.21
Leptin							
R						1.0	−0.1
P							0.52
TNF-α							
R							1.0
P							

P=0.003) and TNF-α (β=0.95, *P*=0.01) independently predicted higher insulin level (model R^2=0.27).

To assess the role of adiposity in hyperinsulinemia, we performed detailed analysis according to lean versus non-lean status (Table 2). There was no significant difference in the serum glucose level between groups. Non-lean subjects had significantly higher serum insulin levels and HOMA-IRs than did lean subjects. The prevalence of hyperinsulinemia was higher in non-lean patients (40%) than in lean patients (29%) but was not statistically significant (*P*> 0.05). Abnormally high HOMA-IR was present in six (40%) non-lean subjects and in only one lean subject (*P*< 0.001). In non-lean subjects (*n*=15), insulin level was significantly correlated with BMI (R=0.37, *P*<0.01), while analysis for lean subjects (*n*=28) showed no significant associations between serum insulin level and BMI (Fig. 1).

Table 2 Comparison of lean and non-lean subjects. The data presented as means ± SDs. *P* values represent the difference between lean and non-lean subjects (*BMI* body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *GFR* glomerular filtration rate, *LDL* low-density lipoprotein, *HDL* high-density lipoprotein, *CRP* C-reactive protein, *TNF-α* tumor necrosis factor-α, *IL-6* interleukin-6)

Variables	Total (*n*=43)	Lean (*n*=28)	Non-lean (*n*=15)	*P*
Age, years	13.9±4.1	14.0±4.0	13.6±4.3	0.74
BMI, kg/m^2	20.9±6.3	17.7±2.7	27.2±6.8	<0.0001
Indexed SBP	0.91±0.09	0.90±0.09	0.93±0.08	0.27
Indexed DBP	0.81±0.14	0.80±0.14	0.81±0.13	0.89
GFR, ml/min/ 1.73 m^2	47.4±21.1	45.8±21	49.5±18	0.59
Cholesterol, mg/dl	188±50	183±46	198±52	0.35
LDL, mg/dl	106±42	103±37	112±39	0.49
HDL, mg/dl	50±15	53.7±15.9	45.6±11.9	0.09
Triglycerides, mg/dl	155±99	129±78	207±118	0.01
Insulin, μU/ml	15.9±14.5	13.4±15.3	21.0±11.6	<0.0001
HOMA-IR	3.7±3.2	3.17±3.4	4.94±2.6	<0.0001
Adiponectin, μg/ml	30.6±14.1	34.1±13.4	23.6±13.3	0.02
Leptin, ng/ml	13.0±20.7	4.6±7.9	29.2±27.9	<0.0001
Resistin, ng/ml	15.5±5.9	14.7±5.8	16.9±5.8	0.23
Homocysteine, ng/ml	11.3±6.4	11.7±7.3	10.6±4.3	0.61
CRP, mg/l	2.3±3.4	1.9±3.2	2.9±3.8	0.36
TNF-α, pg/ml	9.9±6.2	10.3±7.1	9.2±4.4	0.58
IL-6, pg/ml	10.2±10.2	8.5±9.3	11.4±11.9	0.38

Multivariate stepwise regression analysis of lean subjects showed that TNF-α was the only independent predictor of serum insulin (β=0.81, P=0.04).

Discussion

Hyperinsulinemia is a known finding in adults with pre-terminal CKD. Chen et al. [4] reported on data from 6,453 adult non-diabetic patients in the National Health and Nutrition Examination Survey (NHANES) III Study. The authors showed that hyperinsulinemia and insulin resistance based on HOMA-IR is present in adults with mild-to-moderate renal insufficiency (corrected GFR>60 ml/m^2 per minute). This study also identified a strong, positive, significant, and dose-responsive relationship among insulin resistance, insulin level, and risk of CKD. More importantly, this relationship was independent of age, gender, race, or other potential risk factors for CKD, such as blood pressure (BP), obesity, total cholesterol level, education, physical activity, cigarette smoking, non-steroidal anti-inflammatory drug (NSAID) use, and alcohol consumption.

In pediatric patients the majority of data on insulin metabolism comes from small cross-sectional studies of children on chronic dialysis. Mak [5] and others [6, 7] have shown that hyperinsulinemia is a universal finding in these patients. Pediatric studies have also demonstrated a high prevalence of abnormal results of glucose tolerance tests (32.7–45%) and increased HOMA-IR (47.1%) in children before transplantation [6–9]. Haffner et al. [10] demonstrated significantly higher serum insulin levels and abnormal glucose tolerance not only in children with end-stage renal disease (ESRD) and children with transplants but also in children with pre-terminal CKD (mean GFR 27 ml/min per 1.73 m^2).

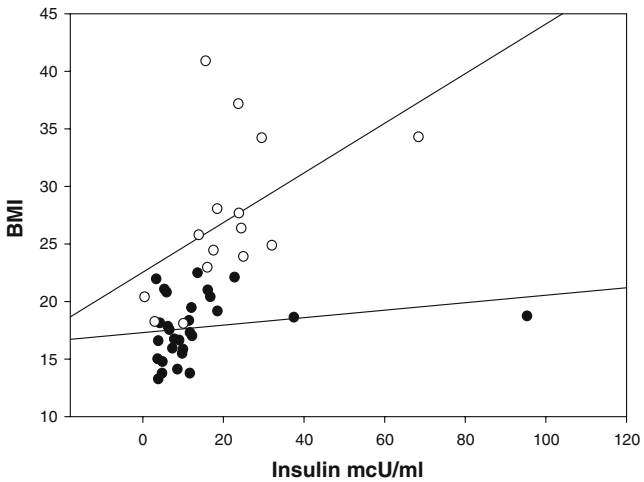

Fig. 1 Relationship between insulin and BMI in lean patients (closed circles) and non-lean patients (open circles). Significant correlation exists between serum insulin and BMI among non-lean subjects (R=0.37, P<0.01), but this correlation was not demonstrated in lean subjects (R=0.23, P=0.24)

The results of our study demonstrated that hyperinsulinemia and insulin resistance are frequent in a cohort of children with mild-to-moderate CKD. In our study renal clearance was not a determinant of serum insulin since there was no significant difference in insulin level or HOMA-IR among children with different stages of CKD.

As expected, the average insulin and HOMA-IR levels were higher in non-lean patients than in lean patients. However, unlike in the general pediatric population, where hyperinsulinemia is closely associated with the obesity epidemic, the prevalence of hyperinsulinemia remained high in lean subjects with CKD. This suggests that, in pediatric patients with mild-to-moderate renal dysfunction, there is a dysregulation of glucose metabolism independent of elevated BMI. For these patients, hyperinsulinemia may lead to increased cardiovascular risk through a mechanistic pathway independent of fat metabolism.

The association of TNF-α with hyperinsulinemia in our lean CKD patients is tantalizing, because it supports a link between metabolic dysregulation, protein wasting and inflammation in the uremic state that may explain, in part, the higher rate of cardiovascular morbidity seen among lean adult ESRD patients [15–17]. TNF-α is a 17 kDa polypeptide cytokine produced primarily by activated macrophages as part of the body's inflammatory response. Uremia, a chronic micro-inflammatory state, is characterized by cytokine dysregulation, oxidative stress, and impaired response to oxidative injury [18–21]. Uremic patients have elevated levels of C-reactive protein (CRP) and TNF-α, together with accumulation of advanced oxidation protein products (AOPPs) and advanced glycation end (AGE) products [21–23]. Additionally, even in mild-to-moderate CKD, decreased levels and activity of glutathione and glutathione peroxidase are found [24]. Guarnieri et al. [25] observed that gene expression for TNF-α in circulating blood cells is enhanced in patients with chronic uremia. It is probable that, as in cancer cachexia and other malnutrition states, [25], in the uremic state TNF-α disrupts the balance of protein turnover by stimulating protein catabolism, resulting in muscle atrophy.

TNF-α interferes with myoblast differentiation and muscle repair following injury and acts in concert with IL-1β to promote catabolism of differentiated muscle [26, 27]. It does so by activating nuclear factor κB (NFκB), a nuclear transcription factor. NFκB inhibits post-translational modification of MyoD, which blocks regeneration of muscle tissue from myoblasts [26, 27]. TNF-α also acts through NFκB to upregulate the ubiquitin/proteosome pathway, which is involved in regulated protein degradation [28–30]. Reactive

oxygen species (ROS) from the mitochondrial electron transport chain appear to modulate this pathway, as ROS blockade inhibits the catabolic effect of TNF-α on skeletal muscle [29]. ROS are themselves regulated by endogenous glutathione and hydrogen peroxide levels [29, 30]. Since the concentrations of glutathione and glutathione peroxidase are decreased in uremia, and their function impaired, we would expect a potentiation of TNF-α stimulated protein degradation through the ubiquitin/proteosome pathway. In mouse models the muscle wasting effect of TNF-α can be blocked by antibodies to TNF-α, antioxidants or nitric oxide synthase [31]. Insulin, an anabolic stimulus, has also been shown to block the effect of TNF-α induced muscle catabolism. TNF-α further tips the balance towards protein wasting and malnutrition by interfering with the synthesis of albumin. It has been shown in mice with genetically activated TNF-α expression that a 90% decrease in albumin mRNA expression and decreased serum albumin levels precede development of cachexia. [32].

In obese subjects or those with type II diabetes mellitus there is a greater than twofold upregulation of TNF-α expression from both central adipocytes and skeletal muscle, which is not seen in lean patients. In these subjects TNF-α mediates insulin resistance by interfering with post-receptor signaling of the insulin molecule. It blocks tyrosine phosphorylation of both the insulin-sensitive GLUT4 receptor and insulin receptor substrate 1 (IRS-1) in adipocytes and peripheral myocytes [33, 34]. It is unclear whether this same mechanism may be responsible for the hyperinsulinemia and elevated HOMA-IR observed in lean CKD patients. If so, this action may compound the risk for protein wasting by leading to inefficient use of carbohydrate resources, as well as by blunting the anabolic effects of insulin. Additionally, TNF-α, previously known as cachexin, induces anorexia. Although the specific mechanism for this is unclear, Breder et al. [35] have demonstrated upregulation of TNF-α expression in the meninges and in the hypothalamic nuclei following lipopolysaccharide injection. These same areas are activated by direct injection of TNF-α into the central nervous system (CNS). Thus, local upregulation of TNF-α in the hypothalamic nuclei, an area that also regulates appetite, is a strong candidate mechanism for its cachectic effect in uremia. Poor nutritional intake, together with the lack of weight-bearing exercise, commonly experienced by CKD patients, may further accelerate loss of lean body mass.

The results of this study suggest that the combination of hyperinsulinemia and elevated TNF-α in the setting of mild-to-moderate CKD could represent early markers for increased cardiovascular risk in children. TNF-α may represent an early therapeutic target to prevent both the development of insulin resistance observed in early CKD and the later development of protein malnutrition syndrome. The monitoring of insulin and TNF-α levels may help us to identify patients who warrant early intervention with aggressive management of nutritional status, insulin resistance, and uremia.

This study has several limitations. This was a single-pediatric-center study lacking healthy controls and limited by the small number of patients and narrow demographics reflecting population/referral bias. Data collected here are cross-sectional and have not been related to actual cardiovascular morbidity. These findings need to be verified with data regarding early cardiovascular abnormalities in children. Further information on pubertal status, nutritional status and protein turnover, by investigation of albumin, lean body mass and normalized protein catabolic rate, would also be useful in furthering this hypothesis. Certainly, multicenter studies with larger numbers of patients and a broader patient demography are needed to confirm that these findings are applicable to the pediatric CKD population as a whole.

References

1. Sechi LA, Catena C, Zingaro L, Melis A, De Marchi S (2002) Abnormalities of glucose metabolism in patients with early renal failure. Diabetes 51:1226–1232
2. Shinohara K, Shoji T, Emoto M, Tahara H, Koyama H, Ishimura E, Miki T, Tabata T, Nishizawa Y (2002) Insulin resistance as an independent predictor of cardiovascular mortality in patients with ESRD. J Am Soc Nephrol 13:1894–2000
3. Knight EL, Rimm EB, Pai JK, Rexrode KM, Cannuscio CC, Manson JE, Stampfer MJ, Curhan GC (2004) Kidney dysfunction, inflammation and coronary events: a prospective study. J Am Soc Nephrol 15:1897–1903
4. Chen J, Muntner P, Hamm LL, Fonseca V, Batuman V, Whelton PK, He J (2003) Insulin resistance and risk of chronic kidney disease in nondiabetic US adults. J Am Soc Nephrol 14:469–77
5. Mak RH (1995) Insulin secretion and growth failure in uremia. Pediatr Res 38:378–383
6. El-Bishti M, Counahan R, Jarrett RJ (1977) Hyperlipidemia in children on regular hemodialysis. Arch Dis Child 15:932–936
7. Parra A, Lopez-Uriarte A, Argote RM, Garcia G, Ledon S, Santos D (1979) Effect of hemodialysis on glucose tolerance in children with chronic renal failure. Arch Invest Med (Mex) 10:39–52
8. Buyan N, Bideci A, Ozkaya O, Ortac E, Bakkaloglu S, Gonen S, Peru H, Soylemezoglu O, Cinaz P (2006) Leptin and resistin levels and their relationships with glucose metabolism in children with chronic renal insufficiency and undergoing dialysis. Nephrology 11:192–196
9. Shishido S, Sato H, Asanuma H, Shindo M, Hataya H, Ishikura K, Hamasaki Y, Goto M, Ikeda M, Honda M (2006) Unexpectedly high prevalence of pretransplant abnormal glucose tolerance in pediatric kidney transplant recipients. Pediatr Transplant 10:1–4
10. Haffner D, Nissel R, Wuhl E, Schaefer F, Bettendorf M, Tonshoff B, Mehls O (1998) Metabolic effects of long-term growth hormone treatment in prepubertal children with chronic renal failure and after kidney transplantation. The German Study Group for Growth Hormone Treatment in Chronic Renal Failure. Pediatr Res 43:209–215

11. Stake G, Monclair T (1991) A single plasma sample method for estimation of the glomerular filtration rate in infants and children using iohexol: establishment of a body weight-related formula for the distribution volume of iohexol. Scand J Clin Lab Invest 51:335–342
12. Schwartz GJ, Gauthier B (1985) A simple estimate of glomerular filtration rate in adolescent boys. J Pediatr 106:522–526
13. Weiss R, Dziura J, Burgert TS, Tamborlane WV, Taksali SE, Yeckel CW, Allen K, Lopes M, Savoye M, Morrison J, Sherwin RS, Caprio S (2004) Obesity and the metabolic syndrome in children and adolescents. N Engl J Med 350:2362–2374
14. Lee JM, Okumura MJ, Davis MM, Herman WH, Gurney JG (2006) Prevalence and determinants of insulin resistance among US adolescents: a population-based study. Diabetes Care 29:2427–2432
15. Kalantar-Zadeh K, Block G, Humphreys MH, Kopple JD (2003) Reverse epidemiology of cardiovascular risk factors in maintenance dialysis patients. Kidney Int 63:793–808
16. Santoro A, Mancini E (2002) Cardiac effects of chronic inflammation in dialysis patients. Nephrol Dial Transplant 17 [Suppl 8]:10–15
17. Churchill DN, Taylor W, Keshaviah PR (1996) Adequacy of dialysis and nutrition in continuous peritoneal dialysis: association with clinical outcomes. CANUSA Peritoneal Dialysis Study Group. J Am Soc Nephrol 7:198–207
18. Kaysen GA (2006) Association between inflammation and malnutrition as risk factors of cardiovascular disease. Blood Purif 25:51–55
19. Kaysen GA (2001) The microinflammatory state in uremia: causes and potential consequences. J Am Soc Nephrol 12:1549–1557
20. Steinvenkel P, Ketteler M, Johnson RJ (2005) IL-10, IL-6, and TNF-α: central factors in the altered cytokine network of uremia—the good, the bad, the ugly. Kidney Int 67:1216–1223
21. Oberg BP, McMenamin E, Lucas FL, McMonagle E, Morrow J, Ikizler TA, Himmelfarb J (2004) Increased prevalence of oxidant stress and inflammation in patients with moderate to severe chronic kidney disease. Kidney Int 65:1009–1016
22. Pereira BJ, Shapiro L, King AJ, Falagas ME, Strom JA, Dinarello CA (1994) Plasma levels of IL-1β, TNF-α and their specific inhibitors in undialyzed chronic renal failure, CAPD and hemodialysis patients. Kidney Int 45:890–896
23. Witko-Sarsat V, Friedlander M, Nguyen Khoa T, Capeillere-Blandin C, Nguyen AT, Canteloup S, Dayer JM, Jungers P, Drueke T, Descamps-Latscha B (1998) Advanced oxidation protein products as novel mediators of inflammation and monocyte activation in chronic renal failure. J Immunol 161:2524–2532
24. Ceballos-Picot I, Witko-Sarsat V, Berad-Boudia M, Nguyen AT, Thévenin M, Jaudon MC, Zingraff J, Verger C, Jungers P, Descamps-Latscha B (1996) Glutathione antioxidant system as a marker of oxidative stress in chronic renal failure. Free Rad Biol Med 21:845–853
25. Guarnieri G, Antonione R, Biolo G (2003) Mechanisms of malnutrition in uremia. J Ren Nutr 13:153–157
26. Reid MB, Li YP (2001) Tumor necrosis factor-α and muscle wasting: a cellular perspective. Respir Res 2:269–272
27. Guttridge DC, Mayo MW, Madrid LV, Wang CY, Baldwin AS Jr (2000) NF-kappaB-induced loss of MyoD messenger RNA: possible role in muscle decay and cachexia. Science 289:2363–2366
28. Li YP, Reid MB (2000) NF-κB mediates the protein loss induced by TNF-α in differentiated skeletal muscle myotubes. Am J Physiol Regul Integr Comp Physiol 279:R1165–R1170
29. Li Y, Schwartz RJ, Waddell ID, Holloway BR, Reid MB (1998) Skeletal muscle myocytes undergo protein loss and reactive oxygen-mediated KF-κB activation in response to tumor necrosis factor α. FASEB J 12:871–880
30. Sen CK, Khanna S, Reznick AZ, Roy S, Packer L (1997) Glutathione regulation of tumor necrosis factor α-induced NF-κB activation in skeletal muscle-derived L6 cells. Biochem Biophys Res Com 237:645–649
31. Buck M, Chojkier M (1996) Muscle wasting and dedifferentiation induced by oxidative stress in a murine model of cachexia is prevented by inhibitors of nitric oxide synthesis and antioxidants. EMBO J 15:1753–1765
32. Brenner DA, Buck M, Feitelberg SP, Chojkier M (1990) Tumor necrosis factor-α inhibits albumin gene expression in a murine model of cachexia. J Clin Invest 85:248–255
33. Hotamisligil GS, Budavari A, Murray D, Spiegelman BM (1994) Reduced tyrosine kinase activity of insulin receptor in obesity-diabetes: central role of tumor necrosis factor-α. J Clin Invest 94:1543–1549
34. Cheung AT, Ree D, Kolls JK, Feselier J, Coy DH, Breyer-Ash M (1998) An in vivo model for elucidation of the mechanism of tumor necrosis facto- α (TNF-α) induced insulin resistance: evidence for differential regulation of insulin signalling by TNF-α. Endocrinology 139:4928–4935
35. Breder CD, Hazuka C, Ghayur T, Klug C, Huginin M, Yasuda K, Teng M, Saper CB (1994) Regional induction of tumor necrosis factor α expression in the mouse brain after systemic lipopolysaccharide administration. Proc Natl Acad Sci USA 91:11393–11397