

Sarcopenia in chronic kidney disease – A brief review

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ABSTRACT

Sarcopenia is a progressive age-related loss of muscle mass associated with a decline in muscle function and physical performance. Patients with chronic kidney disease experience substantial loss of muscle mass, weakness, and poor physical performance. Indeed, with the progression of chronic kidney disease, skeletal muscle dysfunction contributes to mobility limitation, loss of functional independence, and vulnerability to disease complications.

There is a lack of robust data on the negative effect of the impact of kidney disease on skeletal muscle dysfunction, as well as on screening and treatment strategies that can be used in clinical practice to prevent functional decline and disability. Therefore, sarcopenia may be an underestimated condition with major implications for people with chronic kidney disease, even before the start of dialysis, which makes research into this topic necessary.

The purpose of this review is to expand on some fundamental topics of sarcopenia, with an emphasis on the setting of chronic kidney disease patients.

Keywords: Aging; Chronic Kidney Disease; Sarcopenia.

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INTRODUCTION

Sarcopenia is defined by the reduction of mass, strength, and muscle function. This chronic condition, associated with the physiological aging process, is common in patients with chronic kidney disease (CKD) from the early stages of the disease and the more severe the loss of renal function, the greater the risk of sarcopenia.¹⁻³

The importance of maintaining muscle mass and physical and metabolic functions in the elderly is well-recognized. Progressive sarcopenia is ultimately central to the development of frailty, an increased likelihood of falls, and impairment of the ability to perform daily living activities. These alterations in muscle also play an important role in many diseases, such as CKD.⁴

Indeed, sarcopenia negatively affects skeletal muscle health in CKD, impairing the quality of life of these patients and contributing to morbidity and mortality.⁵ Therefore, early diagnosis and treatment of sarcopenia are crucial in all CKD patients to prevent the adverse outcomes related to this syndrome. These evaluations should be incorporated into pre-dialysis, peritoneal dialysis (PD), hemodialysis (HD), and kidney transplant patients.⁶

This article aims to review the impact of CKD on sarcopenia. We summarize general definitions of sarcopenia, its pathophysiology, clinical implications, as well as a diagnostic and therapeutic approach.

DEFINITION AND PATHOPHYSIOLOGY OF SARCOPENIA

The diagnosis of sarcopenia, developed by the European Working Group on Sarcopenia in Older People (EWGSOP), requires documentation of both low muscle mass and low muscle function (strength or performance).⁷ Pre-sarcopenia is defined as loss of skeletal muscle mass alone.⁸

There is another terminology for skeletal muscle loss conditions that must be differentiated from sarcopenia, including dynapenia, protein-energy wasting (PEW), frailty, and cachexia. Table 1 displays the definitions of these potentially confusing terms. This is particularly important for a practical approach as, for example, a patient who is diagnosed with sarcopenia will benefit from physical therapy to improve muscle mass and function, whereas a patient with PEW or cachexia will benefit from greater involvement of nutrition to combat the significant loss of muscle mass.⁹

Sarcopenia can be considered “primary” (or age-related) when no other cause is evident or “secondary” when causes are present, concomitant or not with aging. In the last category, besides activity-related sarcopenia (sedentary lifestyle) and nutrition-related sarcopenia (inadequate dietary intake of energy and/or protein, malabsorption conditions), the group of disease-related sarcopenia, such as CKD, is included.⁷

Table I

Terminology for skeletal muscle loss conditions, adapted from Moorthi RN et al⁹

Dynapenia	Loss of muscle, strength or power, regardless of muscle size
Protein-energy wasting	Syndrome that consists of nutritional and metabolic abnormalities in patients with CKD, especially in those with ESRD
Frailty	Subjective assessment of weakness, exhaustion and physical activity, which may cause multiple limitations
Cachexia	Multifactorial syndrome characterized by an ongoing loss of skeletal muscle mass that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment

CKD – chronic kidney disease, ESRD – end-stage renal disease

With the increase in the world’s older population, sarcopenia is becoming a major clinical problem in public health, and based on the results of a meta-analysis, the overall prevalence of sarcopenia is 10%.¹⁰

Several mechanisms are involved in the pathophysiology of sarcopenia, including age-related factors (mitochondrial dysfunction, apoptosis, atherosclerosis), hormonal imbalance (declines in serum testosterone and growth hormone (GH)), insulin resistance, immobility, neuromuscular integrity, changes in circulating pro-inflammatory cytokines, and muscle fat content.⁷ With aging, more phenomena lead to the development of sarcopenia. There is a progressive reduction in physical activity, increased body fatness, inflammation (increased cytokine levels), insulin resistance, nutritional deficiencies (protein, vitamin D, and other micronutrients), and reduced muscle protein synthesis.¹¹

At the molecular level, sarcopenia may be a result of a disproportionate decrease in skeletal muscle protein synthesis and/or an increased protein breakdown. Proteolytic and lysosomal-dependent degradation, manipulated by myokines (such as myostatin and IL-6) may explain this relationship. Myostatin affects muscle wasting by disrupting skeletal muscle satellite cells and an up-regulation of E3 ligases instigating protein breakdown by the proteasome. IL-6 signaling, present in chronic systemic inflammation, has been associated with myogenesis. In CKD, these myokines are elevated, from the early stages.⁵

Furthermore, elevated levels of angiotensin II stimulate caspase-3, which enhances actin cleavage, allowing actin and myosin to be degraded by the ubiquitin-proteasome system. Angiotensin II is also responsible for low circulating and skeletal IGF-1 levels, which enhances muscle wasting as well. This may explain the association of angiotensin converting enzyme inhibitors with increased muscle mass.^{11,12} In CKD, it has been also observed that FGF23 and Klotho induced muscle atrophy via reduction of insulin/IGF-I signaling.¹³

Also, there are understood factors directly related to muscle mass, strength, and function. Future studies may help to promote some beneficial interventions, including exercise and diet.

■ METHODS TO EVALUATE SARCOPENIA

Although sarcopenia has been emphasized as leading to dynapenia (muscle weakness), a more appropriate focus in sarcopenia includes

the central function of muscle. As such, mobility is perhaps the best way to evaluate muscle impairments and serves as a primary indicator of functional ability.¹⁴

The measurable variables to evaluate sarcopenia are muscle mass, muscle strength, and physical performance, as illustrated in Table II. For clinical use, handgrip strength is a good simple measure of muscle strength and the short physical performance battery, including the usual gait speed, and the timed get-up-and-go test, can serve as performance measurements.⁷

Regarding muscle mass, there are some imaging methods for muscle mass assessment available. Computed tomography (CT) and magnetic resonance imaging (MRI) are considered gold standards to measure skeletal muscle mass in research. However, although these modalities allow precise evaluation of muscle mass, they are of limited availability, costly, time-consuming, and complex technologies. Dual X-ray absorptiometry (DXA) is the preferred alternative method for clinical use and currently the method used the most often to detect sarcopenia, as it requires less time and only a low radiation dose. In this method, the appendicular skeletal muscle mass (ASMM) analyses the sum of the muscle mass of the arms and legs and there is an ASMM index (the ratio between ASMM and height squared) cut-off for diagnosing sarcopenia in men and women.⁸

Bioimpedance analysis (BIA) estimates the volume of fat and lean body mass and it has also been proposed as a practical alternative to imaging modalities in multiple clinical settings.¹⁵ Equations to estimate skeletal muscle index by BIA have been proposed by the EWGSOP and are widely accepted screening tools for low muscle mass in the elderly population.⁷

■ SARCOPENIA IN CHRONIC KIDNEY DISEASE

■ Prevalence, risk factors and comorbidity

There is a greater prevalence of secondary sarcopenia due to CKD than among subjects with normal renal function. The decline in muscle contributes to physical inactivity and multiple outcomes, even during the early stages of CKD.^{2,17-20} Table III summarizes the conclusions of some studies that have analyzed the prevalence of sarcopenia in CKD patients. The different findings suggest that there is not yet an agreement on which operational criteria to apply when diagnosing sarcopenia in CKD.

Skeletal muscle is considered the main source of protein in the body and protein is essential for antibody production, wound healing, and white blood cell production during acute or chronic illnesses. With the development of sarcopenia, the risk of disability and functional impairment is enhanced. It has been observed that HD patients with low lean mass and overhydration have significantly higher mortality.²¹ Furthermore, a study has proved that in patients with type 2 diabetes, the low muscle mass is independently associated with the increment of albuminuria, a surrogate marker of adverse renal and cardiovascular outcomes.²² In fact, the

Table IIMethods available to evaluate sarcopenia, adapted from Sergi G et al⁸, Sabatino et al¹⁶

Technique	Measure variable in sarcopenia	Advantages	Disadvantages
Anthropometry	Muscle mass	Simple Low cost Widely available	Low precision Affected by hydration status Need for high skilled anthropometrics
Bioelectrical impedance	Muscle mass	Simple Low cost Widely available Information about nutritional and hydration status	Affected by hydration status, body temperature, nutrition, exercise Not a direct measurement of lean mass
Physical examination	Muscle mass Malnutrition-Inflammation Score and Subjective Global Assessment	Simple No equipment Information regarding nutritional status	Not an objective measurement, not precise Affected by hydration status
Dual X-ray absorptiometry	Muscle mass Based on the attenuation of two X-ray beams with different energy levels, it estimates bone mineral density, fat mass and fat-free mass of the whole body, or of specific anatomical regions	Accurate quantitative estimate of skeletal muscle mass Low radiation dose	No information on quality changes in muscle mass
Computed tomography	Muscle mass Produces cross-sectional scans enabling segmental and total measures of fat and fat-free mass, based on the average attenuation of the X-ray beam through different body substrates	Accurate quantitative and qualitative estimate of skeletal muscle mass	Ionizing radiation High cost and complexity (availability issue)
Magnetic resonance imaging	Muscle mass Can estimate fat mass or fat-free mass and generate cross-sectional images, by analyzing variations in the radio frequency pulse sequence	Accurate quantitative and qualitative estimate of skeletal muscle mass No ionizing radiation	High cost and complexity (availability issue)
Ultrasound	Muscle mass Can estimate fat mass or fat-free mass and generate cross-sectional images, by analyzing variations in the radio frequency pulse sequence	Quantitative and qualitative estimate of skeletal muscle mass Low-cost	Examiner-dependent
Handgrip strength	Muscle strength	Simple, easily performed Portable Low cost Without contribution from the examiner	May not represent strength in lower limbs/patients with arthritis
Chair stand test	Muscle strength	Simple, easily performed No equipment	Requires patient's collaboration
Gait speed	Physical performance	Simple, easily performed No equipment	Requires large space
Short physical performance battery	Physical performance Combination of scores from balance, gait speed and chair stand	Simple, easily performed No equipment	Requires patient's collaboration Requires large space
Timed get-up-and-go test	Physical performance	Simple, easily performed No equipment	Requires large space Cutoff points are not extensively validated

sarcopenia-related-CKD predisposes a patient to an increased risk of cardiovascular events.²³

Multiple studies have already shown that nutritional disturbances are common in patients with CKD, with a predominance of sarcopenia and central obesity.²⁴⁻²⁸ In patients with CKD and obesity, the production of inflammatory mediators by adipose tissue also increase the prevalence of cardiovascular events.²

CKD patients manifest a phenotype of accelerated aging as a consequence of the several related risk factors (Table IV). Moreover,

this is a 'chicken-or-egg' conundrum, as it is unknown whether reduced physical activity causes muscle loss or loss of muscle causes reduced activity. The loss of skeletal muscle may predispose to a more sedentary lifestyle, increased risk of falls and frailty with subsequently more fractures, hospitalizations, and poorer quality of life.²⁹ Indeed, ameliorating physical function will improve the overall quality of life across the spectrum of CKD and this can be achieved by the implementation of exercise.⁵ Regular muscle mass assessment is strongly recommended in patients with CKD, regardless of the disease stage or the modality of renal replacement therapy.²⁴

Table III

Prevalence of muscle loss conditions in chronic kidney disease.

Author	Population	Prevalence of sarcopenia
Roshanravan et al, ⁴³ 2012	336 (stages 1-4 CKD)	14%
Kim et al, ³⁸ 2013	95 (all stages CKD)	37% in men and 29.3% in women
Pereira et al, ²⁵ 2015	287 (stages 3-5 CKD)	5.9 to 9.8%
Zhou et al, ¹⁷ 2018	148 (stages 3-5 CKD)	14%
Moon et al, ²⁰ 2015	11625 (stages 2-5 CKD)	6.3% (stage 2 CKD) and 15.4% (stage 3-5 CKD stage)
Marini et al, ⁴⁴ 2018	62 (HD)	33%
Isoyama et al, ⁴⁵ 2014	330 (HD)	20%
Kamijo et al, ³² 2018	119 (PD)	11%
Abro et al, ³⁴ 2018	155 (PD)	11-15.5%
Yanishi et al, ⁴⁶ 2016	51 (Kidney transplant recipients)	11.8%

CKD – chronic kidney disease, HD – hemodialysis; PD – peritoneal dialysis; ESRD – end-stage renal disease.

Table IV

Risk factors for high prevalence of sarcopenia in chronic kidney disease patients

Risk factors in CKD patients
<ul style="list-style-type: none"> • Low physical inactivity • Dietary restrictions with reduced protein intake • Inflammation • Aging • Hormonal disorders (vitamin D deficiency, hyperparathyroidism, resistance to growth hormone, resistance to insulin, increased angiotensin II) • Metabolic disorders (metabolic acidosis, electrolyte disorder, uremic toxins accumulation) • Comorbidities (obesity, dementia, cardiovascular disease, diabetes, infections)

Muscle weakness in PD patients is frequent³⁰ and associated with high inflammatory and nutritional markers.³¹ The associated poor outcomes,³⁰ such as physical disability, decreased quality of life, increased morbidity, and a high mortality rate have also been demonstrated in several studies.^{32,33}

Sarcopenia is even more common in HD patients.³⁴ This subgroup of patients is more vulnerable to multiple metabolic and nutrition derangements, leading to changes in body composition, which can affect handgrip strength and muscle mass measurements.^{35,36} Published data showed that sarcopenia is a relatively common condition among patients undergoing maintenance HD and is associated with a worse survival rate.^{37,38}

Kidney transplant recipients frequently also exhibit an abnormal body composition similar to sarcopenic obesity.³⁹ Indeed, the impact of sarcopenia in transplant recipients is relevant.⁴⁰ Patients who are sedentary, protein malnourished, and debilitated have been shown to experience increased mortality after many procedures, including vascular, oncologic, and transplant surgeries.⁴¹

To date, there are a limited number of studies that have examined the relationship between sarcopenia and decreased kidney function.^{20,25,26} In a systematic review and meta-analysis, sarcopenia was significantly associated with urinary protein level and decreased

renal function, in patients with diabetes, although these analyses were performed using few studies.⁴²

■ Pathophysiology

The pathogenesis of uremic muscle loss is complex and multifactorial and is still not fully understood.^{3,12,43} Several mechanisms are summarized in Figure 1, including the conditions of kidney disease itself, dialysis procedure, and typical chronic inflammation present in CKD. These conditions together lead to the dysregulation of the protein synthesis and catabolism, leading to a negative protein balance.^{16,47} Muscle wasting is characterized by increased muscle turnover rate and atrophy of type II muscle fibers.⁴⁸ The final result is sarcopenia that progresses as CKD worsens.²⁹

The kidney’s non-inflammatory factors include hormonal imbalances, such as insulin resistance, decreased sex hormones levels, GH resistance, and vitamin D deficiency, and metabolic disorders such as metabolic acidosis.³

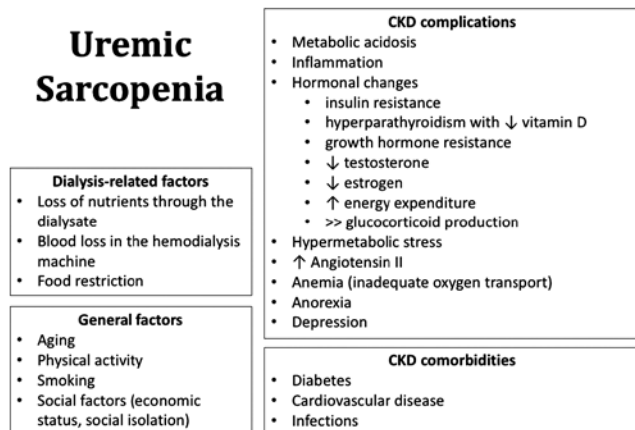
Impaired insulin signaling, involving the impact of low vitamin D status, may be responsible for muscle proteolysis.^{49,50} Insulin is the main hormone responsible for muscle protein synthesis, and vitamin D deficiency not only reduces pancreatic insulin secretion but also diminishes the stimulus for protein synthesis (by decreasing vitamin D receptors present in muscle and reducing the calcium influx from cellular membranes).⁵¹ It is now evidenced that patients with sarcopenia and CKD may share insulin resistance and low vitamin D levels.^{20,48,50}

Another phenomenon involved is the metabolic acidosis in CKD. Accumulation of acid in interstitial compartments, even before a fall in serum bicarbonate, can induce muscle damage and inflammation, produce or worsen bone disease, contribute to the progression of CKD and the development of hypoalbuminemia, increasing mortality.^{22,48}

Other hormonal imbalances (low testosterone and GH resistance) are considered a potential cause of increased protein catabolism, by altering IGF-1 signaling.³

Figure 1

Pathophysiology of uremic sarcopenia, adapted from Souza VA et al³ and Sharma D et al.²⁷



CKD – chronic kidney disease.

Dialysis-related factors include the substantial loss of amino acids during the HD procedure and the reduced energy and protein intake.⁵²

Inflammation conditions related to CKD have been demonstrated to be closely associated with sarcopenia,^{20,38} including early systemic markers of atherosclerosis and endothelial dysfunction such as reduction in high-density lipoprotein levels.¹⁸ For instance, fatty acid-binding protein 4, a novel adipokine primarily synthesized by adipocytes or macrophages that is expressed within human skeletal muscle fibers, has found to be an independent risk factor for sarcopenia in HD patients.⁵³

The renin-angiotensin-aldosterone-system is highly activated in CKD and also seems to provide strong input to the development of uremic sarcopenia, as explained earlier.¹²

Indeed, the chronic inflammation in combination with sarcopenia induces anorexia and fat loss.²⁰

CKD patients have altered cognitive function and mood that could be also associated with sarcopenia. Depression is one of the reasons for reduced appetite and hence for low energy/protein intake.^{18,38}

Other risk factors for sarcopenia among CKD patients, such as drugs, should be investigated. One cross-section analysis revealed that in patients with pre-dialysis CKD patients, loop diuretic use was suggested to be a risk factor of sarcopenia.²³

■ Diagnosis

For diagnostic purposes, skeletal muscle mass is the ideal target in the search for muscle abnormalities in CKD. The accuracy of all methods can be affected by CKD-related factors, especially hydration status. This is particularly important for methods that cannot distinguish between extracellular and intracellular fluid.^{54,55}

Regarding imaging exams, CT has been studied in CKD patients undergoing HD^{56,57} and pre-dialysis patients^{58,59} as a measure of quantification of muscle mass and function.

Ultrasonography (US) was also demonstrated to be a valid and reliable method for evaluating the rectus femoris and cross-sectional area in patients in pre-dialysis CKD.^{60,61} This exam represents a valid potential alternative for identifying changes in muscle.⁸

ASMM, measured by DXA, is currently the most accepted method for muscle mass evaluation in CKD patients.^{8,55,62}

Anthropometry estimates (which include mid-arm and calf circumference) and BIA are also widely available with low costs and are valid tools in CKD patients, however with lower precision.⁵⁴

Finally, simplified screening scores for sarcopenia, using age, grip strength, and calf circumference have also been proposed, suggesting a potentially useful tool for estimating the future adverse event risk in patients with CKD.²³

Among overweight or obese patients, the best way to assess and normalize skeletal muscle mass remains unclear.⁶³

Table V summarizes some considerations about the diagnostic approach of sarcopenia in CKD patients, from the Kidney Disease Quality Initiative–National Kidney Foundation (KDOQI-NKF) guidelines.⁶⁴ We think the choice of appropriate measures will depend on cost, clinical experience and the ease of each one. Beyond anthropometry, a physical exam (muscle wasting and palpation) and BIA, an imaging method to evaluate muscle mass may be considered (particularly those which are part of the clinical workup). However, other sarcopenia features may be more easily assessed and therefore applied, such as handgrip strength and gait speed.

Table V

Diagnostic approach of sarcopenia in chronic kidney disease, adapted from Ikizler T et al.⁶⁴

Diagnostic approach to sarcopenia in chronic kidney disease
Routine nutritional assessment (KDOQI-NKF guidelines)
CKD 3-5D or post transplantation: comprehensive nutrition assessment (appetite, history of dietary intake, body weight and body mass index, biochemical data, anthropometric measurements, and nutrition-focused physical findings) at least within the first 90 days of starting dialysis, annually, or when indicated by nutrition screening
<ul style="list-style-type: none"> Bioimpedance Impedance <ul style="list-style-type: none"> CKD 5D on HD: 30 minutes after HD session (minimize the impact of hydration status) CKD 1-5 or CKD 5D on PD: insufficient evidence to suggest Dual-Energy X-Ray Absorptiometry <ul style="list-style-type: none"> CKD 1-5D or post transplantation: use when feasible Body Composition and Body Mass Index <ul style="list-style-type: none"> CKD 5D: at the first visit and to monitor at least monthly CKD 4-5 or post transplantation: at the first visit and to monitor at every 3 months CKD 1-3: at the first visit and to monitor at every 6 months

CKD – chronic kidney disease; HD – hemodialysis; PD – peritoneal dialysis

There is a need for not only simple techniques capable of monitoring changes in muscle size with disease progression but also appropriate cutoffs for CKD patients. In addition, we should make an effort to apply those available.

■ Early interventions

Once sarcopenia is identified, interventions should be immediately carried out and monitored by specialized exercise physiologists or other appropriately trained health professionals, and nutritionists.⁹

Reduced physical activity in sarcopenic subjects, compared to healthy subjects, has been reported, and low muscle mass may reduce ability to participate in physical activities.²⁰ Therefore, physical activity from the early stages of CKD may have protective benefits against the loss of muscle mass.

The KDOQI-NKF clinical practice guidelines recommend that all dialysis patients should have their physical activity levels assessed and should be regularly encouraged by dialysis staff to increase their physical activity levels.⁶⁵ Resistance training promotes muscle growth and strength, and theoretically, this may be considered to be the preferred type of exercise to promote physical function in the CKD population.¹⁶ Some studies have investigated various modalities of exercise in the CKD population, including patients undergoing HD⁶⁶ and renal transplant recipients.⁶⁷

Regarding nutrition, the 2020 updated practice guideline for nutrition in CKD from the KDOQI-NKF guidelines recommends a protein intake of 0.6-0.8 g/kg/day for stages 3-5 CKD and 1.0-1.2 g/kg/day for stage 5D CKD, with an energy intake of 30 kcal/kg/day.⁶⁴ In the case of sarcopenia, it is reasonable to change the dietary scheme to recover the nutritional status.

Interventions to reverse sarcopenia usually include the use of energy and protein supplementation combined with physical exercise.

However, many promising pharmacological interventions for sarcopenia are currently under investigation. In HD patients, angiotensin II receptor blockade has been associated with preserved muscle strength⁶⁸ and treatment with the androgenic steroid oxymetholone has been associated with an increase in fat-free mass and handgrip strength.⁶⁹

Potential therapeutic strategies targeting specific toxins have also been proposed, such as indoxyl sulfate, a uremic toxin that accelerates skeletal muscle atrophy by inducing mitochondrial dysfunction.^{70,71}

Another with promising results is the high-tone external muscle stimulation that could improve microcirculation and, through this mechanism, reduce kidney damage in elderly patients with CKD and severe muscle atrophy.⁷²

■ FINAL REMARKS

Sarcopenia represents a devastating complication that not only contributes to a sedentary lifestyle and poor quality of life but also

increases the incidence of cardiovascular complications, morbidity, and mortality. CKD is a progressive condition that adversely affects musculoskeletal health and the prevalence of CKD-sarcopenia is higher than it is in primary sarcopenia, especially in HD patients.

There is increasing interest in the early diagnosis of sarcopenia, considering the adverse complications of this underestimated condition. In our daily practice, methods and criteria to diagnose sarcopenia in our CKD patients should start to be routinely applied and followed by the implementation of therapeutic strategies that could have improved clinical outcomes.

In the future, better management of sarcopenic patients will be possible by identifying novel therapy pathways, through a better understanding of pathogenic mechanisms, by optimizing the tools to monitor the impact of therapy, and by addressing individual therapeutic approaches.

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