UREMIC SARCOPENIA PATHOPHYSIOLOGY AND ITS IMPLICATIONS

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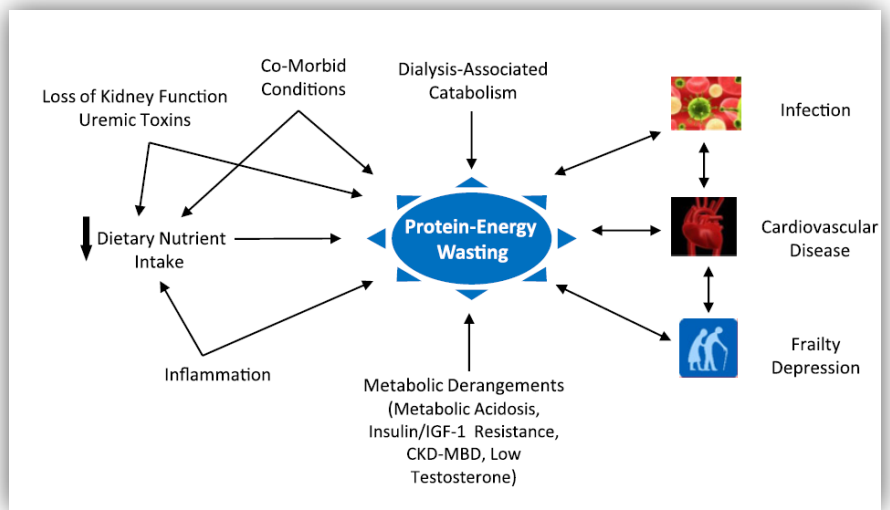
INTRODUCTION :

Sarcopenia is a chronic condition associated with physiological aging process and is defined by the reduction of the mass, muscle strength and function[1]. In Chronic Kidney Disease (CKD), sarcopenia is prevalent and is associated with increased morbidity and mortality and the occurrence of cardiovascular complications. By analysing sarcopenia in patients with renal insufficiency, complex mechanisms that contribute to loss of muscle mass are highlighted, such as accumulation of uremic toxins, chronic inflammation, insulin resistance, hormonal imbalance, malnutrition, vitamin D deficiency, inadequate oxygen transport as a consequence of anaemia, metabolic acidosis, electrolyte disorder, and a protein-restricted diet leading to the activation of mediators that stimulate the ubiquitin-proteasome system. The therapeutic approach to sarcopenia in CKD includes exercises, correction of metabolic acidosis, hormone replacement therapy and insulin resistance. Thus, it is of paramount importance early recognition of sarcopenia in this population, in order to establish effective therapeutic interventions, thus avoiding the full range of complications associated with muscle wasting in CKD.

The prevalence of sarcopenia was higher in elderly Korean patients with even mildly reduced kidney function. Stage of CKD was associated with an increased prevalence of sarcopenia in men but not women[2]. Thus, one should evaluate the risk of sarcopenia and work to prevent it, even in patients with early CKD.

These pathological conditions all can contribute to the progression of sarcopenia and increased physical inactivity in CKD patients.

The loss of muscle mass in Chronic Kidney Disease (CKD) is considered an important complicating factor, contributing to a sedentary lifestyle and compromising cardiovascular health due to increased morbimortality. Aging is associated with sarcopenia and increased CKD prevalence. It is important to emphasize that both sarcopenia as uraemia are progressive diseases, which contribute to maximizing morbidity and raise healthcare costs. The term uremic sarcopenia seems more appropriate to describe the process of progressive and cumulative loss of muscle mass that occurs in CKD, thus becoming a priority therapeutic target towards prevention and treatment of muscle wasting in these patients. Sarcopenia occurs in all CKD stages and the more severe the loss of renal function[2], the greater the risk of sarcopenia.

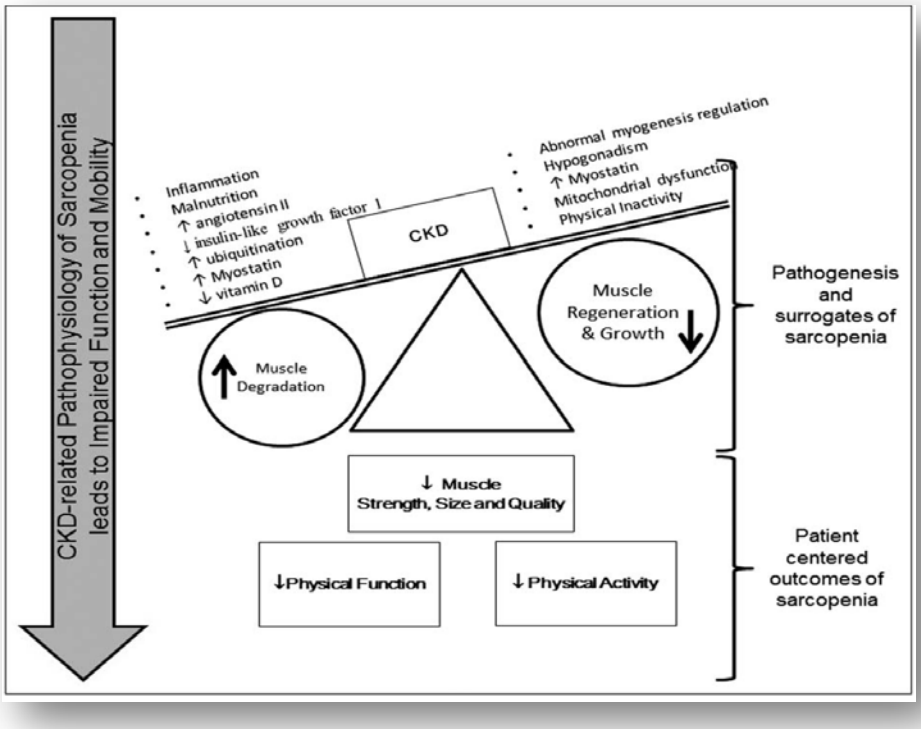


Etiology of PEW in CKD and direct clinical implications are as shown above[3,4] .PEW is the result of multiple mechanisms inherent to CKD, including undernutrition, systemic inflammation, comorbidities, hormonal derangements, the dialysis procedure, and other consequences of uremic toxicity. PEW may cause infection, CVD, frailty, and depression, but these complications may also increase the extent of PEW.

Sarcopenia leads to greater functional impairment in the patients with the advanced stages of CKD, as proved by McIntery et al[5], comparing CKD patients in stages 4 and 5 in Haemodialysis (HD) and peritoneal dialysis (PD). Data showed a significant difference in the cross-sectional area of the examined muscles and in the functional capacity of patients in stages 4 and 5; however, there was no difference between patients in HD and PD, which shows that the dialysis modality may not have a different impact on sarcopenic patients.

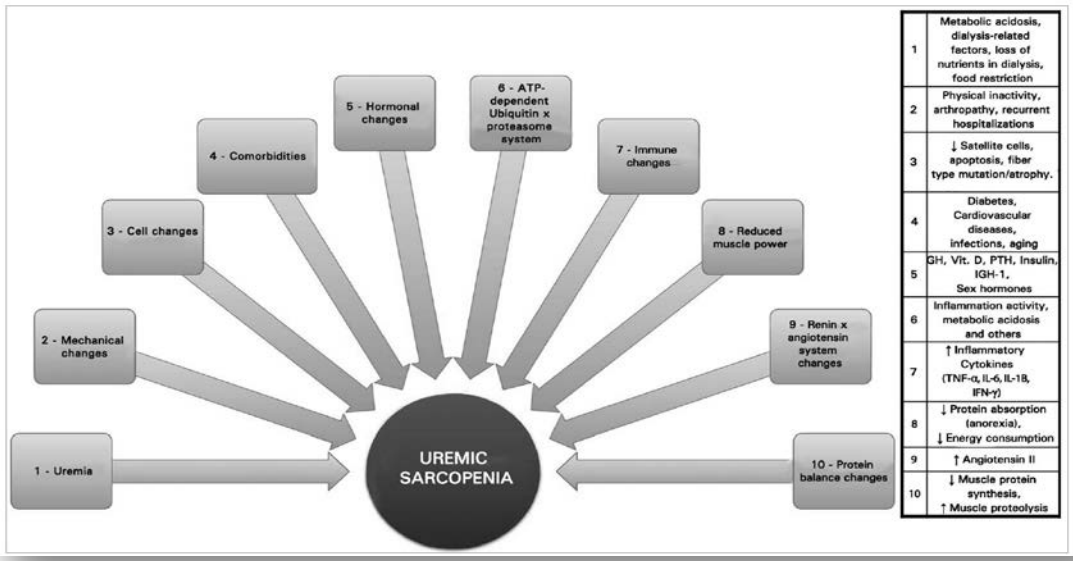
Skeletal muscle abnormalities in CKD

Muscle weakness and fatigue are frequently reported by patients with CKD and there are several mechanisms responsible for these symptoms, such as hormonal imbalance, malnutrition, ATP and glycogen depletion, inadequate oxygen transport as a consequence of anaemia, metabolic acidosis and electrolyte disorder, lifestyle changes, muscle wasting and weakness due to muscle fibre atrophy[5,6]. The most common abnormality



in muscle biopsies of uremic patients is type II muscle fibre atrophy, which have a smaller cross-sectional area, and muscle fibre grouping.

Figure 1. Uremic sarcopenia etiology. Drawing representing the etiological mechanisms of uremic sarcopenia.



1	Metabolic acidosis, dialysis-related factors, loss of nutrients in dialysis, food restriction
2	Physical inactivity, arthropathy, recurrent hospitalizations
3	↓ Satellite cells, apoptosis, fiber type mutation/atrophy.
4	Diabetes, Cardiovascular diseases, infections, aging
5	GH, Vit. D, PTH, Insulin, IGH-1, Sex hormones
6	Inflammation activity, metabolic acidosis and others
7	↑ Inflammatory Cytokines (TNF-α, IL-6, IL-1β, IFN-γ)
8	↓ Protein absorption (anorexia), ↓ Energy consumption
9	↑ Angiotensin II
10	↓ Muscle protein synthesis, ↑ Muscle proteolysis

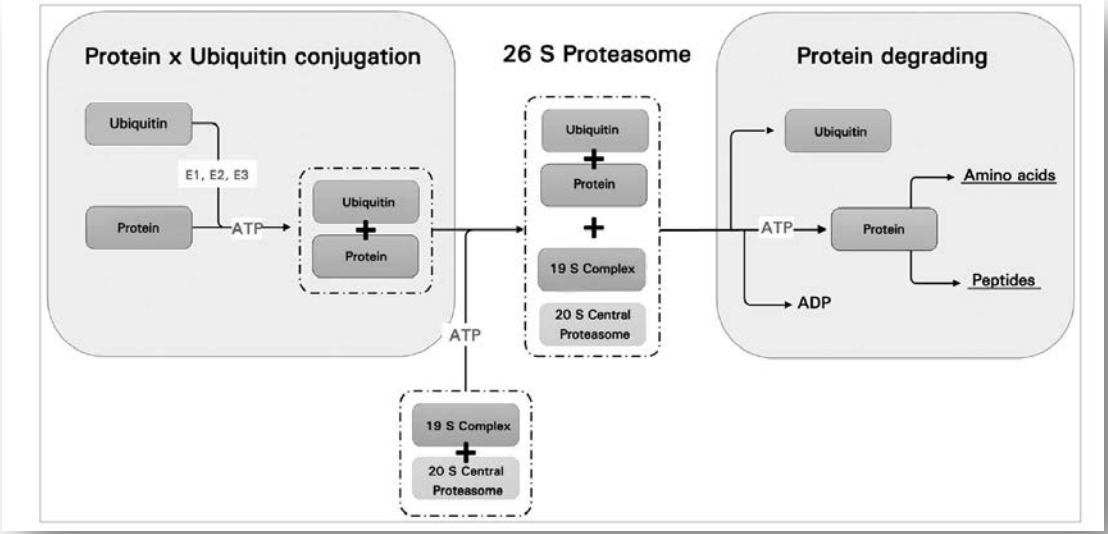


Figure 2. ATP-dependent ubiquitin-proteasome system. The proteins that will be degraded are first ubiquitinated. The E1 enzyme activates ubiquitin, which is then transferred to one of E2 protein-carrier enzymes. An E3 enzyme catalyzes the transfer of ubiquitin to the protein substrate in an ATP-dependent reaction. This process is repeated, forming a chain of ubiquitin molecules. This chain is then recognized by the 19S proteasome, which catalyzes the input of protein substrate in the 20S proteasome, and split into a peptide in the 26S proteasome. The peptides are degraded into amino acids, which will be used in the creation of cell proteins or released by the cells. ADP: Adenosine diphosphate; ATP: adenosine triphosphate.

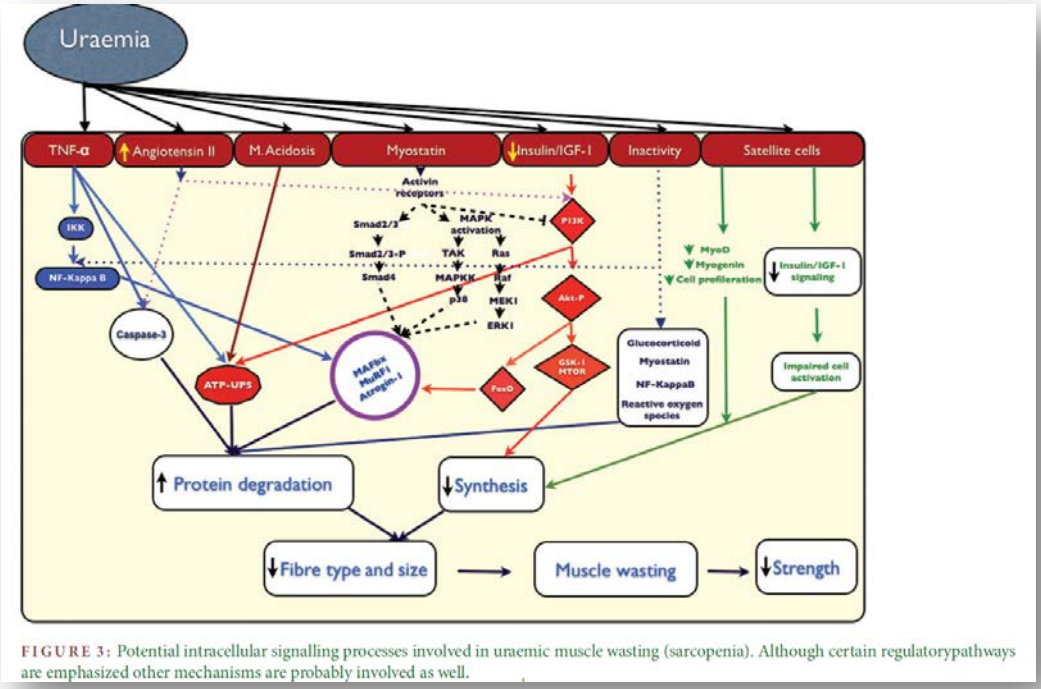


FIGURE 3: Potential intracellular signalling processes involved in uraemic muscle wasting (sarcopenia). Although certain regulatorypathways are emphasized other mechanisms are probably involved as well.

Muscle protein loss mechanisms

Muscle wasting etiology in renal patients is multifactorial[2,6] and similar to that of sarcopenia in general, involving hormonal and immunological causes; myocellular changes; inflammation; metabolic acidosis; protein intake reduction; physical inactivity; excess angiotensin II; abnormalities in insulin/IGF-1 signaling and in myostatin expression; and reduced function of satellite cells . Most of these mechanisms stimulate the ATP-dependent SUP pathway, which is recognized as one of the most important forms of muscle loss.

Progenitor cells and satellite cells

After muscle injury, satellite cells are activated and express MyoD and myogenin[6] transcription factors on their surfaces, which leads to myoblast formation and proliferation, and they differentiate to form new muscle fibers to repair the damaged muscle. In CKD, the function of satellite cells is impaired, producing low levels of myogenin and MyoD proteins, hampering muscle regeneration.

Inflammation

In CKD there are high circulating levels of inflammatory markers such as C reactive protein (CRP), interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF-α); and inflammation is a major cause of muscle wasting in this population. Several mechanisms may explain the role inflammation plays in this context, such as NFκβ path induction; inhibition of insulin induced protein synthesis, and changes in the insulin/IGF-1 pathway signaling. Inflammation also causes muscle loss through the activation of SUP[6,7,8].

ATP-dependent UPS

The ATP-dependent proteolysis via the ubiquitin- -proteasome system (UPS) is characterized as the primary cause of muscle mass degradation in CKD. Inflammation and metabolic acidosis play key roles in UPS activation

Metabolic acidosis

Metabolic acidosis stimulates the UPS pathway and causes muscle protein loss and calorie and protein loss (CPL) through protein degradation and protein synthesis reduction[6,7,9],.

Changes in vitamin D

Suitable serum vitamin D levels are associated with the proliferation and differentiation of various cells including skeletal muscle cells. Vitamin D supplementation is associated with muscle function improvements, reduced falls, and it may impact muscle fiber composition and morphology in the elderly. CKD patients have more prolonged muscle contraction phases, regardless of calcium, phosphorus and PTH serum levels.

Changes in angiotensin II

The renin-angiotensin system is activated in various catabolic conditions, including CKD, which leads to activation of caspase-3 in skeletal muscles, resulting in actin cleavage. Angiotensin II can increase muscle proteolysis by reducing circulating levels of IGF-1 and activating the TGF-β pathway, which is a major mechanism of muscle mass loss.

Changes in appetite

Anorexia is a common and complex change in CKD. The main causes reported in the literature are disorders of hormones that act in the regulation of appetite, such as leptin and ghrelin, reduced ability to distinguish flavors, gastrointestinal symptoms associated with uremia, depression, hemodynamic instability resulting from exposure to antihypertensive agents or hemodialysis, and feeling of fullness during peritoneal dialysis.

Changes in sex hormones

More than 60% of patients with advanced CKD have low serum levels of testosterone, which could contribute to muscle mass loss. Potential mechanisms by which low testosterone levels could lead to muscle catabolism include altered IGF-1 signalling and an increase in myostatin levels. Women with CKD usually have oligomenorrhea and estrogen deficiency in the early stages of the disease, which could lead to reduced muscle strength.

Changes in growth hormone

CKD is associated with GH resistance, being considered a potential cause of increased protein catabolism and skeletal muscle loss[6]. This can be explained by an IGF-1 anabolic hormone resistance to protein turnover in skeletal muscle and reduction in IGF bioactivity in ESRD, which would lead to a reduction of free IGF-1 in proportion to the degree of kidney failure.

Calorie and protein loss

The cause of CPL in CKD is complex, including inflammation; diseases associated with increased catabolism, which may occur together with CKD; loss of nutrients through the dialysate, metabolic acidosis, insulin resistance, GH and IGF-1; hyperglucagonemia, hyperparathyroidism and blood loss in the hemodialysis machine, feces or blood drawing.

Sleep and physical inactivity

CKD patients undergoing dialysis have a reduced level of physical activity, which may lead to loss of muscle proteins and muscle atrophy via a complex mechanism that includes physical inactivity and lack of training.

Changes in myostatin and follistatin

Myostatin and follistatin are members of the TGF-β family[12]. Myostatin expression is increased in uremic cachexia, representing a negative impact on skeletal muscle mass and growth, leading to muscle atrophy. Follistatin, a regulatory glycoprotein previously recognized as an FSH-suppressing protein, is a powerful myostatin antagonist, and experimental evidence suggests that its exacerbated expression induces a significant improvement in muscle mass. However; the mechanisms involved in the effects related to follistatin are still unknown.

IMPLICATIONS OF URAEMIC SARCOPENIA

Sarcopenia is a powerful predictor of morbidity and mortality in dialysis patients. Several studies suggested that a larger body size in maintenance dialysis patients has survival advantages and poor survival in dialysis patients with a low body size and reduced serum creatinine . However this phenomenon of the reverse epidemiology of obesity is not unique to the dialysis population. Patients with chronic heart failure, elderly patients and patients with malignancy or AIDS also exhibit a risk factor reversal and all share a degree of muscle wasting.

Several studies investigated whether lean body mass or fat mass confers this survival advantage[9,11]. Kalantar-Zadeh *et al*. reported that low baseline body fat percentage and fat loss over time are independently associated with higher mortality in maintenance dialysis patients even after adjustment for demographics and surrogates of muscle mass and inflammation. Noori *et al*. also reported that higher fat mass in both sexes and higher lean body mass in women appear to be protective[9,13], and in a different study the same group reported that the mid-arm muscle circumference is a surrogate of larger lean body mass and an independent predictor of better mental health and greater survival in dialysis patients . Other recent studies have suggested that higher lean body mass, but not fat mass, is associated with greater survival in CKD patients .

Muscle wasting is a devastating complication because it leads to decreased quality of life, increases cardiovascular complications and increases morbidity and mortality associated with CKD . Importantly, low exercise capacity as a consequence of muscle wasting is also a powerful, independent predictor of mortality in patients with CKD.

INTERVENTIONS AND EMERGING THERAPIES FOR SARCOPENIA IN CHRONIC KIDNEY DISEASE

Aerobic and resistance exercise Exercise and exercise capacity have been shown to be important in the development of CKD demonstrated by an inverse relationship between exercise capacity and CKD incidence; the risk of CKD was 22% lower for every one metabolic equivalent increase in exercise capacity [14]. Further, lifestyle factors such as physical activity, smoking, no bedtime snacking and habitual moderate exercise were associated with reduced CKD incidence[15]. Although not an exhaustive list, a few examples of recent exercise studies in CKD have been provided . In a recent Cochrane review, exercise interventions were administered in patients on dialysis in 45 of 59 randomized controlled trials (RCTs), whereas a smaller proportion included patients with CKD predialysis (11 of 59 RCTs) [16].

In the predialysis population, the following exercise types were used: aerobic (six studies), resistance training (three studies), and aerobic and resistance (two studies). The conclusion was that there were insufficient data to support a role of exercise mitigating CKD progression but there was evidence for aerobic exercise improving aerobic capacity and health-related quality of life.

In another review that focused on six studies that performed aerobic and resistance exercise intervention in patients not yet on dialysis, the conclusion was that the results were conflicting and plagued by small sample size [17,18] . Although patients undergoing dialysis are a more convenient population to study, greater efforts should be made to study the predialysis population, as exercise interventions prior to dialysis may improve functional status once dialysis is initiated. To evaluate resistance training in patients with stages 3–5 CKD, Cheema et al. [19] performed a systematic review.

PHARMACOLOGICAL INTERVENTIONS

Myostatin is a myokine and an inhibitor of skeletal muscle growth [51]. In a 5/6 nephrectomy mouse model, subcutaneous myostatin antibody injections (5 mg/kg) had multiple beneficial effects upon skeletal muscle, including reduced protein degradation, increased protein synthesis and improved satellite cell function . In postmenopausal healthy volunteers, a single dose of a soluble form of activin receptor type IIB that binds myostatin led to an increase in thigh muscle volume and lean mass[19]. But, stopped due to the side effects (bleeding).

Phase 2 humanized mAb against myostatin LY2495655 showed dose-dependent and significant increases in appendicular leanmass atweeks 8 and 16 as compared with placebo after total hip arthroplasty randomized clinical trial of 400 patients. A pilot RCT study[20] of PINTA 745, an antimyostatin peptibody, in patients undergoing hemodialysis has completed recruiting, but results are not yet published outcome is percentage change in lean mass using DXA after 4 weeks of treatment.

ROLE OF NEPHROLOGISTS

A recent survey showed that though61.2% of polled nephrologists felt that their patients' physical activity was poor, 53% did not prescribe exercise to dialysis patients. As would be expected, the majority did not receive training regarding exercise in their medical school or residency [21]. Another survey of nephrologists also showed that a lack of time while rounding in dialysis units and a significant number believed that other 'medical' issues were more important than the lack of physical activity [22]. Once sarcopenia is identified it is important to combat it with interventions lead by exercise and nutrition professionals. In patients undergoing dialysis, a structured physical therapy program has been shown to increase distance walked on the 6-min walk test and in quadriceps strength [23,24].

Exercise and rehabilitation, such as physical therapists, may benefit the patient. Further, increased awareness and education regarding physical activity, muscle performance, exercise and frailty at the level of medical school, residency and Nephrology fellowship programs may be warranted to improve patient quality of life.

CONCLUSIONS

Pathogenesis of uraemic muscle wasting is complex and progressive. Older persons are particularly susceptible to renal failure and this accelerates the physiological muscle wasting in this patient group. This devastating complication not only promotes a sedentary lifestyle and decreased quality of living, but also increases cardiovascular complications, morbidity and mortality.

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