Adipokines in children with chronic renal failure

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Chronic Renal Failure (CRF) has negative impact on nutrition, growth, puberty, glycometabolic homeostasis, adipokines secretion. Adipokines play a role on these patients' short term complications and they influence their long term outcome. Many studies highlighted the influence of adipokines on cardiovascular complications, glycometabolic assess, nutrition of adults and children with CRF. High serum resistin and adiponectin levels can have a possible role in the development of protein-energy wasting among CRF patients. Elevated serum leptin levels were thought to contribute to the anorexia and poor nutrition in children on haemodialysis for CRF. Several studies have demonstrated leptin influence on growth and puberty, resistin role on glycaemic profile and insulin resistance, the meaning of adiponectin as an anti-inflammatory and antiatherogenic factor.

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Introduction

CRF is a possible fearful evolution of severe paediatric congenital and/or acquired kidney diseases. In the most severe cases it could impose dialysis with further complications on the patients’ clinical outcome [1].

The CRF compromises the long term prognosis of growth [2,3], puberty, glycometabolic and lipid homeostasis, nutritional assess [4,5], endocrine profile in children and adolescents. Growth and pubertal delay, and/or short stature are present in more than 50% of CRF children and many of these patients have a stature <-2 SDS [4].

The endocrine patterns of hypothalamic-hypophyseal axis, adrenals, gonads and thyroid, if not promptly diagnosed and treated, could be negatively involved with severe sequelae.

Adipokines start several cell signalling pathways of many tissues and organs, with possible secondary effects as pubertal delay, growth retardation and infertility.

Adipose tissue is a candidate of secretive disarray in patients with CRF, with possible interference on the adipokines secretion also mediated by inflammation mediators as Interleukin 6 (IL-6), Interleukin 1 (IL-1), Tumor Necrosis Factor α (TNFα) [6].

Inflammation and adipokines

Adipocytes secrete several peptides with endocrine and immunologic properties as leptin, adiponectin, resistin, visfatin, apelin, and also TNFα, IL-1 and IL-6. These molecules can work together with a network of cooperation between immunologic and endocrine systems.

An inflammatory state induces secretion of several peptides, as adipokines and cytokines, by adipocytes: macrophages are the bridge between inflammation and adipocytes activity. In fact the two specific lines of cells show common genes expression of both adipokines and cytokines synthesis [7,8].
Adiponectin may play a significant role as an anti-inflammatory and anti-atherosclerotic molecule. A reduction of adiponectin levels has been registered in patients with an increased risk for cardiovascular disease.

The role of adipokines on growth and puberty

Several studies have demonstrated leptin influence on growth and puberty [9], resistin role on glycometabolic assess and insulin resistance [10] and the importance of adiponectin role as an anti-inflammatory and antiatherogenic factor [11].

However, it has to be emphasized that in literature only a few studies evaluated adipokines role in CRF children and adolescents [12-17].

Leptin showed a significant direct correlation with BMI, bone age and pubertal stage [16].

Neurons expressing kisspeptins, the products of the Kiss1 gene recently emerged as essential regulators of GnRH secreting neurons, have a role as key sensors of the metabolic state and guide of the reproductive effects of leptin. However leptin shows extra-hypothalamic and peripheral actions (as direct gonadal control), influences from and on adipose tissue, which may contribute to puberty and reproduction metabolic management in conditions in which body weight is not adequate [18].

Malnutrition is a severe consequence of paediatric CRF with low caloric and protein intake. It depends on several factors as: anorexia, ageusia linked to Zn deficiency, catabolic state and muscular protein catabolism, endocrine anomalies, dialysis with possible growth failure and pubertal delay [5].

Adipokines and nutrition in CRF

Patients with CRF are at high risk for decreased spontaneous nutrient intake and patients with end-stage renal disease (ESRD) have malnutrition as a heavy problem. Leptin can interact with the appetite and satiety centres of the brain as an afferent satiety signal. Anorexia and poor nutrition in CRF were thought to be in part linked to elevated serum leptin levels. However non homogeneous results are found in studies on the relationship between nutritional status and leptin concentration in CRF. Furthermore plasma levels of Insulin-like Growth Factor 1 (IGF-1) are considered a marker of nutritional status in CRF patients. The relationship between leptin and IGF-1 is still debated. A study on 17 ESRD paediatric and adolescent patients (8 male, 9 female; age: 8-18 years), treated by standard haemodialysis showed that the BMI was reduced in 13 (76%) of the patients. Triceps skinfold thickness (TST) was lower of the 5th Centile in 7 (41%), whereas mid arm circumference was reduced in 14 (82.5%) and mid arm muscle circumference was reduced in 13 (76.5%), respectively. Leptin was significantly higher in patients than in healthy children, while IGF-1 was lower in CRF patients than in healthy children. IGF-1 was lower in children with severe malnutrition, defined according to TST, than in patients without malnutrition and in healthy children. The plasma insulin concentration was not correlated with leptin and IGF-1 levels. This study verifies that high circulating plasma leptin concentrations may be one of the several causes of malnutrition pathogenesis in children on haemodialysis [19].

In a study on 134 children in different stages of CRF, the main determinant of serum leptin levels remains the percentage of body fat. However leptin levels increase with GFR decline, presumably by the reduction of renal clearance. Leptin was inversely correlated with spontaneous food intake, evaluated by written dietary diaries, and directly correlated with to the percentage of body fat. Therefore leptin in CRF might generate a deregulation of the physiological peripheral-central leptin feedback, playing a part in the reduced food intake in uraemia [20].

Furthermore adiponectin and resistin in pre-dialysis, peritoneal dialysis and haemodialysis patients were significantly increased than in controls. A positive correlation statistically significant between the presence of protein-energy wasting and adiponectin and resistin levels were demonstrated in adults with CRF. A statistically significant correlation was not present between protein-energy wasting and leptin, neuropeptide Y, ghrelin, acylated-ghrelin levels. CRF patients, except transplanted patients, had higher resistin and adiponectin levels than healthy subjects. Protein-energy wasting was directly correlated with adiponectin and resistin, sustaining the possible role of high serum adiponectin and resistin levels in the development of protein-energy wasting among dialysis patients [21].

Additionally obesity and overweight are linked to a higher risk of developing chronic kidney disease. The disarray of adiponectin, leptin, resistin and visfatin secretion, in fact, can enhance events typically present in chronic kidney disease, between these can reduce the glomerular filtration rate, can increase albuminuria and glomerular permeability, can fuse podocytes, can enhance mesangial cells hypertrophy [22]. This cascade increases the evolution of CRF and further adipokines secretion worsens.

A study on adult patients showed higher plasma leptin and resistin concentrations in patients with CRF respect to healthy controls, while adiponectin are not different between...
CRF patients and controls. Leptin, adiponectin and resistin are significantly directly associated with the severity of CRF evaluated by eGFR and urinary albumin. Leptin, adiponectin, resistin are associated either with the risk as with the severity of CRF and not linked to BMI and CVD [23].

**Adipokines and glycometabolic profile**

In a study on 192 non-diabetic haemodialysis adult patients, leptin and adiponectin were related to insulin sensitivity in end-stage CRF. In these patients leptin and adiponectin contributed to determine insulin resistance. Insulin resistance showed a 6 times higher risk in end-stage CRF patients who associated high leptin and low adiponectin levels, than in patients with low leptin and high adiponectin levels. Incident cardiovascular events were predicted by low adiponectin but not by high leptin levels. Leptin and adiponectin showed an opposite correlation with insulin sensitivity and inflammation in CRF patients [24].

Homeostasis Model assessment of Insulin Resistance (HOMA-IR) was higher than 2.5 in a significant percentage (47.1%) of a cohort of paediatric patients with CRF, on peritoneal dialysis treatment and on haemodialysis. Leptin and resistin levels of patients with CRF and on peritoneal dialysis and haemodialysis treatment were significantly higher than in healthy subjects. However, this aspect was found not to be associated with hyperinsulinism [25].

In another study on paediatric patients with CRF, HOMA-IR, fasting and 2-hour serum insulin levels were higher than in controls. Adiponectin and resistin were inversely correlated with GFR [26].

Insulin resistance and hyperinsulinemia are risk factors of cardiovascular disease, also mediated by inflammation and malnutrition. High glycaemia, insulinemia and HOMA-IR relieved in children with mild-moderate CRF are expression of insulin resistance. The early occurrence in young patients, also in moderate involvement of GFR, is a significant cardiovascular risk factor with a significant prognostic impact [16].

Adiponectin levels in CRF are two to three times higher than in subjects with preserved kidney function. Adiponectin has anti-inflammatory, anti-diabetic and anti-atherogenic properties, however patients with CKD show chronic systemic inflammation signs, insulin resistance, accelerated atherogenesis [27]. Recently it was demonstrated that CRF results in an up regulation of AdipoR1 in vivo and in vitro, but in these patients postreceptorial adiponectin resistance was also demonstrated. These observations can explain why patients with CRF maintain risk factors and progression of the secondary effects of uremia [27].

**Adiponectin, leptin and cardiovascular risk**

Low adiponectin levels are demonstrated to be a cardiovascular risk factor in adults with CRF. Adiponectin levels and the association with other cardiovascular risk factors were studied in children with preterminal CRF. Serum adipokines, lipoproteins, flogistic markers and insulin levels were assayed in 44 paediatric patients (age: 6 - 21 years) with CRF stages 2 - 4. The 83% of these patients showed elevated adiponectin levels, and between these 29 were lean, with a BMI <85th percentile, and 15 were non-lean with a BMI > or = 85th percentile. Children of the two groups had comparable kidney function, however adiponectin levels were significantly higher in patients with BMI <85th percentile in than non-lean patients. Adiponectin levels showed statistically significant negative correlation with age, GFR, leptin, insulin, BMI, and a positive correlation with ApoA2. The authors concluded that adiponectin levels are increased in children and adolescents with CRF and that a reduction of kidney function has a fundamental influence on increased adiponectin levels. Furthermore patients with overweight presented reduced adiponectin levels and could have a higher risk for cardiovascular complications [28].

Children with CRF are at high risk for endothelial dysfunction, secondary to non-traditional risk factors as oxidative stress and inflammation [11]. Adiponectin is a possible protective factor of vascular injury, in fact in vitro it modulates endothelial inflammatory response [29] and it down regulates endothelial nuclear factor kappa B (NF-kB) signalling [30].

CRF is characterized by a high incidence of enhanced cardiovascular disease risk [31-33]; however it is shows paradoxical increased adiponectin levels. Patients in end-stage CRF, with higher adiponectin levels, showed a lower cardiovascular risk [24; 34-35]. It is suggested that in patients with advanced CRF adiponectin-dependent cardiovascular and metabolic protection is guaranteed, however its efficacy could be reduced by further CRF-linked risk factors as higher BMI values. Furthermore high adiponectin levels in CRF could be partially linked to reduced glomerular filtration rate [36].

Another study reports that patients with CRF show a higher prevalence of inflammation and cardiovascular disease. Adiponectin demonstrates significant anti-inflammatory and anti-atherosclerotic properties. In patients with high risk for cardiovascular disease a reduction
of adiponectin was previously described. The authors demonstrated a significant association of the +276G>T SNP in the adiponectin gene and paediatric CRF. Genetic polymorphisms of +276 gene could show a favourable role on plasma adiponectin in CRF [15].

Leptin was significantly higher in haemodialysis children than in healthy children when the influence of sex and BMI were analyzed separately, however peritoneal dialysis children and the control group had equivalent leptin concentrations. Furthermore PAI-1 was significantly higher in haemodialysis patients than in control subjects, while PAI-1 levels were not significantly different in peritoneal dialysis patients and in control group. A significant correlation was found between PAI-1 and leptin levels; these parameters were independent from the influence of BMI in haemodialysis and peritoneal dialysis groups.

Haemodialysis patients showed higher leptin and PAI-1 concentrations and a significant correlation between PAI-1 and leptin levels were relieved in the two groups of patients, in haemodialysis and in peritoneal dialysis. Further studies are useful to clarify the effects of increased serum PAI-1 and leptin levels on the risk of future cardiovascular diseases [37]. In a study on 82 CRF patients on haemodialysis, peritoneal dialysis and on conservative management authors demonstrated a significant link between resistin and heart complications. Leptin concentrations were higher in patients treated by peritoneal dialysis, while resistin levels were higher in peritoneal dialysis and in haemodialysis patients than in patients on conservative management. Furthermore adiponectin levels were comparable in the 3 groups. There was a link between resistin levels and the incidence of heart diseases [38].

Conclusions

Resistin levels are correlated with both adequate nutritional assess and controlled inflammatory state. Adiponectin could protect against chronic inflammation, atherosclerosis, cardiovascular diseases.

The high prevalence of cardiovascular disease and inflammatory markers in patients with CRF is described, and children with CRF may develop precocious cardiovascular complications in the course of their life. Adiponectin may play as an anti-inflammatory and anti-atherosclerotic cytokine, and its secretion has a correlation with BMI. Low serum adiponectin was found in patients who presented a high risk for cardiovascular disease.

Leptin has a crucial role in nutrition, growth and puberty in CRF children and adolescents. Its influence can be expressed on central and peripheral tissues.

Obesity prevention and the guarantee of a correct nutritional state are primary goals for physicians following children with CRF. Adipokines could be useful markers in the follow-up.

References


