

Malnutrition in Patients with End-Stage Renal Disease - Anorexia, Cachexia and Catabolism

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Abstract: Patients with end-stage renal disease (ESRD) commonly present both anorexia (defined as reduced appetite) and a catabolic state leading to loss of protein from skeletal muscle and other tissues. Additionally, these patients carry an inflammatory burden, which may play a pivotal role in the evolution of not only the observed cachexia, but also in the massive increase in relative risk of cardiovascular disease (CVD) in this population. Evidence suggests that a facilitative interaction between pro-inflammatory cytokines and other factors, including central nervous system regulation of appetite, co-morbidities, acidosis, anaemia and hormonal derangements combine to produce both anorexia and cachexia in this patient group. So far, interventional therapies have failed to significantly alleviate the cachexic state in ESRD, presumably because of the need to attack other causative factors. Therefore, new treatment strategies such as multiple appetite stimulants, various “anti-inflammatory diets” and new potentially useful anti-inflammatory pharmacological agents should be tested alone or in combination to evaluate if these new therapeutic modalities could improve the poor outcome of ESRD patients. As the etiology of cachexia in ESRD is multifactorial, we propose that its treatment should comprise a number of concomitant therapies to provide an integrated strategy aiming to reverse this devastating complication.

INTRODUCTION

Protein-energy malnutrition is a common feature in end-stage renal disease (ESRD) patients [1], which becomes even more common after patients start on either peritoneal dialysis (PD) [2] or haemodialysis (HD) [3]. Although it is well established that malnutrition is one important predictor of survival in ESRD patients [2, 3], less is known about malnutrition and its impact on clinical outcomes in patients with a modest degree of chronic kidney disease. As noted by Mitch [4] the use of the word malnutrition has previously often been used incorrectly in the renal literature. Literally, the word “malnutrition”, derived from Latin *malus*, means “not correctly nourished” and includes any disorder of nutrition (i.e. both under- and overnutrition). In the following text, we will therefore refer to cachexia, defined as a state of undernutrition deriving from both anorexia, i.e. insufficient food intake, and low serum protein levels and the loss of muscle mass as the result of a catabolic state. All of these factors occur in the ESRD patient, usually as the consequence of a number of interrelated mechanisms stimulated by renal insufficiency. Indeed, the aetiology of the cachexia in ESRD is very complex and may include numerous factors including loss of appetite, delayed gastric emptying, impaired protein assimilation, hormonal derangements, inadequate control of acidosis, co-morbidity, inflammation, depression and other psychosocial factors [4]. Therefore, it is not likely that wasting in ESRD can be adequately treated by only one single therapy; instead we propose the concept of an integrated therapy of wasting consisting of both dietary and pharmacological components.

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PREVALENCE OF CACHEXIA IN THE ESRD POPULATION

Assessment and monitoring of nutritional status are essential to prevent, diagnose and treat uremic cachexia, anorexia and catabolism [5]. Common signs of cachexia in ESRD patients (Table 1) include reduced muscle mass as assessed by anthropometric methods as well as low serum concentrations of albumin, transferrin, prealbumin and other

Table 1. Markers of Malnutrition and Cachexia in ESRD Patients

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| <ul style="list-style-type: none"> ▪ Body weight (% relative body weight, % preuremic body weight) ▪ Body mass index ▪ Visceral proteins (serum protein, albumin, prealbumin, transferrin and IGF-1) ▪ Subjective global assessment of nutritional status ▪ Handgrip strength ▪ Anthropometrics (skinfold thickness and midarm muscle circumference) ▪ Lean body mass (estimated by DEXA, bioimpedance or creatinine kinetics) ▪ Body fat mass (estimated by DEXA or CT) ▪ Total body nitrogen and total body potassium ▪ Essential (low in ESRD) and non-essential (high in ESRD) plasma amino acids ▪ Protein intake estimated by nPNA^a |
|---|

^anPNA, protein equivalent of nitrogen appearance in urine and dialysate, normalized to actual or desirable body weight.

liver-derived proteins. Subjective global assessment of nutritional status (SGA) [6], a clinical scoring system taking into account both subjective and objective factors, is the most commonly used methods to identify cachexia in scientific studies.

Several reports have shown a high prevalence (about 20-60%) of cachexia in ESRD patients, both before and after initiation of dialysis therapy [2, 7, 8]. Whereas, the prevalence and severity of both anorexia and catabolism is clearly related to residual renal function [9], the choice of dialysis modality does not seem to play a major role. A few studies [10, 11] have compared the prevalence of malnutrition in PD and HD patients, and in most of these studies, no major differences were found. A common finding is that there is a larger gain in body fat in PD compared with HD patients [8], most likely due to the impact of glucose absorption from the dialysate, and the absence of the intermittent catabolic stimulus associated with the HD procedure. In addition, part of the reported weight gain may be due to increased body water associated with poor control of fluid balance.

THE IMPACT OF DIALYSIS THERAPY

Before initiation of dialysis therapy, ESRD patients usually spontaneously decrease their protein intake as a consequence of declining renal function and uremic symptoms [12], or because they are prescribed low protein diets to avoid these symptoms. Also, some of the many drugs used by ESRD patients may worsen anorexia. In addition, underlying or intercurrent diseases, such as diabetes mellitus (DM), cardiovascular disease (CVD), infections, various complications of dialysis therapy as well as medications, in particular corticosteroid therapy, and not least a state of chronic systemic inflammation, may all contribute to anorexia in this patient group [13].

Once dialysis therapy begins, uremic symptoms are usually alleviated, and the diet restrictions relaxed. This leads to an improved appetite in most patients [8], while it is less common to see a reversal of the objective signs of cachexia. Indeed, additional metabolic and nutritional problems may be induced by the dialysis procedure, including losses of proteins, amino acids, water-soluble vitamins and other essential small molecular solutes into the dialysate, as well as catabolism and suppression of appetite mediated by systemic inflammation due to bioincompatibility of the therapy or, in PD, from dialysate glucose absorption and abdominal discomfort induced by the treatment.

As the dialysis dose was increased during the 1980s and 1990s, additional changes in Kt/V resulted in only marginal, or not even significant, reductions in patient mortality, as recently shown in the HEMO [14] and ADEMEX [15] studies. Thus, factors other than dialysis dose, such as cardiovascular complications, inflammation and catabolism appear to be more important determinants of patient cachexia and survival in ESRD. In fact, most premature deaths in ESRD patients are now thought to be associated with the presence of a Malnutrition/wasting, Inflammation and Atherosclerosis (MIA) syndrome. This is an important consequence of the uremic syndrome as well as both a cause and a consequence of the coexisting co-morbidities such as

diabetes mellitus and left ventricle hypertrophy of the heart [13, 16].

CACHEXIA, INFLAMMATION AND CARDIOVASCULAR DISEASE

Low-grade chronic and systemic inflammation, with increased circulating levels of C-reactive protein (CRP) and pro-inflammatory cytokines, such as tumour necrosis factor (TNF)- and interleukin (IL)-6, has been proposed to be one of the most important contributors to cachexia in ESRD patients [17]. Moreover, since the idea that inflammation plays a key role in the atherogenic process has received much attention in non-renal patients [18], it has been speculated that inflammation also contributes to increased CVD and thus links these two important causes of morbidity in dialysis patients [19].

Although cachexia, since the 1980s, and systemic inflammation, since the 1990s, have both been reported to be strong predictors of mortality in dialysis patients, they usually do not appear as documented direct causes of mortality. Instead, CVD is by far the most common documented cause of mortality in the dialysis population, while malnutrition is a reported direct cause of less than 5% of deaths [20]. The causes of CVD in ESRD patients are multifactorial including both traditional Framingham risk factors, such as age, smoking, DM and hypertension, as well as emerging non-traditional risk factors, such as inflammation, oxidative stress and vascular calcification. Over the last several years, the role of inflammation in the pathogenesis of atherosclerosis has received much attention [18], and it is possible that inflammation may contribute to increased cardiovascular morbidity and mortality also in dialysis patients. In ESRD, although total protein metabolism is not changed, a shift is observed towards synthesis of acute phase and immunocompetent proteins, at the expense of muscle anabolism [21]. Indeed, pro-inflammatory cytokine levels have recently been shown to predict cachexia and mortality in ESRD patients with or without ongoing dialysis treatment [19, 22]. Moreover, both cachexia and inflammation are strongly associated with CVD, resulting in higher mortality rates in malnourished patients [16]. Indeed, cachexia (evaluated by SGA) is more common in patients with clinical CVD [17] and Beddhu *et al.* [23] have demonstrated a significantly greater prevalence of coronary artery disease in dialysis patients with low S-albumin. However, in another study by Beddhu *et al.* [24], he found no association between malnutrition (defined BMI <18.5 kg/m² and by a low urinary creatinine excretion) and acute coronary syndromes in a large group of dialysis patients. Although BMI may not be a precise marker of nutritional status it is clear that further studies are needed to resolve the putative associations between atherosclerotic cardiovascular disease and anorexia and protein-energy undernutrition on the one hand and inflammatory-associated muscle catabolism on the other.

INFLAMMATION AS A CAUSE OF ANOREXIA, CATABOLISM AND CACHEXIA

In patients who have signs of systemic inflammation, symptoms such as anorexia, loss of body weight, malaise, fatigue and depression are commonly observed. As weight

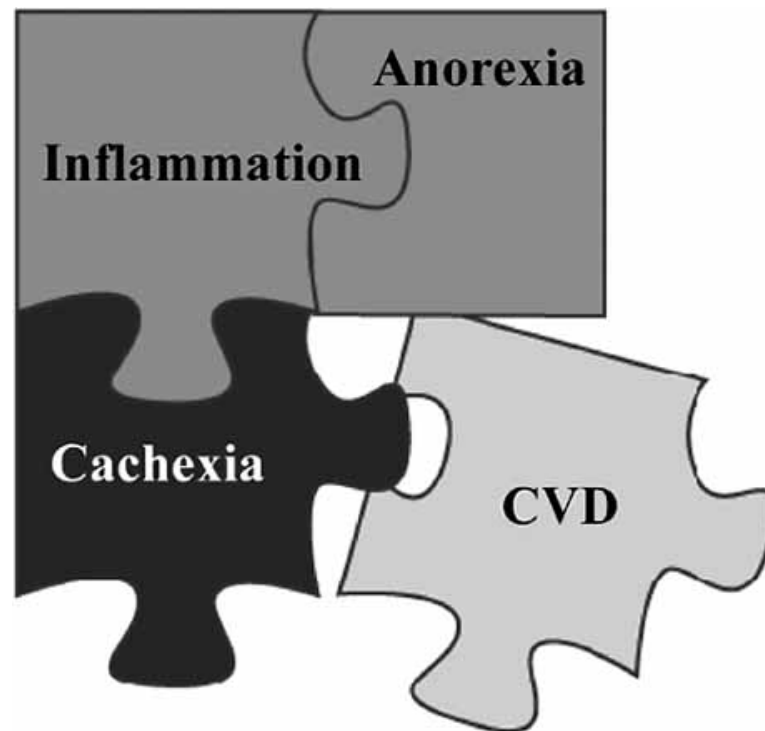


Fig. (1). Cachexia in end-stage renal disease consists of both anorexia, leading to inadequate energy and nutrient intake, and a catabolic state leading to protein depletion. The aetiology is multifactorial and strongly linked to systemic inflammation and cardiovascular mortality.

loss is such a common feature of many inflammatory disorders, it has been suggested that subclinical inflammation is a principal component of the pathophysiology of cachexia by causing both anorexia through central mechanisms [25, 26] as well as increased muscle catabolism [27]. It is therefore not surprising that pro-inflammatory cytokines have been shown to have significant effects on wasting and sickness behaviours in dialysis patients [26, 28] and may play a central role in the development and maintenance of the MIA syndrome [29, 30].

TNF- has been recognized as the prototype of an anorectic cytokine [28]. Important mechanisms by which elevated levels of TNF- may mediate catabolism include increased protein hydrolysis coupled with local insulin resistance [31]. TNF- has also been shown to activate the transcription factor NF- B to suppress MyoD mRNA and disrupt skeletal muscle differentiation and repair of damaged muscle tissue [32]. A decrease in muscle mass may also be caused by activation of the ubiquitin-proteasome proteolytic system, which accelerates degradation of muscle protein [33]. Since TNF- increases ubiquitin gene expression in skeletal muscle [34], it is possible that this cytokine causes muscle wasting by stimulating protein catabolism via the ubiquitin proteasome pathway [35]. It has also been reported that TNF- increases the rate of DNA fragmentation in cancer cachexia promoting apoptosis [36]. Indeed, cachexia is usually associated with elevated concentrations of TNF- in older patients without renal disease [37]. In dialysis patients, elevated TNF- levels has been reported to be associated with anorexia [25]. Furthermore, Grunfeld *et al.* [38] found that administration of TNF- resulted in an increase in leptin mRNA levels in hamsters and noted a

strong inverse correlation between leptin mRNA level and subsequent food intake.

IL-6 is another pro-inflammatory cytokine proposed to play an important role in the muscle catabolism which occurs with normal aging [39]. It has been suggested that the process of age-related muscle loss (sarcopenia) is related to loss of sex hormones (particularly testosterone) that act to suppress IL-6 expression [40]. Indeed, IL-6 has been shown to stimulate the breakdown of muscle protein [41] and promote cancer-related wasting [42] while the administration of IL-6 receptor antibody has been shown to inhibit muscle atrophy that occurs in IL-6 transgenic mice [43]. Since IL-6 also inhibits the secretion of insulin-like growth factor (IGF-1), reduced IGF-1 signaling may be yet another reason for IL-6-associated muscle atrophy [44]. The close association between IL-6 and muscle wasting (evaluated by thigh muscle area) in HD patients [45] provides compelling evidence that this cytokine may be catabolic also in this patient group. Finally, since intra-cerebroventricular injection of IL-6 increases energy expenditure and decreases body fat in rodents, IL-6 may play an important role in appetite and body weight control mediated by the central nervous system [46].

Recently, the role of elevated circulating levels of cytokines such as leptin on signaling through the central melanocortin system has been proven to be of importance in causing anorexia in ESRD [26]. Also, impaired protein assimilation may contribute to cachexia in renal disease. Indeed, a recent study [47] indicated both that protein uptake from the gut is increased in ESRD, and that the severity of this decrease is associated with the severity of MIA present.

Among the large number of other cytokines that may have nutritional impact, IL-15 has recently attracted much interest as it exerts important effects in skeletal muscle where it behaves as an anabolic cytokine both *in vitro* [48] and *in vivo* [49] and favours muscle fibre hypertrophy. This cytokine exerts its effects in muscle cells by both decreasing the rate of protein degradation and increasing the rate of proliferation. This distinct mode of IL-15 action suggests that it may be of potential usefulness in the treatment of wasting disorders, and early trials in rodents [50, 51] have been encouraging, attenuating muscle protein breakdown and increasing muscle mass. Therefore, studies on the effects of IL-15 administration are warranted in experimental renal failure models.

TREATING CACHEXIA IN ESRD

The strong association between inflammation and nutritional status is of importance when considering strategies to treat or prevent cachexia in dialysis patients. Indeed, if the cause of malnutrition was only anorexia, ie. inadequate nutritional intake was the predominant cause, one would expect that nutritional supplementation alone would be effective in restoring nutritional deficits. However, as oral nutritional supplements or intradialytic supplementation have proved either only partial effective [52], or totally ineffectual [53], in the repair of nutritional status in the majority of ESRD patients, dialysis patients are not likely to be able to feed themselves out of a malnourished state. Instead, new therapies designed to help these patients must also be used to address the catabolic state.

Inflammation appears not only to decrease muscle protein synthesis, but may also raise resting energy expenditure and protein catabolic rate - changes that will promote a negative protein and energy balance – as well as decrease protein assimilation from the gut. Thus, it is unlikely that we can reverse the catabolic process unless we also treat inflammation and its' associated co-morbidities. Indeed, we believe that inflammation-driven hypercatabolism and failure to deposit nutrients may be the main reason for a poor nutritional status in uremic patients. It is thus interesting that most studies done on nutritional supplementation in ESRD patients used a low S-albumin to identify patients considered malnourished. As S-albumin is much more a marker of inflammation than of nutrition, it is not surprising that the results often could not demonstrate any beneficial effects on nutritional status. Clearly, in the clinical setting anorexia, catabolism, cachexia and inflammation occur together and are difficult to isolate.

THE ROLE OF APPETITE STIMULANTS IN ESRD

Anorexia is a common phenomenon in ESRD patients that is associated with higher levels of pro-inflammatory cytokines, greater hospitalization rates and poor clinical outcomes [54]. Thus, a simple inquiry about appetite may yield important information about the future risk of poor outcome in the ESRD patient. There are several different mechanisms contributing to anorexia in dialysis patients, including inadequate dialysis, delayed gastric emptying, elevated levels of anorectic substances, like leptin and pro-inflammatory cytokines, as well as effects of the haemodialysis procedure and the intraperitoneal infusion of dialysis

fluid in PD patients [55]. Although some of these causes of anorexia can be treated through measures such as an increased dialysis dose in underdialysed patients and decreased intraperitoneal volume in PD patients with local symptoms, it is evident that these measures not always are effective. Therefore, the use of appetite stimulants is a tempting part of an *integrated therapy* against malnutrition in dialysis patients. Examples of pharmacological agents that may stimulate appetite are given in Table 2. Unfortunately, most appetite stimulatory drugs available are relatively ineffective and they have not been systematically tested in dialysis patients.

Table 2. Lifestyle and Diets that May have Anti-Inflammatory Effects

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|--|
| • Soy (phytoestrogen) |
| • Fiber-rich food |
| • Fish (eicosapentaenoic acid) |
| • Nuts and seeds (-tocopherol) |
| • Moderate alcohol consumption (ethanol and flavonoids) |
| • Diets rich in anti-oxidants (living food, antocyanins) |
| • Probiotics (living microorganisms) |
| • Diets low in advanced glycation end-products |
| • Weight reduction |
| • Exercise training |

Ghrelin is an appetite-stimulating gut hormone that in at least one randomized, placebo-controlled trial [56] has been shown to be able to attenuate short-term food intake in dialysis patients with mild to moderate malnutrition.

Megesterol acetate, a steroid like progestagen used for treatment of breast cancer, showed increased appetite and weight gain as an unexpected side effect [57]. Subsequently, the orexigenic and weight gaining effects of megesterol acetate have been attributed to its anti-cytokine effects via reduced levels of IL-6 and TNA- [58]. Megesterol acetate is the most extensively studied appetite stimulant and is widely used in cancer and AIDS-patients [59] but currently not in ESRD. However, serious side effects mean that the treatment may be risky and must be monitored closely [60].

Cannabinoids, such as dronabinol (-9 tetrahydrocannabinol), have been reported to increase appetite and weight gain. In HIV and Alzheimer disease patients, dronabinol may reduce cachexia and induce weight gain [61]. The possible mechanisms of action include interactions with endorphin receptors, inhibition of prostaglandin synthesis and IL-1 secretion [59]. Although the drug is eliminated primarily through the biliary system, the therapeutic window is narrow and several CNS side effects have been reported, including somnolence, dizziness, paranoid reactions and other mental effects [62]. A comparison of dronabinol against megesterol acetate in a group of patients with advanced cancer found

that megestrol acetate had a significantly better effect on appetite and weight gain [63]. To the best of our knowledge, no studies have been performed to study the putative appetite stimulating effects of cannabinoids in ESRD patients.

Several studies have demonstrated that corticosteroids increase appetite and well being in cancer patients although a long lasting weight gain is often not observed [64]. Since the effect is short lasting and the side effects (including the stimulation of muscle proteolysis through the ubiquitin-proteasome pathway) may be serious, however, corticosteroids have no primary role in the treatment of malnutrition in dialysis patients. Cyproheptadine, an antihistamine with serotonin antagonist properties has mainly been used for the treatment of cancer-induced weight loss, and in anorexia nervosa, but the effects have been questionable [62]. Other possible anti-anorectic drugs, such as thalidomide (because of its effect on TNF- α) and melatonin (because of its effect on muscle metabolism), are presently reaching the clinical trial stage [65].

NUTRITIONAL SUPPLEMENTS WITH PHARMACOLOGICAL EFFECTS

Based on epidemiological studies in both renal and non-renal populations, it is obvious that important differences regarding the prevalence and outcome of wasting, inflammation and atherosclerosis exist in different parts of the world [66]. In this respect it is of interest that although CVD is the leading cause of death in dialysis patients in Asian countries, the prevalence of inflammation [67, 68] and vascular disease [69] are substantially lower in Asian countries than in Western countries. The observation that Asian patients who receive dialysis in the United States have a markedly lower adjusted relative death risk than Caucasians [69] implies that factors unrelated to dialysis treatment characteristics, such as dietary and/or cultural habits, may contribute to the observed differences (Table 1). Thus, recent interest has focused on the putative anti-inflammatory effects of various dietary components of the diet consumed in many parts of Asia.

In general, the population in Southeast Asia, China and Japan consumes a substantial amount of fish and soy, resulting in a lower fat content and a higher fibre diet than the typical Western diet. Soybeans are a unique source of the phytoestrogens (natural compounds that mimic some of the effects of estrogen *in vivo*) and in the Japanese population the phytoestrogen concentration is markedly higher than in other populations [70]. Phytoestrogens modulate the intranuclear estrogen receptor system, and thus have numerous biological functions, such as modulation of cell growth-proliferation, inflammation and oxidative stress. The phytoestrogen genistein is effective in blocking inflammatory gene expression [71], but no randomized, controlled studies have been performed in humans to evaluate either an anti-inflammatory effect or a hypothetical effect on cachexia. Based on these findings, prospective studies on the impact of a high-soy diet on both the prevalence of MIA and outcome in ESRD patients are warranted [72].

Other components of the East-Asian diet that may contribute to a lower risk of inflammation and CVD include higher dietary fibre content as well as increased fish

consumption. The importance of dietary fibres is underscored by a recent evaluation of 4,900 participants of the 1999-2000 NHANES demonstrating that subjects in the 3rd and 4th highest quartiles of fibre consumption had a lower risk of elevated CRP [73]. The anti-inflammatory and cardioprotective effects of the omega-3 fatty acids of fish oil, mainly eicosapentaenoic acid, are well recognized. For example, dietary fish oil decreases CRP and IL-6 levels in non-renal subjects [74]. In addition, Kutner *et al.* [75] found that dialysis patients who reported fish consumption were 50% less likely to die during the observation period. Therefore, the potential beneficial effects of this culinary form of anti-cytokine therapy certainly merit further investigation.

Lifestyle modification may be another important component in normalizing the dysregulated cytokine system activity in ESRD patients [76]. A recent epidemiological study [77] showed that frequent exercise of up to 4 to 5 times/wk with was associated with improved survival. Also, a 2-year multidisciplinary program that included both consumption of a Mediterranean-style diet and increased physical activity resulted in a reduction in IL-6, IL-18 and CRP levels in obese women [78]. Among other nutritional factors that may affect inflammation, moderate alcohol consumption should definitely be mentioned as it has been shown to be associated with all-cause mortality in a J- or U-shaped manner in the general population. It should be noted that although changes in lipids, such as increased HDL-cholesterol and apolipoprotein A-I, and a favourable haemostatic profile may contribute to the favourable effects of a moderate intake of alcohol, anti-inflammatory effects may also be important [79].

Perhaps one of the most intriguing findings in nutritional epidemiology over the last couple of years has been the observation that increased seed, nut and berry consumption seems to protect against coronary artery disease [80]. In general, nuts and seeds constitute an important part of plant-based diets, such as the Mediterranean and most Asian diets. Furthermore, nuts and seeds are a major source of gamma-tocopherol [81], an anti-inflammatory and anti-oxidant compound believed to modulate the risks for aging-related diseases such as cancer and heart disease [82]. Meanwhile, blue or red fruits and berries contain high levels of anthocyanins, which have been proven to exert powerful anti-oxidative effects *in vitro*. Increased oxidative stress is a common feature of ESRD that seems to be strongly associated with both MIA features [83] and outcome [84]. Plants are rich natural sources not only of antioxidants but also of other nutrients. For example, a number of interventions and cross sectional studies have been performed on subjects consuming an uncooked vegan diet, so called "living food" (such as berries, fruits, vegetables and roots, nuts, germinated seeds and sprouts, i.e. food sources rich in carotenoids, vitamins C and E) in rheumatoid arthritis (RA) patients, in which inflammation is a hallmark, with positive subjective and objective results [85]. Such studies have yet to be performed in the renal population, however two recent studies using the anti-oxidant compound N-acetylcysteine have shown positive impact on both inflammation and CVD-mortality in HD patients [86] and in a mouse model [87].

Advanced glycation end-products (AGEs), the result of the nonenzymatic reaction of reducing sugars with proteins, lipids and nucleic acids, are usually markedly elevated in ESRD patients. It has been proposed that AGEs promote atherosclerosis through interaction with endothelial receptors [88]. Although reduced renal clearance and increased oxidative stress may be the most important causes of elevated AGEs in ESRD patients, diet may be an important source of highly reactive AGEs. As correlations have been found between one form of AGE, pentosidine, and CRP in both renal [89] and non-renal [90] patients, it has been suggested that AGEs can trigger an inflammatory response [91]. Uribarri *et al.* [92] have shown that dietary glycotoxins contribute to significantly elevated AGE levels in ESRD patients. Further studies are thus warranted to elucidate if dietary restrictions of the intake of AGE may reduce both excess toxic AGE and inflammation in this patient group. Importantly, a reduction in dietary AGE content can be obtained safely without compromising the content of vital nutrients, such as dietary protein, fat, and carbohydrates [93]. It may also be possible to use drug therapy to induce the breakdown of pre-existing AGEs. One example of such a drug, which is presently being evaluated in clinical trials, is ALT-711 [94]. This cross-linked breaker also has beneficial effects on putative mediators of renal injury, such as pro-sclerotic cytokines and oxidative stress [95], that might be beneficial for ESRD patients.

PHARMACOLOGICAL THERAPY DIRECTED AGAINST INFLAMMATION

Given the strongly documented associations between pro-inflammatory cytokines and complications common in ESRD, such as CVD and cachexia, various pharmacological and anti-cytokine treatment strategies have been proposed for these patients (Table 3). In this respect it is notable that several commonly used drugs in clinical practice, such as statins and ACE-inhibitors (ACEI), possess significant anti-cachectic and anti-inflammatory effects.

Conventional Anti-Inflammatory Drugs

It is now evident that statins not only inhibit cholesterol synthesis but also have "pleiotropic effects", such as anti-inflammatory actions [96]. Randomization to pravastatin after myocardial infarction resulted in significant reductions in CRP [97] and one study showed that atorvastatin inhibits IL-6 secretion in adipocytes [98]. Part of this immunoprotective effect may be due to promotion of Th2 development [99] and this may have a therapeutic potential not only in atherosclerosis but also in inflammatory and wasting disorders [100]. Indeed, two studies have demonstrated that statins, in addition to its lipid-lowering effect, also had an anti-inflammatory effect in HD patients [101, 102]. However, although simvastatin reduced the inflammatory response, it did not prevent muscle wasting in an experimental model of cancer cachexia [103]. Paradoxically, since lipoproteins isolated from normal human plasma can bind and neutralize bacterial lipopolysaccharide [104], a cholesterol-lowering may represent a disadvantage in wasted ESRD patients. In fact, it has been speculated that "non-lipid lowering statins" may be as effective and even more beneficial than "lipid-lowering statins" in wasted and

Table 3. Examples of Pharmacological Interventions with Proposed Direct or Indirect Effect on Malnutrition, Wasting and Inflammation Syndrome

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| <p>Compounds that may stimulate appetite.</p> <ul style="list-style-type: none"> • Megestrol acetate • Ghrelin • Corticosteroids • Dronabinol • Cyproheptadine • Melatonin • Thalidomide |
| <p>Drugs that may have secondary anti-cytokine effects.</p> <ul style="list-style-type: none"> • HMG-CoA reductase inhibitors • ACE inhibitors • PPAR- activators, glitazones • -Tocopherol • N-acetylcysteine • Non-steroidal anti-inflammatory drugs • Testosterone |

inflamed patients [105]. This hypothesis has been challenged by the observation by Liu *et al.* [106] that the inverse association between total cholesterol with mortality in dialysis patients is related to the cholesterol-lowering effect of systemic inflammation and wasting. We thus now wait for the several large, ongoing, randomized clinical trials in the renal population to be published in order to learn more about this interesting therapy option.

Another commonly used drug with hypothetical anti-inflammatory properties *in vivo* are the ACEI [107]. Brull *et al.* [108] have noted that ACEI treatment was associated with a reduction in IL-6 in response to coronary artery graft surgery while we have found lower plasma levels of TNF- α in ESRD patients treated by ACEI [109]. A recent study of 1,920 patients with congestive heart failure (CHF) from the SOLVD trial demonstrated that treatment with an ACEI reduced the risk of weight loss [110], supporting the hypothesis of strong relationships between cachexia, the renin-angiotensin system and inflammation. Since the use of ACEI is independently associated also with a decreased rate of decline in residual renal function in dialysis patients [111], it is furthermore not surprising that ACEI improves the prognosis of renal patients [112], however to which extent this is due to decreased malnutrition is not clear.

Several other drugs also have anti-inflammatory effects. Peroxisome proliferators-activated receptor (PPAR-activators, i.e. glitazones) have also been shown to inhibit the activation of inflammatory response genes, and promote a deviation of the immune system away from Th1 toward Th2 cytokine production [113, 114]. Recently, the calcium-free phosphate binder sevelamer has been shown to have both anti-inflammatory and LDL-lowering effects [115], and it has been hypothesized that these effects are the main cause

of the reduced CVD and mortality observed in clinical trials with this drug [116].

Anabolic Drugs

Anabolic androgenic steroids, such as testosterone, nandrolone, oxandrolone and stanozol, include a diverse family of steroidal hormones and synthetic hormone derivatives, which have anabolic and anti-catabolic effects. These drugs have been studied in a number of settings of catabolic weight loss, such as AIDS and cancer cardiac wasting. In addition, they have been abused to improve muscle mass in sports doping. In cachectic ESRD, injections of rhGH induce a strong and sustained anabolic effect, as indicated by a positive nitrogen balance [117]. Also of interest are sex hormones, which have pleiotropic effects and may be important for atheroprotection as men with low testosterone levels as well as women with low estrogen levels are at increased risk of CVD. The reported ability of sex hormones to interfere with cytokine production by expression of IL-6 mRNA may contribute to these protective effects [118].

Recombinant insulin-like growth factor (rhIGF-1) may induce an anabolic response in patients in whom the primary cause of malnutrition is a low protein intake. Indeed, injections of rhIGF-1 has been shown to induce a strong and sustained anabolic effect in PD patients [119]. However, the effectiveness of anabolic hormones, such as rhGH and rhIGF-1, has proved to be blunted if inflammation is present [120]. This again underlines the need to provide an integrated therapy for wasting in ESRD. Clearly, larger studies are needed to establish the respective role of anabolic hormones in inflamed and non-inflamed ESRD patients with wasting.

Other Drugs

A variety of other agents that are not commonly used in ESRD patients may also have a role in the treatment of inflammatory-associated wasting. There have been numerous reports suggesting that inhibition of prostaglandin production by non-steroidal anti-inflammatory drugs may impact tumor-mediated wasting [121]. However, as these drugs may have serious side effects in ESRD patients, such as bleeding from the gastrointestinal tract, increased risk of acute cardiovascular events, haematopoietic toxicities and reduced residual renal function, nephrologists have been reluctant to use them widely. However, COX-2 inhibitors also have been reported to reverse tumor-mediated wasting and associated humoral factors, such as IL-6 in different experimental models of cachexia [122], and the potential of this new class of drug in reversing uremic wasting needs to be addressed in order for evaluate the risks and benefits (Fig. 1).

Targeted anti-cytokine treatment strategies, which have been tested in patients with other inflammatory states, should also be considered for use in ESRD patients [22].

CONCLUSIONS

Cachexia is a common clinical feature of ESRD that encompasses both anorexia and catabolism and seems to be associated with increased inflammatory activity as well as with cardiovascular disease. Cachexia in ESRD patients is multifactorial and, as such, single therapeutic strategies are

not likely to be successful. Given the hitherto rather poor results of energy and protein supplementation, new treatment strategies are needed. We believe that much could be learned from other wasted and inflamed patients groups, such as those with HIV, CHF, and cancer, in which various anti-inflammatory treatment strategies in combination with efforts to improve nutritional intake have led to improved nutritional status and outcome. With this goal in mind, we encourage further studies towards establishing an effective and safe integrated therapy against cachexia in ESRD, evaluating both traditional and non-traditional strategies.

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REFERENCES

- [1] Heimbürger O, Qureshi AR, Blaner WS, *et al.* Hand-grip muscle strength, lean body mass, and plasma proteins as markers of nutritional status in patients with chronic renal failure close to start of dialysis therapy. *Am J Kidney Dis* 2000; 36: 1213-1225.
- [2] Young GA, Kopple JD, Lindholm B, *et al.* Nutritional assessment of continuous ambulatory peritoneal dialysis patients: an international study. *Am J Kidney Dis* 1991; 17: 462-471.
- [3] Qureshi AR, Alvestrand A, Danielsson A, *et al.* Factors predicting malnutrition in hemodialysis patients: a cross-sectional study. *Kidney Int* 1998; 53: 773-782.
- [4] Mitch WE. Malnutrition: a frequent misdiagnosis for hemodialysis patients. *J Clin Invest* 2002; 110: 437-439.
- [5] Pupim LB, Ikizler TA. Assessment and monitoring of uremic malnutrition. *J Ren Nutr* 2004; 14: 6-19.
- [6] Enia G, Sicuso C, Alati G, *et al.* Subjective global assessment of nutrition in dialysis patients. *Nephrol Dial Transplant* 1993; 8: 1094-1098.
- [7] Jansen MAM, Korevaar JC, Dekker FW, *et al.* Renal function and nutritional status at the start of chronic dialysis treatment. *J Am Soc Nephrol* 2001; 12: 157-163.
- [8] Jager KJ, Merkus MP, Huisman RM, *et al.* Nutritional status over time in haemodialysis and peritoneal dialysis. *J Am Soc Nephrol* 2001; 12: 1272-1279.
- [9] Duenhas MR, Draibe SA, Avesani CM, *et al.* Influence of renal function on spontaneous dietary intake and on nutritional status of chronic renal insufficiency patients. *Eur J Clin Nutr* 2003; 57: 1473-1478.
- [10] Nelson EN, Hong CD, Pesce AL, *et al.* Anthropometric norms for the dialysis population. *Am J Kidney Dis* 1990; 16: 32-37.
- [11] Cianciaruso B, Brunori G, Kopple JD, *et al.* Cross-sectional comparison of malnutrition in continuous ambulatory dialysis and hemodialysis patients. *Am J Kidney Dis* 1995; 26: 475-483.
- [12] Ikizler TA, Greene JH, Wingard RL, *et al.* Spontaneous dietary intake during progression of chronic renal failure. *Kidney Int* 1995; 6: 1386-1391.
- [13] Stenvinkel P, Heimbürger O, Lindholm B, *et al.* Are there two types of malnutrition in chronic renal failure? Evidence for relationships between malnutrition, inflammation and atherosclerosis (MIA syndrome). *Nephrol Dial Transplant* 2000; 15: 953-960.
- [14] Eknoyan G, Beck GJ, Cheung AK, *et al.* Effect of dialysis dose and membrane flux in maintenance hemodialysis. *N Engl J Med* 2002; 347: 2010-2019.
- [15] Paniagua R, Amato D, Vonesh E, *et al.* Effects of increased peritoneal clearances on mortality rates in peritoneal dialysis: ADEMEX, a prospective, randomized, controlled trial. *J Am Soc Nephrol* 2002; 13: 1307-1320.
- [16] Bergström J, Lindholm B. Malnutrition, cardiac disease and mortality - An integrated point of view. *Am J Kidney Dis* 1998; 32: 834-841.
- [17] Stenvinkel P, Heimbürger O, Paultre F, *et al.* Strong association between malnutrition, inflammation, and atherosclerosis in chronic renal failure. *Kidney Int* 1999; 55: 1899-1911.

- [18] Ross R. Atherosclerosis: an inflammatory disease. *N Engl J Med* 1999; 340: 115-126.
- [19] Zimmermann J, Herlinger S, Pruy A, *et al.* Inflammation enhances cardiovascular risk and mortality in hemodialysis patients. *Kidney Int* 1999; 55: 648-658.
- [20] Foley RN, Parfrey PS, Sarnak MJ. Clinical epidemiology of cardiovascular disease in chronic renal failure. *Am J Kidney Dis* 1998; 32 (Suppl 5): S112-S119.
- [21] Adey D, Kumar R, McCarthy JT, *et al.* Reduced synthesis of muscle proteins in chronic renal failure. *Am J Physiol Endocrinol Metab* 2000; 278: E219-225.
- [22] Stenvinkel P, Ketteler M, Johnson RJ, *et al.* IL-10, IL-6, and TNF- α : central factors in the altered cytokine network of uremia--the good, the bad, and the ugly. *Kidney Int* 2005; 67: 1216-1233.
- [23] Beddhu S, Kaysen GA, yan G, *et al.* Association of serum albumin and atherosclerosis in chronic hemodialysis patients. *Am J Kidney Dis* 2002; 40: 721-727.
- [24] Beddhu S, Pappas LM, Ramkumar N, *et al.* Malnutrition and atherosclerosis in dialysis patients. *J Am Soc Nephrol* 2004; 15: 733-742.
- [25] Aguilera A, Codoceo R, Selgas R, *et al.* Anorexigen (TNF- α , cholecystokinin) and orexigen (neuropeptide Y) plasma levels in peritoneal dialysis (PD) patients. Their relationship with nutritional parameters. *Nephrol Dial Transplant* 1998; 13: 1476-1483.
- [26] Cheung W, Yu PX, Little BM, *et al.* Role of leptin and melanocortin signaling in uremia-associated cachexia. *J Clin Invest* 2005; 115: 1659-1665.
- [27] Roubenoff R. Catabolism of aging: is it an inflammatory process? *Curr Opin Clin Nutr Metab Care* 2003; 6: 295-299.
- [28] Stenvinkel P, Heimbürger O, Lindholm B: Wasting, but not malnutrition, predicts cardiovascular mortality in end-stage renal disease. *Nephrol Dial Transplant* 2004; 19: 2181-2183.
- [29] Stenvinkel P, Heimbürger O, Jogestrand T. Elevated interleukin-6 predicts progressive carotid atherosclerosis in dialysis patients: association to chlamydia pneumoniae seropositivity. *Am J Kidney Dis* 2002; 39: 274-282.
- [30] Stenvinkel P, Barany P, Heimbürger O, *et al.* Mortality, malnutrition and atherosclerosis in end-stage renal disease: What is the role of interleukin-6? *Kidney Int* 2002; 61: S103-S108.
- [31] Strle K, Broussard SR, McCusker RH, *et al.* Proinflammatory cytokine impairment of insulin-like growth factor I-induced protein synthesis in skeletal muscle myoblasts requires ceramide. *Endocrinology* 2004; 145: 4592-4602.
- [32] Guttridge DC, Mayo MW, Madrid LV, *et al.* NF- κ B-induced loss of MyoD messenger RNA: Possible role in muscle decay and cachexia. *Science* 2000; 289: 2363-2365.
- [33] Mitch WE, Du J, Bailey JL, *et al.* Mechanisms causing muscle proteolysis in uremia: the influence of insulin and cytokines. *Miner Elect Metab* 1999; 25: 216-219.
- [34] García-Martínez C, Llovera M, Agell N, *et al.* Ubiquitin gene expression in skeletal muscle is increased by tumor necrosis factor- α . *Biochem Biophys Res Comm* 1994; 201: 682-686.
- [35] Plata-Salamán CR: Cytokines and anorexia: A brief overview. *Semin Oncology* 1998; 25: 64-72.
- [36] Katschinski DM, Robins HI, Schad M, *et al.* Role of tumor necrosis factor alpha in hyperthermia-induced apoptosis of human leukemia cells. *Cancer Res* 1999; 59: 3404-3410.
- [37] Yeh SS, Schuster MW: Geriatric cachexia: the role of cytokines. *Am J Clin Nutr* 1999; 70: 183-197.
- [38] Grunfeld C, Zhao C, Fuller J, *et al.* Endotoxin and cytokines induce expression of leptin, the ob gene product in hamsters. A role for leptin in the anorexia of infection. *J Clin Invest* 1996; 97: 2152-2157.
- [39] Payette H, Roubenoff R, Jacques PF, *et al.* Insulin-like growth factor-I and interleukin 6 predict sarcopenia in very old community-living men and women: The Framingham Heart Study. *J Am Geriatr Soc* 2003; 51: 1237-1243.
- [40] Bonafe M, Olivieri F, Cavallone L, *et al.* A gender-dependent genetic predisposition to produce high levels of IL-6 is detrimental for longevity. *Eur J Immunol* 2001; 31: 2357-2361.
- [41] Goodman MN: Interleukin-6 induces skeletal muscle protein breakdown in rats. *Proc Soc Exp Biol Med* 1994; 205: 182-185.
- [42] Strassman G, Fong M, Kenney JS, *et al.* Evidence for the involvement of interleukin 6 in experimental cancer cachexia. *J Clin Invest* 1992; 89: 1681-1684.
- [43] Tsujinaka T, Fujita J, Ebisuri C, *et al.* Interleukin-6 receptor antibody inhibits muscle atrophy and modulates proteolytic systems in interleukin-6 transgenic mice. *J Clin Invest* 1996; 97: 244-249.
- [44] Barbieri M, Ferruci L, Ragno E, *et al.* Chronic inflammation and the effect of IGF-1 on muscle strength and power in older persons. *Am J Physiol Endocrinol Metab* 2003; 284: E481-E487.
- [45] Kaizu Y, Ohkawa S, Odamak M, *et al.* Association between inflammatory mediators and muscle mass in long-term hemodialysis patients. *Am J Kidney Dis* 2003; 42: 295-302.
- [46] Stenlof K, Wernstedt I, Fjallman T, *et al.* Interleukin-6 levels in the central nervous system are negatively correlated with fat mass in overweight/obese subjects. *J Clin Endocrinol Metab* 2003; 88: 4379-4383.
- [47] Bammens B, Evenepoel P, Verbeke K, *et al.* Impairment of small intestinal protein assimilation in patients with end-stage renal disease: extending the malnutrition-inflammation-atherosclerosis concept. *Am J Clin Nutr* 2004; 80: 1536-1543.
- [48] Quinn LS, Anderson BG, Drivdahl RH, *et al.* Overexpression of interleukin-15 induces skeletal muscle hypertrophy in vitro: implications for treatment of muscle wasting disorders. *Exp Cell Res* 2002; 280: 55-63.
- [49] Carbo N, Lopez-Soriano J, Costelli P, *et al.* Interleukin-15 antagonizes muscle protein waste in tumour-bearing rats. *Br J Cancer* 2000; 83: 526-531.
- [50] Figueras M, Busquets S, Carbo N, *et al.* Interleukin-15 is able to suppress the increased DNA fragmentation associated with muscle wasting in tumour-bearing rats. *FEBS Lett* 2004; 569: 201-206.
- [51] Harcourt LJ, Holmes AG, Gregorevic P, *et al.* Interleukin-15 administration improves diaphragm muscle pathology and function in dystrophic mdx mice. *Am J Pathol* 2005; 166: 1131-1141.
- [52] Capelli JP, Kushner H, Canmiscioli TC, *et al.* Effect of intradialytic parenteral nutrition on mortality rates in end-stage renal disease care. *Am J Kidney Dis* 1994; 23: 808-816.
- [53] Wolfson M. Use of nutritional supplements in dialysis patients. *Semin Dial* 1992; 5: 285-290.
- [54] Kalantar-Zadeh K, Block G, McAllister CJ, *et al.* Appetite and inflammation, nutrition, anemia, and clinical outcome in hemodialysis patients. *Am J Clin Nutr* 2004; 80: 299-307.
- [55] Mehrotra R, Kopple JD: Causes of protein-energy malnutrition in chronic renal failure., in *Nutritional management of renal disease* (vol 167-182), edited by Kopple JD, Massry SG, 2nd ed, Philadelphia, Lippincott Williams & Wilkins, 2004.
- [56] Wynne K, Giannitsopoulou K, Small CJ, *et al.* Subcutaneous Ghrelin Enhances Acute Food Intake in Malnourished Patients Who Receive Maintenance Peritoneal Dialysis: A Randomized, Placebo-Controlled Trial. *J Am Soc Nephrol* 2005; (7): 2111-8.
- [57] Tchekmedyian N, Tait N, Moody M, *et al.* Appetite stimulation with megestrol acetate in cachectic cancer patients. *Semin Oncol* 1986; 13(Suppl 4): 37-43.
- [58] Lambert CP, Sullivan DH, Evans WJ. Effects of testosterone replacement and/or resistance training on interleukin-6, tumor necrosis factor alpha, and leptin in elderly men ingesting megestrol acetate: a randomized controlled trial. *J Gerontol A Biol Sci Med Sci* 2003; 58: 165-170.
- [59] Argiles JM, Meijsing SH, Pallares-Trujillo J, *et al.* Cancer cachexia: a therapeutic approach. *Med Res Rev* 2001; 21: 83-101.
- [60] Boccanfuso JA, Hutton M, McAllister B: The effects of megestrol acetate on nutritional parameters in a dialysis population. *J Ren Nutr* 2000; 10: 36-43.
- [61] Beal JE, Olson R, Laubenstein L, *et al.* Dronabinol as a treatment for anorexia associated with weight loss in patients with AIDS. *J Pain Symptom Manage* 1995; 10: 89-97.
- [62] Golden AC, Daiello LA, Silverman MA, *et al.* University of Miami Division of clinical Pharmacology therapeutic rounds: Medications used to treat anorexia in the frail elderly. *Am J Ther* 2003; 10: 292-298.
- [63] Jatoi A, Windschitl HE, Loprinzi CL, *et al.* Dronabinol versus megestrol acetate versus combination therapy for cancer-associated anorexia: a North Central Cancer Treatment Group study. *J Clin Oncol* 2002; 15: 567-573.
- [64] Nelson KA. Modern management of the cancer anorexia-cachexia syndrome. *Curr Pain Headache Rep* 2001; 5: 250-256.
- [65] Gagnon B, Bruera E. A review of the drug treatment of cachexia associated with cancer. *Drugs* 1998; 55: 675-688.

- [66] Nascimento MM, Pecoits-Filho R, Lindholm B, *et al.* Inflammation, malnutrition and atherosclerosis in end-stage renal disease: a global perspective. *Blood Purif* 2002; 20: 454-458.
- [67] Iseki K, Tozawa M, Yoshi S, *et al.* Serum C-reactive (CRP) and risk of death in chronic dialysis patients. *Nephrol Dial Transpl* 1999; 14: 1956-1960.
- [68] Noh H, Lee SW, Kang SW, *et al.* Serum C-reactive protein: a predictor of mortality in continuous ambulatory peritoneal dialysis patients. *Nephrol Dial Transpl* 1998; 18: 387-394.
- [69] Wong JS, Port FK, Hulbert-Shearon TE, *et al.* Survival advantage in Asian American end-stage renal disease patients. *Kidney Int* 1999; 55: 2515-2523.
- [70] Morton MS, Arisaka O, Miyake N, *et al.* Phytoestrogen concentrations in serum from Japanese men and women over forty years of age. *J Nutr* 2002; 132: 168-171.
- [71] Evans MJ, Eckert A, Lai K, *et al.* Reciprocal antagonism between estrogen receptor and NF-kappaB activity *in vivo*. *Circ Res* 2001; 89: 823-830.
- [72] Ranich T, Bhatena SJ, Velasquez MT. Protective effects of dietary phytoestrogens in chronic renal disease. *J Ren Nutr* 2001; 11: 183-193.
- [73] King DE, Egan BM, Geesey ME. Relation of dietary fat and fiber to elevation of C-reactive protein. *Am J Cardiol* 2003; 92: 1335-1339.
- [74] Ciubotaru I, Lee YS, Wander RC. Dietary fish oil decreases C-reactive protein, interleukin-6 and tricylglycerol to HDL-cholesterol ratio in postmenopausal women on HRT. *J Nutr Biochem* 2003; 14: 513-521.
- [75] Kutner NG, Clow PW, Zhang R, *et al.* Association of fish intake and survival in a cohort of incident dialysis patients. *Am J Kidney Dis* 2002; 39: 1018-1024.
- [76] Gielen S, Adams V, Mobius-Winkler S, *et al.* Anti-inflammatory effects of exercise training in the skeletal muscle of patients with chronic heart failure. *J Am Coll Cardiol* 200; 342: 869-872.
- [77] Stack AG, Molony DA, Rives T, *et al.* Association of physical activity with mortality in the US dialysis population. *Am J Kidney Dis* 2005; 45: 690-701.
- [78] Esposito K, Pontillo A, Di Palo C, *et al.* Effect of weight loss and lifestyle changes on vascular inflammatory markers in obese women: a randomized trial. *JAMA* 2003; 9: 1799-1804.
- [79] Imhof A, Koenig W: Alcohol inflammation and coronary heart disease. *Addict Biol* 2003; 8: 271-277.
- [80] Sabaté J. Nut consumption, vegetarian diets, ischemic heart disease risk, and all-cause mortality: evidence from epidemiologic studies. *Am J Clin Nutr* 1999; 79(Suppl): 500S-503S.
- [81] Cooney RV, Custer LJ, Okinaka L, *et al.* Effects of dietary sesame seeds on plasma tocopherol levels. *Nutr Cancer* 2001; 39: 66-71.
- [82] Jiang Q, Elson-Schwab I, Courtemanche C, *et al.* Gamma-tocopherol and its major metabolite, in contrast to alpha tocopherol, inhibit cyclooxygenase activity in macrophages and epithelial cells. *Proc Natl Acad Sci USA* 2000; 97: 11494-11499.
- [83] Himmelfarb J, Stenvinkel P, Ikizler TA, *et al.* The elephant of uremia: oxidative stress as a unifying concept of cardiovascular disease in uremia. *Kidney Int* 2002; 62: 1524-1538.
- [84] Stenvinkel P, Diczfalussy U, Lindholm B, *et al.* Phospholipid plasmalogen, a surrogate marker of oxidative stress, is associated with increased mortality in patients on renal replacement therapy. *Nephrol Dial Transpl* 2004; 19: 972-976.
- [85] Hanninen O, Kaartinen K, Rauma A, *et al.* Antioxidants in vegan diet and rheumatic disorders. *Toxicology* 2000; 30: 45-53.
- [86] Tepel M, van der Giet M, Statz M, *et al.* The antioxidant acetylcysteine reduces cardiovascular events in patients with end-stage renal failure: a randomized, controlled trial. *Circulation* 2003; 107: 992-995.
- [87] Ivanovski O, Szumilak D, Nguyen-Khoa T, *et al.* The antioxidant N-acetylcysteine prevents accelerated atherosclerosis in uremic apolipoprotein E knockout mice. *Kidney Int* 2005; 67: 2288-2294.
- [88] Miyata T, Ishikawa S, Asahi K, *et al.* 2-isopropylidenehydrazono-4-oxo-thiazolidin-5-ylacetanilide (OPB-9195) treatment inhibits the development of intimal thickening after balloon injury of rat carotid artery: role of glycooxidation and lipooxidation reactions in vascular tissue damage. *FEBS Lett* 1999; 445: 202-206.
- [89] Suliman M, Heimbürger O, Barany P, *et al.* Plasma pentosidine is associated with inflammation and malnutrition in end-stage renal disease patients starting on dialysis therapy. *J Am Soc Nephrol* 2003; 14: 1614-1622.
- [90] Miyata T, Ishiguro N, Yasuda Y, *et al.* Increased pentosidine, an advanced glycation end product, in plasma and synovial fluid from patients with rheumatoid arthritis and its relation to inflammatory markers. *Biochem Biophys Res Commun* 1998; 244: 45-49.
- [91] Schwedler S, Schinzel R, Vaith P, *et al.* Inflammation and advanced glycation end products in uremia: simple coexistence, potentiation or causal relationship? *Kidney Int* 2001; 59 (Suppl 78): S32-S36.
- [92] Uribarri J, Peppas M, Cai W, *et al.* Restriction of dietary glycotoxins reduces excessive advanced glycation end products in renal failure patients. *J Am Soc Nephrol* 2003; 14: 728-731.
- [93] Uribarri J, Peppas M, Cai W, *et al.* Dietary glycotoxins correlate with circulating advanced glycation end product levels in renal failure patients. *Am J Kidney Dis* 2003; 42: 532-538.
- [94] Bakris GL, Bank AJ, Kass DA, *et al.* Advanced glycation end-product cross-link breakers: a novel approach to cardiovascular pathologies related to the aging process. *Am J Hypertens* 2004; 17: 23S-30S.
- [95] Forbes JM, Thallas V, Thomas MC, *et al.* The breakdown of preexisting advanced glycation end products is associated with reduced renal fibrosis in experimental diabetes. *FASEB J* 2003; 17: 1762-1764.
- [96] Libby P. Inflammation in atherosclerosis. *Nature* 2002; 420: 868-874.
- [97] Ridker PM, Rifai N, Pfeffer MA, *et al.* Long-term effects of pravastatin on plasma concentrations of C-reactive protein. *Circulation* 1999; 100: 230-235.
- [98] Zhao SP, Zhang DQ. Atorvastatin reduces interleukin-6 plasma concentration and adipocyte secretion of hypercholesterolemic rabbits. *Clin Chim Acta* 2003; 336: 103-108.
- [99] Hakamada-Taguchi R, Uehara Y, Kuribayashi K, *et al.* Inhibition of hydroxymethylglutaryl-coenzyme a reductase reduces Th1 development and promotes Th2 development. *Circ Res* 2003; 93: 948-956.
- [100] Nath N, Giri S, Prasad R, *et al.* Potential targets of 3-hydroxy-3-methylglutaryl coenzyme a reductase inhibitor for multiple sclerosis therapy. *J Immunol* 2004; 172: 1273-1286.
- [101] Chang JW, Yang WS, Min WK, *et al.* Effects of simvastatin on high-sensitivity C-reactive protein and serum albumin in hemodialysis patients. *Am J Kidney Dis* 2002; 39: 1213-1217.
- [102] Vernaglion L, Cristofano C, Muscogiuri P, *et al.* Does atorvastatin influence serum C-reactive protein levels in patients on long-term hemodialysis? *Am J Kidney Dis* 2004; 43: 471-478.
- [103] Muscaritoli M, Costelli P, Bossola M, *et al.* Effects of simvastatin administration in an experimental model of cancer cachexia. *Nutrition* 2003; 19: 936-939.
- [104] Wurfel MM, Kunitake ST, Lichenstein H, *et al.* Lipopolysaccharide (LPS)-binding protein is carried on lipoproteins and acts as a cofactor in the neutralization of LPS. *J Exp Med* 1994; 180: 1025-1035.
- [105] Rauchhaus M, Coats AJ, Anker SD: The endotoxin-lipoprotein hypothesis. *Lancet* 2000; 356: 930-933.
- [106] Liu Y, Coresh J, Eustace JA, *et al.* Association between cholesterol level and mortality in dialysis patients. Role of inflammation and malnutrition. *JAMA* 2004; 291: 451-459.
- [107] Peeters ACTM, Netea MG, Kullberg BJ, *et al.* The effect of renin-angiotensin system inhibitors on pro- and anti-inflammatory cytokine production. *Immunology* 1998; 94: 376-379.
- [108] Brull DJ, Sanders J, Rumley A, *et al.* Impact of angiotensin converting enzyme inhibition on post-coronary artery bypass interleukin 6 release. *Heart* 2002; 87: 252-255.
- [109] Stenvinkel P, Andersson A, Wang T, *et al.* Do ACE-inhibitors suppress tumor necrosis factor- α production in advanced chronic renal failure? *J Int Med* 1999; 246: 503-507.
- [110] Anker SD, Negassa A, Coats AJ, *et al.* Prognostic importance of weight loss in chronic heart failure and the effect of treatment with angiotensin-converting-enzyme inhibitors: an observational study. *Lancet* 2003; 361: 1077-1083.
- [111] Moist LM, Port FK, Orzol SM, *et al.* Predictors of loss of residual renal function among new dialysis patients. *J Am Soc Nephrol* 2000; 11: 556-564.
- [112] Mann JF, Gerstein HC, Pogue J, *et al.* Renal insufficiency as a predictor of cardiovascular outcomes and the impact of ramipril: the HOPE randomized trial. *Ann Intern Med* 2001; 134: 629-636.
- [113] Saubermann LJ, Nakajima A, Wada K, *et al.* Peroxisome proliferator-activated receptor gamma agonist ligands stimulate a

- Th2 cytokine response and prevent acute colitis. *Inflamm Bowel Dis* 2002; 8: 330-339.
- [114] Chinetti G, Fruchart JC, Staels B. Peroxisome proliferator-activated receptors (PPARs): nuclear receptors at the crossroads between lipid metabolism and inflammation. *Inflamm Res* 2000; 49: 497-505.
- [115] Ferramosca E, Burke S, Chasan-Taber S, *et al.* Potential antiatherogenic and anti-inflammatory properties of sevelamer in maintenance hemodialysis patients. *Am Heart J* 2005; 149: 820-825.
- [116] Qunibi WY. Dyslipidemia and progression of cardiovascular calcification (CVC) in patients with end-stage renal disease (ESRD). *Kidney Int* 2005; Suppl: s43-50.
- [117] Kopple JD, Brunori G, Leiserowitz M, *et al.* Growth hormone induces anabolism in malnourished maintenance haemodialysis patients. *Nephrol Dial Transplant* 2005; 20: 952-958.
- [118] Ershler WB, Keller ET. Age-associated increased interleukin-6 gene expression, late-life diseases, and frailty. *Ann Rev Med* 2000; 51: 245-270.
- [119] Fouque D, Peng SC, Shamir E, *et al.* Recombinant human insulin-like growth factor-1 induces an anabolic response in malnourished CAPD patients. *Kidney Int* 2000; 57: 646-654.
- [120] Ericsson F, Divino JD, Lindgren B: Low grade inflammatory activity abolishes the anabolic effect of growth hormone (GH) on metabolism in hemodialysis patients. *J Am Soc Nephrol* 1999; 10: 162A.
- [121] Okamoto T. NSAID zaltoprofen improves the decrease in body weight in rodent sickness behavior models: proposed new applications of NSAIDs. *Int J Mol Med* 2002; 9: 369-372.
- [122] Davis TW, Zweifel BS, O'Neal JM, *et al.* Inhibition of COX-2 by Celecoxib Reverses Tumor Induced Wasting. *Pharmacol Exp Ther* 2004; 308: 929-34.