INTERNATIONAL JOURNAL OF
Clinical and Pharmaceutical Innovations
An International Peer Reviewed Open Access Journal

Review Article

ISSN (Online): 3142-8665
CODEN (USA): IJCPSM

2026, Volume 1, Issue 4, Page No: 21-31.

# SHRUNKEN PORE SYNDROME: AN OVERLOOKED ENTITY WITH MAJOR CLINICAL CONSEQUENCES

**Shaik Ayesha Laharin, Singuluri Monica, Lingineni Mani Deepa Chandrika*, Nalam Vineela Nirmala, Uma Maheswari Vuyala, Syed Rukhsana, Palthe Mounika Bai**

KVSR Siddhartha College of Pharmaceutical Sciences, Vijayawada, Andhra Pradesh, Pin Code-520008, India.

**Article Info:** **Received:** 04 May 2026, **Revised:** 24 May 2026, **Accepted:** 14 June 2026

***Corresponding Author: Lingineni Mani Deepa Chandrika**

KVSR Siddhartha College of Pharmaceutical Sciences, Vijayawada, Andhra Pradesh, Pin Code-520008, India.

**Citation:**
Shaik Ayesha Laharin, Singuluri Monica, Lingineni Mani Deepa Chandrika*, Nalam Vineela Nirmala, Uma Maheswari Vuyala, Syed Rukhsana, Palthe Mounika Bai. (2026). Shrunken Pore Syndrome: An Overlooked Entity With Major Clinical Consequences. International Journal of Clinical and Pharmaceutical Innovations, 1(4), 21-31.
**DOI:** https://doi.org/10.5281/zenodo.21037137



**ABSTRACT**
Shrunken Pore Syndrome (SPS) represents an underappreciated form of kidney filtration disorder that is characterized by inadequate filtration of medium-sized molecules in the presence of a relatively preserved glomerular filtration rate (GFR). SPS is usually detected when the GFR measured based on cystatin C levels is significantly below the GFR obtained based on creatinine. SPS has received considerable attention recently due to its association with unfavorable clinical outcomes such as cardiovascular disease, progression of chronic kidney disease, frailty, hospitalization, and death. SPS occurs as a consequence of structural changes in the glomerular filtration barrier that impair the filtration of larger molecules. SPS may be observed in diabetic, hypertensive, inflammatory, or age-related conditions; however, it often goes undetected due to normal results of kidney evaluation based on creatinine. Therefore, early detection of SPS is crucial since it provides a possibility of predicting an unfavorable outcome and identifying patients at risk. The current literature highlights the importance of measuring cystatin C in evaluating kidney function.

**KEYWORDS:** Shrunken Pore Syndrome, glomerular filtration rate, kidney disease, chronic kidney disease, renal function impairment, cardiovascular disease.

## 1 - From Neglect to Necessity: The Emergence of Shrunken Pore Syndrome

### 1.1 Early observations in renal filtration research

The idea that the permeability of the glomerulus is not determined by a single factor, such as a single pore size, was not immediately apparent. Early clinical observations and education in renal function tests emphasized the role of the nephron in the filtration process (historical clinical reviews).The research on the size- and charge-selective properties of the glomerular filtration barrier using uncharged and negatively charged probes (Ficoll, Ficoll sulfate), as well as modelling, provided the background to explain the behavior of different probes in the glomerular filtration barrier, such as creatinine, cystatin C, and others.[1]

The research on the biology of podocytes and the structure of the slit diaphragm provided the background to explain the behavior of the filtration barrier in relation to changes in the proteins of the podocytes, as well as the role of the cytoskeleton in these cells, providing the background for the syndrome of selective hypofiltration of certain sizes.[2]

### 1.2 Why SPS was overlooked in clinical nephrology

Clinical tradition and reliance on creatinine (and hence eGFR) and other classical tests of renal function meant that selective changes in permeability to molecules of different sizes could be overlooked, particularly if only measuring creatinine. Classical texts and reviews traditionally taught about classical tests of renal function.

Experimental and theoretical studies (Ficoll sieving, fiber matrix models) highlighted that size, rather than charge, was more important for glomerular filtration, which suggested that subtle changes in the architecture of the glomerular basement membrane could selectively affect proteins of a particular size range, without causing obvious proteinuria or creatinine elevations. Recent podocyte and slit diaphragm molecular studies illustrate the potential for subtle changes at the cellular level (for example, slit diaphragm proteins) to lead to selective changes in permeability, which were not traditionally assessed and therefore could be overlooked.

**1.3 Turning point:** the scientific interest in SPS was sparked by the systematic comparison of the filtration markers of different sizes and the recognition of the "selective glomerular hypofiltration" pattern. This systematic comparison of the filtration markers of different sizes was a turning point in the scientific interest in SPS. This was a direct continuation of the earlier models of size selectivity using Ficoll or other size probes. The willingness of the wider nephrology community to question established dogmas (pore size vs. electrical field strength debates) in the years around 2015 and thereafter created a space for the recognition of the syndromes caused by the changes in selective permeability rather than the global reduction of the GFR.[3]

Investigations into the podocyte cell structure provided a mechanistic rationale for the potential reduction of the effective pore size or the slit diaphragm function (e.g., by the changes in the expression of the slit diaphragm proteins or the podocyte cytoskeleton).

## 2 - The Glomerular Filter Revisited: More Than Just a Sieve

### 2.1 Anatomy of the Glomerular Filtration Barrier

The Glomerular Filtration Barrier (GFB) consists of three main layers. These include the fenestrated endothelium of the glomerular capillaries, the glomerular basement membrane (GBM), and the epithelial cell layer of the podocytes with the slit diaphragm. The podocytes, along with the slit diaphragm, have a major role in the filtration barrier. Any changes in the podocyte proteins or cytoskeleton can significantly impact the filtration barrier. Studies have also shown that both the endothelial and epithelial cell layers of the glomerular filtration barrier have a major role in size and charge selectivity. The GBM also has a role in the filtration barrier.

### 2.2 Role of Pore Size in Selective Filtration

The size of the macromolecule, also related to hydrodynamic radius, and molecular conformation are major factors in the passage of macromolecules through the GFB. The use of neutral and anionic macromolecules, such as Ficoll and Ficoll-sulfate, in hydrodynamic/pore models demonstrates that the distribution of pore sizes can explain the sieving of macromolecules of different sizes more effectively than a model of a uniform sieve or purely electrostatic model. The distribution of pore sizes limits the filtration of macromolecules of specific sizes. Therefore, even small reductions in the effective pore radius or in the population of larger pores can disproportionately limit the filtration of mid-size proteins, with small solutes such as creatinine and inulin-equivalents being relatively unaffected—a phenomenon related to selective hypofiltration and shrunken pore syndrome. Same up.

### 2.3 Dynamic nature of glomerular permeability

It has been established that the GFB is a dynamic structure, and changes in the slit-diaphragm proteins and podocyte cytoskeleton have been demonstrated to be influenced by a variety of signals and agents, including mTOR signaling, pharmacological agents, and systemic diseases. Recent experimental studies have demonstrated that changes in the mTOR and rapamycin pathways influence the slit-diaphragm proteins and podocyte cytoskeleton, thereby altering permeability and selectivity.

From the theoretical and experimental studies of transport through the GFB, it has been established that electrical charges have only a moderate influence on permeability compared to size and conformation; therefore, changes in the structural geometry of the GFB have a major impact on selectivity.[4]

Clinical and experimental studies of the effects of diseases, such as diabetic glomerulopathy, and the neonatal excretion of low-molecular-weight proteins and the effects of drug treatment have demonstrated changes in permeability and the effects of these changes on the selectivity of the GFB.[5]

## 3 -The Science of “Shrunken Pores”: Structural and Functional Changes

### 3.1 The endothelial glycocalyx

Normal structure and function

The endothelial glycocalyx (EG) is a carbohydrate-rich layer on the luminal surface of endothelial cells, which consists of cell-bound proteoglycans (e.g., heparan sulfate proteoglycans), glycosaminoglycans, and sialoproteins. The EG serves as a barrier to vascular permeability, an antithrombotic surface, and a modulator of shear sensing and leukocyte adhesion, and it contributes to sodium and interstitial fluid volume homeostasis. The EG layer is thin in pulmonary microvasculature, making it particularly susceptible to injury.[6] Mechanism of alteration.

Inflammation, e.g., sepsis/cytokine storm and severe viral illness like COVID-19/MIS-C, directly damages the EG. The mechanism by which this occurs includes the action of proteolytic enzymes and reactive oxygen species on the EG and leukocyte adhesion to the endothelial surface, which damages the EG. The action of inflammatory mediators on the EG causes shedding of proteoglycans and glycosaminoglycans, e.g., heparan

sulphate. The EG injury occurs locally and at a distance, and the EG is present throughout the vasculature.

Functional consequences relevant to "shrunken pores"
Removal of the glycocalyx layer increases endothelial permeability and enhances the likelihood of trans vascular fluid shifts (capillary leak syndrome), resulting in interstitial edema and reduced intravascular volume despite fluid overload. Additionally, the degradation of EG leads to the loss of antithrombotic activity and increases leukocyte and platelet adhesion, which can lead to coagulopathy and microvascular occlusion, resulting in a reduction of the effective pore size (i.e., "shrunken pores") due to the reduced filtration surface. Pulmonary micro vessels are especially prone to edema formation due to the thin layer of EG. This explains the involvement of the lungs in systemic inflammatory syndromes and SARS-CoV-2-related endothelial dysfunction.

### 3.2 Basement membrane remodeling

Normal structure and function
The basement membrane (BM), which is the extracellular matrix layer immediately beneath the endothelial cells and the podocytes of the glomerulus, is important for the selectivity of the filtration barrier and for the mechanical strength of the vessel wall. In the kidney, the GBM is a key selective barrier for the filtration of blood components. In the vasculature, the BM plays a key role in the regulation of the blood-tissue barrier function.[7]

**Mechanism of alteration**
Remodeling of the BM is a key process in the alteration of the barrier function due to various pathological conditions such as ischemia/reperfusion injury, chronic hypertension, inflammation, viral infections, and others. Ischemia can lead to the loss of glycosylated proteins from the lumen side of the BM. In reperfusion injury, some components of the BM may return to the vessel wall, but the flow-sensitive proteins may still be lost.

**Functional consequences relevant to "shrunken pores"**
BM changes affect the size, charge, and mechanical properties of pores. Acute dissolution or fragmentation may increase permeability, causing leaky capillaries, while chronic thickening or changes in BM composition may decrease the radius of pores or affect the sieving properties, resulting in reduced filtration of larger molecules without proportional changes in the clearance of smaller molecules, a pattern observed in the "shrunken pores" phenomenon. BM changes in the BBB and lungs may affect edema and breakdown in response to stroke or lung insults, and changes in the glomerular basement membrane may affect the filtration properties and result in proteinuria or paradoxical filtration.

### 3.3 Podocyte and slit diaphragm dysfunction

**Normal structure and function**
The podocytes are specialized epithelial cells of the glomerular filtration barrier. The podocyte cell bodies interdigitate to produce interdigitating foot processes that are connected by the slit diaphragm, which is composed of a complex of proteins. The slit diaphragm is composed of proteins that provide a final size/charge selective barrier to large proteins. The podocyte glycocalyx, which is composed of heparan sulfate proteoglycans and slit diaphragm proteins (such as nephrin and podocin) are critical for normal podocyte function.

**Mechanisms of alteration**
Aging, inflammatory responses, metabolic and hemodynamic stresses, and injury (toxins, ischemia, infection) cause podocyte dysfunction. Aging causes structural alterations of heparan sulfate, which is a component of the podocyte glycocalyx and GBM. The alterations of heparan sulfate impair endothelial progenitor cell migration and signaling. Similarly, alterations of podocyte HS and slit diaphragm proteins impair podocyte function. The alterations cause changes to the slit diaphragm that reduce the pore size of the slit diaphragm.

**Functional consequences relevant to "shrunken pores"**
The alterations of podocyte/slit diaphragm function reduce the pore size of the slit diaphragm, which causes alterations of sieving. The small molecules pass normally, but medium- to large-sized molecules are restricted. Podocyte injury also predisposes to progressive glomerular damage and proteinuria, and changes in heparan sulfate composition of the glycocalyx/GBM further modulate filtration selectivity and repair processes.

## 4 -Biomarkers Under Distortion: Cystatin C vs. Creatinine

### 4.1 Why Creatinine Can "Underestimate" SPS

The reason why creatinine may "underestimate" SPS is because it is a small molecule with a molecular weight of 113 Da, which is freely filtered at the glomeruli and variably secreted by the tubules. Creatinine is much smaller than the mid-sized proteins retained in SPS and therefore reflects the clearance of small molecules and the gross GFR rather than the clearance of mid-sized proteins.[8]

Tubular secretion and non-GFR factors such as muscle mass and diet, and drug effects on creatinine metabolism and clearance, may obscure changes in glomerular filtration and therefore may not reflect changes in the glomerular filtration rate of mid-sized proteins.To state it another way, SPS is a disturbance in the size selectivity of the glomerular filtration barrier that affects the clearance of mid-sized proteins but not small molecules. Creatinine clearance does not reflect the clearance of

mid-sized proteins because it is a small molecule and therefore cannot reflect SPS.

**4.2 Cystatin C is a more sensitive marker for SPS**

Cystatin C is a low-molecular-weight protein (molecular weight of 13 kDa) that is cleared by the kidneys at a constant rate and is minimally affected by tubular secretion. Most importantly, cystatin C has a molecular weight within the range of 5 to 30 kDa, which is the most affected in SPS; therefore, the level of cystatin C increases in the blood when the filtration of mid-sized proteins is reduced.[9]

Since the clearance of cystatin C is related to the glomerular filtration of mid-sized proteins affected in SPS, cystatin C-based eGFR (eGFRcys) reflects the selective hypofiltration of mid-sized proteins more accurately than the eGFR using the clearance of creatinine (eGFRcrea). In SPS, eGFRcys is reduced compared to eGFRcrea; therefore, the low eGFRcys/eGFRcrea ratio is used as a diagnostic criterion. Clinical studies have demonstrated the ability of cystatin C (with or without creatinine) to detect SPS and to predict prognosis, while the use of creatinine alone does not detect SPS and does not allow prognosis.

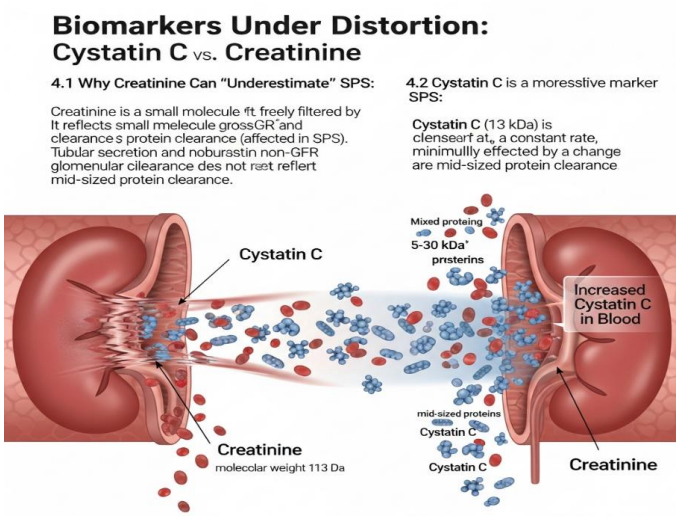
**4.3 The clinical significance of discordant eGFR (low eGFRcys in comparison to eGFRcrea)**

Low eGFRcys/eGFRcrea ratio (typically less than 0.6-0.7, although specific cut-offs vary slightly between studies) indicates SPS, which is linked to significantly increased morbidity and mortality in a range of populations (general population, cardiac surgery, heart failure, COVID-19 ICU patients, diabetes, pregnancy/preeclampsia risk) independently of other measures of kidney function.[10]

Studies have indicated that SPS can occur even with normal measured GFR (mGFR) and in the absence of albuminuria. Thus, relying on the eGFRcrea does not capture a clinically important form of kidney damage with prognostic significance.

The clinical implications of identifying discordant eGFRs with low eGFRcys in comparison to eGFRcrea:
Risk stratification: SPS can be used to stratify patients at increased risk of cardiovascular events, kidney disease progression, and all-cause mortality beyond CKD staging. SPS has been used to predict adverse outcomes in cardiac surgery, percutaneous coronary intervention, heart failure, and in COVID-19 patients in the ICU.[11]

Diagnostic expansion: The identification of SPS/SGHS supports the use of cystatin C in the initial investigation of kidney damage.




**5 -Diagnostic Dilemmas: Why SPS Slips Through the Cracks**

**5.1 What routine kidney tests measure and their limits**

Serum Creatinine and Creatinine-based eGFR: These are the most commonly used kidney filtration rate tests. Creatinine levels measure the rate of filtration of the kidneys but are affected by muscle mass, age, sex, and diet.[12]

Cystatin C and Cystatin C-based eGFR: This test is less affected by muscle mass and is a better predictor of outcomes in certain patients. Combining the Creatinine and Cystatin C-based equations for eGFR is more accurate than the Creatinine-based equation alone. Spot Urine Test for UACR and Urinalysis: This test is useful for identifying albuminuric forms of glomerular disease but is not useful for identifying non-albuminuric forms of glomerular or tubular/interstitial kidney disease or for identifying changes in the filtration rate for certain pore sizes or selective filtration.[13]

Why is it important for the diagnosis of SPS?
SPS is a condition in which the ratio of eGFRcystatinC to eGFRcreatinine is low. This is a selective filtration defect that is not apparent unless both values are measured. Creatinine is routinely used for the measurement of eGFR.

**5.2 The mechanisms by which routine testing fails to detect SPS (detailed)**
**A.** Compensatory whole-kidney filtration circumvents selective pore defects
Creatinine is an estimate of global GFR. If glomerular filtration is selectively impaired for medium-sized molecules (like cystatin C, which is 13 kDa), but total small molecule filtration and GFR are within normal limits, then serum creatinine and creatinine-based eGFR will be within normal limits, masking SPS. This is a fundamental limitation of creatinine-based testing for SPS detection.

**B.** non-GFR factors that affect markers make it difficult to interpret
Serum creatinine is also dependent on muscle mass. Cystatin C is less dependent on muscle mass but is influenced by inflammatory states, thyroid function, and corticosteroids. Without routine testing of both markers, non-GFR factors can affect the interpretation of each marker individually.

**C.** Routine testing rarely involves a comparison of eGFRcreat and eGFRcyst
The routine testing of creatinine-based eGFR is more common than cystatin C-based eGFR. SPS requires routine testing of both eGFRcreat and eGFRcyst and then comparing them. SPS is often missed because routine testing of eGFRcreat is performed without routine testing of eGFRcyst.

**D.** Limited availability and standardization of heterogeneous assays
Although creatinine tests have achieved a level of standardization (enhancing eGFR accuracy with MDRD/CKD-EPI formulas), cystatin C tests and approaches to interpreting results have not achieved the same level of standardization, which can impede detection of conditions associated with discordant results.

**E.** Single-point assessment and lack of trend evaluation
Routine clinical care often relies on isolated laboratory values instead of comparative assessments of serial marker levels. SPS may be evident only in the presence of persistent or developing discordance between markers; isolated normal values for creatinine can be misleading.

**5.3--How SPS is misclassified as normal renal function**
A patient with normal serum creatinine and hence normal creatinine-based eGFR would be classified as having "normal renal function." However, this patient would also have an elevated cystatin C level and low eGFRcyst, which are the defining features of SPS. This misclassification of patients with SPS occurs because the routine test used (serum creatinine) fails to detect the selective impairment of filtration of mid-sized molecules, which is characteristic of SPS. The clinical implication of this misclassification is that patients with SPS can have "normal GFR" but still be at an increased risk (for example, patients with SPS have higher mortality rates, even though they are classified as having "normal renal function").

**5.4- Lack of standardized diagnostic criteria and implementation issues**
**A.** Diagnostic definition variability
The operationally defined SPS in literature has been based on the criteria of the eGFRcyst/eGFRcreat ratio, with specific thresholds being less than 0.6. However, these criteria vary in clinical practice. No universally accepted, guideline-supported diagnostic criteria have been incorporated in clinical practice.

**B.** Limited guideline/institutional adoption of routine cystatin C measurement
Although the clinical utility of cystatin C has been proven in literature, with better outcome prediction in most patient groups and better accuracy in combination with creatinine, the adoption of routine cystatin C measurement in clinical practice is lacking. This is possibly because of the additional cost of incorporating cystatin C in clinical practice. Furthermore, no specific guidelines or institutional recommendations have been implemented in clinical practice regarding the routine measurement of cystatin C or the mandatory use of the combined eGFRcreat + cystatin C in the diagnosis of SPS.

**C.** Insufficient standardization of assay methods and reporting practices
Although the assays for creatinine have been standardized with the MDRD re-expression of the formula for standardized creatinine, the same cannot be said for cystatin C. The assays for cystatin C have not been standardized in clinical practice.

**6 --Molecular Consequences: Accumulation of Middle Molecules**
The condition of SPS, as well as its broader equivalent of SGHS, can be characterized as having a relatively low eGFRcystatinC in comparison to eGFRcreatinine. In other words, SPS can be defined as having a low ratio of eGFRcystatinC to eGFRcreatinine. This means that there is a decreased rate of glomerular filtration of middle-sized molecules, such as cystatin C. The rate of filtration of small molecules such as creatinine (~113 Da) is relatively preserved. The clinical studies have established SPS as being characterized by certain thresholds, such as eGFRcystatinC being less than 60 to 70% of eGFRcreatinine.[14]

**6.1 Impaired clearance of inflammatory and other middle molecules**

Mechanism: If the pores of the glomeruli or the effective permeability for mid-sized molecules is reduced, then the plasma concentrations of low molecular weight proteins and peptides, which include many inflammatory mediators, adipokines, and other active middle molecules, increase because of reduced clearance of these molecules, with small molecule clearance being relatively preserved.

Evidence: Proteomic studies in HF patients with SPS revealed that SPS correlated with increased plasma concentrations of proteins related to atherosclerosis and cell proliferation, indicating that impaired filtration of pathologic middle molecules occurs in SPS. Several studies in patients with kidney disease have revealed that SPS correlates with disease progression and with increased concentrations of middle molecules that are linked with poor outcomes.[15]

**6.2 Systemic effects of retained middle molecules (toxin retention)**

Retention of biologically active middle molecules can lead to systemic inflammatory response syndrome, endothelial dysfunction, prothrombotic states, and metabolic disorders. Studies from cohorts with SPS have found an association between SPS and poor clinical outcomes, including increased mortality, cardiovascular events, and risk of acute kidney iStep.

**6.3 Impact on Immune System**

The accumulated middle molecules include cytokines, chemokines, and other immunomodulatory proteins. The clearance of these proteins occurs normally through glomerular filtration. The decreased clearance of these proteins may cause chronic low-grade systemic inflammation, leading to changes in the immune system.[16]

**Supporting Findings**

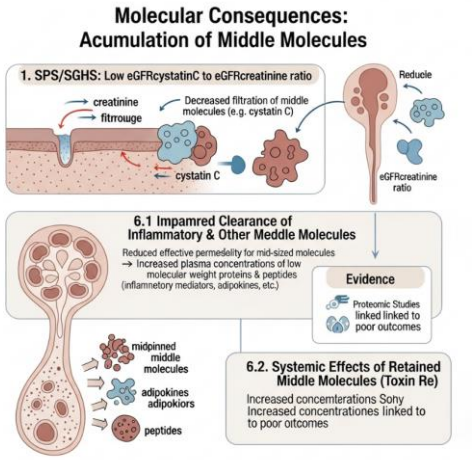
Proteomics studies have identified proteins in HF patients with SPS. The identified proteins are involved in inflammatory responses and atherosclerosis. The findings suggest that there are changes in the inflammatory environment in SPS patients. The findings of the observational studies on SPS patients, in whom the disease condition increases the risk of adverse outcomes if they are exposed to an inflammatory environment (for example, severe COVID-19 infection), support the concept that there are changes in the inflammatory environment in SPS patients.

**Clinical Implications**

The chronic presence of pro-inflammatory middle molecules in the body may cause chronic systemic inflammatory responses. The chronic systemic inflammatory responses may impair the immune system, leading to adverse outcomes.

**6.4 Impact on the vascular and endothelial systems**

- Middle molecules that remain in the SPS include mediators of endothelial function, nitric oxide metabolism, and vascular tone.
- Pregnancy study example: SPS in the first trimester of pregnancy predicted markers of abnormal NO metabolism, e.g., abnormal Arg/ADMA ratio, and SPS was associated with the subsequent occurrence of preeclampsia, relating to the hypofiltration and retention of middle molecules that affect endothelial function and vascular tone.
- Heart failure and cardiovascular study examples: SPS is associated with proteins involved in atherosclerosis and is associated with increased cardiovascular events and mortality, relating to endothelial dysfunction and changes in the cardiovascular system due to the retention of middle molecules.
- Inference of the pathophysiological processes: The retention of middle molecules active on endothelial function leads to proinflammatory, prooxidative, and prothrombotic states, and reduced nitric oxide bioavailability, resulting in vascular diseases and poor patient outcomes.



**7 - SPS and Systemic Diseases: A Dangerous Connection**

Core Pathophysiology of SPS:SPS stands for a selective reduction in glomerular filtration of middle-sized molecules, roughly ranging from 1 to 30 kDa, with cystatin C-based eGFR being significantly decreased compared to creatinine-based eGFR, i.e., eGFRcys/eGFRcr < 0.6 to 0.7. This leads to the accumulation of a variety of low-molecular-weight proteins and peptides, including inflammatory mediators, adipokines, osteopontin, and proteins involved in atherosclerosis. These proteins are normally partly eliminated by the renal system.

Consequence: The accumulation of these middle-sized molecules can trigger systemic inflammation, endothelial dysfunction, and pro-atherogenic signaling and remodeling in various organs, as seen in the pathophysiology of cardiovascular disease, inflammaging, and maybe even in the pathogenesis of neurodegenerative disorders.

**7.1` Relationship with cardiovascular disease (evidence + mechanism)**

Proteomic and biomarker studies: Several studies have demonstrated that SPS is associated with increased levels of proteins that are involved in atherosclerosis, cell proliferation, and cardiovascular disease. In heart failure patient cohorts, SPS was associated with increased levels of proteins involved in cardiovascular disease. In a proteomic study, Almén et al. demonstrated that SPS was associated with increased levels of proteins involved in atherosclerosis. This provided a potential mechanistic link to increased cardiovascular disease in SPS patients.

Clinical outcome studies: Observational studies have demonstrated that in patient cohorts, a decreased eGFRcys/eGFRcr ratio (i.e., SPS) predicts adverse clinical outcomes.

The decreased eGFRcys/eGFRcr ratio (i.e., SPS) in patient cohorts is associated with: Myocardial infarction in women in a population study.

Worse cardiac function in heart failure patient cohorts, including decreased right ventricular systolic function. Increased renal failure hospitalization in heart failure patient cohorts. Osteopontin levels are increased in SPS patient cohorts. In acute heart failure patient cohorts, osteopontin levels in SPS are associated with increased renal failure hospitalization. The decreased eGFRcys/eGFRcr ratio (i.e., SPS) in patient cohorts is associated with increased cardiovascular morbidity and mortality. The association of SPS with increased cardiovascular morbidity and mortality.

**7.2 Link with chronic inflammation and aging (inflammaging)**

Protein retention and systemic inflammation: SPS leads to the retention of inflammatory mediators and other biologically active middle-sized proteins. The proteomic signals in SPS cohorts show inflammation-related proteins, supporting the presence of a chronic proinflammatory systemic milieu. Epidemiologic signals consistent with aging-related risk: SPS is common in middle-aged, otherwise healthy individuals. It has consistently been associated with increased all-cause mortality and morbidity in population and disease cohorts. This suggests that SPS may contribute to or be a marker of accelerated biological aging/inflammaging and multimorbidity. Clinical consequences: The chronic low-grade inflammation caused by the retention of middle-sized proteins can accelerate vascular aging, frailty, bone-mineral metabolism disorders (e.g., in rheumatic disease cohorts, SPS was associated with changes in PTH levels and decreased BMD), as well as other pathologies associated with aging.

**7.3 Possible association with neurodegenerative diseases (rationale and indirect evidence)**

Biological plausibility: There is a plausible biological basis for an association of neurodegenerative diseases (such as Alzheimer's disease) with the accumulation of pathogenic proteins and neuroinflammatory responses. Similarly, systemic accumulation of middle molecules that affect systemic inflammatory responses, atherosclerosis, and proteostasis could be associated with neurodegenerative diseases through systemic inflammatory responses, cerebrovascular dysfunction, and systemic proteostasis.

Evidence from Contexts: There is no direct evidence from the provided Contexts proving that SPS is associated with certain neurodegenerative diseases. However, several Contexts report that SPS causes systemic accumulation of proteins associated with atherosclerosis and inflammatory responses, which is associated with increased mortality and adverse outcomes. These pathways are similar to those of Alzheimer's disease and other dementia.

**8 -Risk Factors and Pathophysiology**

Why Pores Shrink

SPS is operationally defined by a relative decrease in the filtration rate of mid-sized molecules (e.g., cystatin C, ~13 kDa) relative to small molecules (e.g., creatinine). The ratio of eGFRcys to eGFRcr is decreased (usually < 0.6-0.7). This mechanistically suggests a change in the filtration selectivity of the kidney's glomerular filtration apparatus, which is consistent with a decrease in the size of the pores in the filtration apparatus.[17]

SPS is diagnosed by the measurement of cystatin C and creatinine levels and the recognition of the discordance in the eGFR values for these two compounds. It has been reported in a variety of populations, including the elderly, patients with heart failure, patients with COVID-19 infection, and patients with kidney disease.

**8.1 Aging-related renal changes that favor pore shrinkage Mechanisms**

Kidney aging involves structural and functional changes, including glomerulosclerosis, decreased number of nephrons, thickening of the GBM, and changes to the endothelial and epithelial layers. These changes can result in the selective restriction of mid-sized molecules, with smaller molecules continuing to pass through with little restriction. Evidence from Contexts. Epidemiological studies of large cohorts, including elderly patients, indicate a high prevalence of low eGFRcys/eGFRcr ratios, which is associated with increased mortality. This supports the view that filtration selectivity is an important aspect of kidney function. Studies of young patients, including those with pediatric conditions, indicate that the SPS, or the concept of the eGFRcys/eGFRcr ratio, can be applied to all ages, supporting the view that filtration pore size/permeability is an important physiological parameter that can change with age and disease.

Clinical implication: Kidney aging can result in selective filtration restriction, or SPS, even with normal creatinine levels, implying that patients with normal creatinine levels can still have selective filtration restriction, which can be identified by a low eGFRcys/eGFRcr ratio.

**8.2 Fibrosis and microvascular damage as final common pathways Mechanisms**

Prolonged injury and inflammation lead to interstitial fibrosis, glomerulosclerosis, and microvascular rarefaction. Fibrosis and scarring alter the glomerular structure, compress the capillary tufts, and reduce the surface area and GBM structure, leading to decreased sieving of middle molecules. Damage to the microvasculature (loss and dysfunction of capillaries) affects the filtration surface area and can alter the pore size, leading to increased selective hypofiltration.

Evidence from Contexts: SPS is associated with poor prognosis in patients with heart failure and renal outcomes, such as SPS predicting eGFR decline in women with kidney disease, consistent with progressive structural injury to the kidney and fibrosis.

Clinical implication: It is difficult to correct the pore size reduction and resulting hypofiltration once fibrosis and microvascular damage have occurred, and it is important to recognize the presence of SPS (with combined cystatin C and creatinine measurements) and interrupt the pathological process (inflammation, hypertension, diabetes control).

**9 --Clinical Implications**

Why SPS Matters in Patient Care

In the context of the articles provided, SPS stands for nonclassical exposures or comorbid pathophysiologic stresses (such as those illustrated throughout the Contexts: sleep-disordered breathing/hypoxic burden, chronic inflammation/infection, metabolic/hepatic disease such as NAFLD, environmental exposures such as air pollution/smog, uremic/CKD-related toxins and metabolic derangements, hyperthermia/heat stress, dietary exposures such as ultraprocessed foods, hypertension of pregnancy, and frailty/visceral obesity), which drive systemic inflammation, oxidative stress, and endothelial or neurohormonal dysfunction, which act to prolong and augment classical cardiovascular and renal risk pathways.[18]

**9.1- Increased cardiovascular morbidity**

Explanation from Contexts: Patients with NAFLD have a "substantially increased risk of hypertension, coronary heart disease, cardiomyopathy, and cardiac arrhythmias."

OSA (hypoxic burden): "OSA is associated with a variety of cardiovascular disorders including hypertension, stroke, heart failure, coronary heart disease, and atrial fibrillation. It is associated with worsening outcomes in patients with established CVD."

Air pollution/smog: "Air pollution/smog is associated with hypertensive and cardiovascular morbidity."

The CKM paradigm "recognizes that the mechanisms of inflammatory/oxidative stress and neurohormonal activation provide a common link between metabolic/kidney disorders and cardiovascular disease."[19]

Clinical takeaway: Identification and management of SPS (NAFLD, OSA/hypoxic burden, air-pollution exposure, systemic inflammatory states) should be included in the evaluation and management of cardiovascular risk and secondary cardiovascular prevention because they "substantially add" to cardiovascular morbidity.

**9.2- Higher risk of kidney disease progression**

Explanation from Contexts: The cardiovascular-kidney-metabolic syndrome hypothesis emphasizes the common pathways of inflammation, oxidative stress, and activation of the RAAS that lead to the progression of both cardiovascular events and kidney disease. Therefore, the progression of kidney disease is accelerated by SPS that cause systemic inflammation/oxidative stress. Peripheral arterial disease is more common and severe in patients with CKD. Disturbances associated with kidney disease, such as mineral disorders and systemic inflammation, worsen the severity of peripheral arterial disease. Metabolic stress associated with systemic disorders such as NAFLD, obesity, and malnutrition is associated with cardiovascular and kidney disease.

Clinical takeaway: SPS that cause systemic inflammation, hemodynamic stress, or metabolic toxicity (e.g., uncontrolled OSA, NAFLD/metabolic syndrome, environmental toxins, volume/heat stress) should be acknowledged and addressed to slow the progression of kidney disease and reduce the associated morbidity.

**9.3 - Importance in high-risk populations**

Which of the following populations would be of particular interest to study (from Contexts):

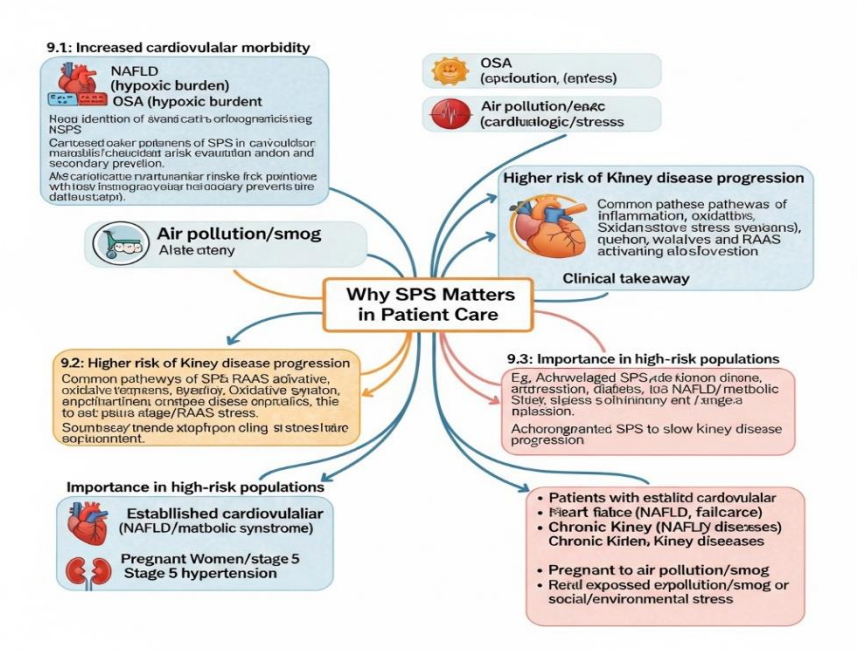
Patients with established cardiovascular diseases or heart failure – OSA is very prevalent and adversely impacts the prognosis of these patients.

Patients with metabolic syndromes such as NAFLD, obesity, or diabetes – these patients have a higher cardiovascular and renal risk profile.

Patients suffering from chronic kidney diseases or stage 5 kidney diseases – PAD, along with the proinflammatory environment, increases the cardiovascular events and the susceptibility to other stressors.

Pregnant women suffering from hypertension – these patients have a poor prognosis and warrant long-term follow-up.[20]

Patients suffering from exposure to air pollution/smog or social and environmental stress – these patients have a higher prevalence of hypertension and cardiovascular diseases and warrant mitigation strategies.




**10 - Future Perspectives: Redefining the Assessment of Kidney Function**

**10.1 The need to develop new diagnostic guidelines for kidney function assessment**

The limitations of using creatinine-based eGFR in the assessment of kidney function cannot be overemphasized, and the Contexts underscore the importance of diagnostic accuracy and the development of standardized diagnostic processes across different medical fields and populations—reiterating the need to develop conditional diagnostic guidelines to accompany the use of commonly employed diagnostic tests such as creatinine.[21]

The Contexts underscore the increasing importance of the kidney in the context of the cardiovascular and metabolic systems and the increasing appreciation that the assessment of kidney function is integral to the assessment and management of cardiovascular and drug-related processes. The limitations of point-of-care and diagnostic tests underscore the relevance and importance of developing diagnostic guidelines that address the limitations and the need to develop standardized diagnostic processes and the use of adjunct diagnostic tests.[22]

The development and assessment of direct methods for the assessment of kidney function using advanced imaging and tracer methods are being developed and employed in the broader context of diagnostic fields; therefore, it is important to develop diagnostic guidelines that address the role and utility.

**10.2 Role of cystatin C in routine practice**

Rationale: The Contexts identify groups and circumstances where a standard test result may be misleading (body composition, frailty, extreme age, malnutrition), and recommend condition-specific diagnostic accuracy. It follows that a filtration marker less affected by muscle mass (cystatin C) can be used when creatinine is likely to be misleading.

Practical recommendations (conditional use, inferred from the Contexts' emphasis on specific guideline recommendations and test standardization):

Use cystatin C (or combined creatinine-cystatin C methods) as a secondary test for patients with discordant

results between creatinine-based eGFR and clinical circumstances (frail elderly, major weight or muscle mass change, eating disorders, extreme body habitus) or when GFR results are critical for management decisions. Apply cystatin C reflex testing in cases where misclassification has major management implications (geriatrics, pre-contrast imaging, specialty clinics with high rates of comorbidity), as recommended by the Contexts for specific diagnostic standards and guideline recommendations. Apply a combination of markers, rather than substituting one marker for another: the Contexts recommend enhanced diagnostic accuracy and risk stratification through multi-marker methods.

**10.3 Research gaps and future directions**

Need for outcome-oriented evidence: The Contexts underscore the guideline panel and research community roles of identifying gaps and developing the necessary evidence for practice change. For cystatin C, studies are needed prospectively (or trials) to demonstrate that cystatin C-based decisions lead to improved patient-oriented outcomes (CKD progression, cardiovascular events, hospitalizations, safe drug dosing) compared with creatinine-based strategies.

Comparative effectiveness and implementation studies: We need studies to evaluate the extent to which cystatin C reclassifies patients with CKD, whether this reclassification results in management change, and whether the change is cost-effective and equitable. The Contexts' sections on guideline development and health policy implications underscore the need for these studies before widespread implementation.

Multimarker and multimodal diagnostic algorithms: The Contexts indicate the benefits of combining markers and standardized reporting/checklists, as exemplified by CLAIM for imaging AI, or STROBE for improvement of reporting. We need to do the same for kidney disease, with validation of the panel (creatinine, cystatin C, albuminuria, and imaging or tracer GFR as needed) and clear, actionable thresholds for clinicians.

Standardization and Accessibility: Standardization and access issues, such as those raised with respect to the implementation of the recommendations in the context of the guideline, must be addressed prior to the implementation of the recommendations regarding cystatin C.

Special Populations and Pediatrics: Special population studies, such as the elderly with frailty, the malnourished, pregnancy and postpartum, and pediatric populations, are necessary to determine the changes in thresholds and management with the use of cystatin C, as emphasized in the Contexts sections regarding the development of guidelines for special populations.

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