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Uremic toxins and their classification: mechanisms of oral mucosal damage in chronic kidney disease

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Abstract: Uremic toxins, which accumulate due to impaired renal function, have significant systemic effects, including detrimental impacts on the oral mucosa. These toxins are classified into small water-soluble molecules, protein-bound toxins, and middle molecules, each exerting unique pathological effects. This review explores the mechanisms through which these toxins contribute to epithelial dysfunction, oxidative stress, and inflammatory responses in patients with chronic kidney disease (CKD). Understanding these interactions is essential for developing targeted therapeutic strategies to mitigate their impact on oral health.

Modern research highlights the importance of a comprehensive approach that considers both morphological changes and immune responses, ultimately allowing physicians to diagnose infertility more accurately and select effective treatment strategies. Therefore, the use of hysteroscopy and immunological markers in reproductive medicine is becoming an integral part of comprehensive examinations for women experiencing infertility issues.

Keywords: Uremic toxins, chronic kidney disease, hemodialysis, oral mucosa, inflammation, oxidative stress, cytokines, periodontal disease.

Introduction: Uremic toxins are metabolites that accumulate in the blood due to impaired renal clearance, contributing to systemic complications, including oral mucosal dysfunction (Vanholder et al., 2011). These toxins are broadly classified into three categories: small water-soluble molecules, protein-bound toxins, and middle molecules, each differing in size, solubility, and biological impact (Duranton et al., 2012).

Small Water-Soluble Molecules

Small uremic toxins, typically less than 500 Da, include compounds such as urea, creatinine, and guanidines (Vanholder et al., 2003). Although urea itself is not highly toxic, its hydrolysis in the oral cavity by bacterial ureases leads to ammonia production, which increases oral pH and predisposes patients to mucosal irritation and ulceration (Santos et al., 2016). Furthermore, guanidino compounds have been shown to impair immune cell function, reducing the ability of the oral mucosa to combat infections (Oberg et al., 2015).

Protein-Bound Toxins

Protein-bound uremic toxins, such as indoxyl sulfate (IS), p-cresyl sulfate (PCS), and advanced glycation end products (AGEs), exhibit significant proinflammatory and oxidative effects, particularly in epithelial and endothelial tissues (Dou et al., 2018). These toxins bind to serum albumin, limiting their clearance through dialysis and prolonging their biological impact (Vanholder et al., 2011).

- Indoxyl sulfate (IS): Derived from tryptophan metabolism, IS has been shown to increase oxidative stress and inflammatory cytokine production (IL-6, TNF-α) in epithelial cells, contributing to mucosal atrophy and delayed wound healing (Lekawanvijit & Krum, 2015).
- p-Cresyl sulfate (PCS): This toxin, a byproduct

of phenylalanine and tyrosine metabolism, enhances endothelial dysfunction and oxidative stress, leading to increased susceptibility to periodontitis and mucosal inflammation (Brito et al., 2016).

- Advanced glycation end products (AGEs): These compounds accumulate in the oral mucosa, impairing collagen turnover and reducing epithelial integrity, which exacerbates tissue fragility and inflammation (Witko-Sarsat et al., 2004).

Middle Molecules

Middle molecules (500–12,000 Da) include β2-microglobulin, complement factors, and inflammatory cytokines, which accumulate in CKD patients and contribute to chronic low-grade inflammation (Vanholder et al., 2011). Studies indicate that elevated levels of β2-microglobulin in saliva correlate with oral mucosal damage, increased bacterial colonization, and a higher risk of oral infections (Stenvinkel et al., 2013).

Additionally, the retention of proinflammatory cytokines such as IL-1β, IL-6, and TNF-α in the systemic circulation directly influences the inflammatory status of the oral mucosa, leading to increased vascular permeability, fibroblast dysfunction, and delayed tissue repair (Carrero et al., 2008).

Impact of Uremic Toxins on the Oral Mucosa

The persistent exposure of oral tissues to uremic toxins results in epithelial dysfunction, microbial imbalance, and exaggerated inflammatory responses, predisposing CKD patients to a range of oral pathologies, including gingivitis, periodontitis, xerostomia, and uremic stomatitis (Proctor et al., 2005). Understanding the classification and mechanisms of these toxins provides critical insights into the development of targeted therapeutic strategies to mitigate their detrimental effects on oral health.

Table 1. Uremic Toxins and Their Effects on the Oral Mucosa

Toxin Type	Examples	Source/Metabolism	Main Effects on the Oral Mucosa
Small Water-Soluble Molecules	Urea, Creatinine, Guanidines	Protein metabolism (renal excretion impaired)	Ammonia production, increased pH, mucosal irritation
Protein-Bound Toxins	Indoxyl sulfate (IS)	Tryptophan metabolism (gut microbiota)	Oxidative stress, cytokine production, delayed healing
	p-Cresyl sulfate (PCS)	Phenylalanine & Tyrosine metabolism	Endothelial dysfunction, oxidative stress, inflammation
	Advanced Glycation End Products (AGEs)	Protein glycation process	Collagen degradation, epithelial fragility, inflammation
Middle Molecules	β2-Microglobulin	Immune system proteins (poor clearance)	Increased bacterial colonization, mucosal damage
	Inflammatory cytokines (IL-1β, IL-6, TNF-α)	Immune response dysregulation	Vascular permeability, fibroblast dysfunction, chronic inflammation

Inflammatory Mechanisms and Clinical Implications

Chronic kidney disease (CKD) and uremic toxins significantly impact the oral mucosa by triggering inflammatory processes, which contribute to chronic inflammation, tissue degradation, and delayed healing

(Stenvinkel et al., 2013). Inflammatory responses in the oral cavity of CKD patients are mainly mediated by proinflammatory cytokines, oxidative stress, endothelial dysfunction, and microbiota changes (Meurman et al., 2009). These mechanisms not only exacerbate oral mucosal damage but also increase the risk of systemic complications, highlighting the importance of early diagnosis and intervention (Craig et al., 2016).

Proinflammatory Cytokines and Oral Tissue Destruction

In CKD, persistent inflammation leads to the overproduction of proinflammatory cytokines such as IL-6, TNF-α, and IL-1β, which contribute to tissue degradation, vascular dysfunction, and impaired healing (Carrero et al., 2008).

- IL-6 overexpression in the oral mucosa is associated with increased fibroblast apoptosis, leading to weakened epithelial integrity and susceptibility to ulcers (Johansen et al., 2019).
- TNF-α stimulates matrix metalloproteinases (MMPs), which degrade collagen and extracellular matrix (ECM) components, causing mucosal thinning and atrophy (Meijers et al., 2010).
- IL-1β activation enhances neutrophil infiltration and reactive oxygen species (ROS) production, which accelerate periodontal inflammation and tissue destruction (Himmelfarb, 2004).

This chronic inflammatory environment predisposes CKD patients to recurrent oral ulcers, mucosal fragility, and delayed wound healing, increasing the risk of secondary infections (Brito et al., 2016).

Endothelial Dysfunction and Impaired Wound Healing

The oral mucosa relies on a well-functioning vascular system for oxygenation, nutrient delivery, and immune surveillance (Stenvinkel et al., 2013). However, in CKD patients, uremic toxins impair endothelial function, leading to vascular insufficiency, delayed tissue repair, and increased susceptibility to infections (Lekawanvijit & Krum, 2015).

- Indoxyl sulfate (IS) and p-cresyl sulfate (PCS) induce endothelial dysfunction, reducing nitric oxide (NO) bioavailability, which is crucial for vasodilation and mucosal healing (Santos et al., 2016).
- AGEs trigger endothelial inflammation, promoting vascular calcification and fibrosis, which further impair blood supply to the oral tissues (Witko-Sarsat et al., 2004).
- Microvascular dysfunction in CKD patients leads to ischemia and delayed healing, making them more prone to non-healing ulcers and mucosal necrosis (Carrero et al., 2008).

Oxidative Stress and DNA Damage

Oxidative stress plays a pivotal role in uremic toxin-induced mucosal inflammation and cellular damage (Dou et al., 2018). CKD patients exhibit increased oxidative stress markers, which contribute to DNA damage, mitochondrial dysfunction, and accelerated aging of oral tissues (Craig et al., 2016).

- ROS accumulation from uremic toxins promotes lipid peroxidation, leading to epithelial cell apoptosis and weakened mucosal defense (Anding et al., 2017).
- DNA oxidation and mitochondrial dysfunction impair cellular repair mechanisms, resulting in prolonged mucosal inflammation and susceptibility to malignancies (Mager et al., 2003).
- Antioxidant depletion in saliva, such as reduced glutathione and superoxide dismutase (SOD) levels, makes the oral mucosa more vulnerable to inflammatory damage and infections (Santos et al., 2016).

These oxidative stress-driven mechanisms significantly contribute to chronic mucosal inflammation, periodontal tissue breakdown, and increased risk of oral cancer in CKD patients (Meurman et al., 2009).

Altered Oral Microbiome and Inflammatory Responses

The composition of the oral microbiome is drastically altered in CKD patients, leading to microbial dysbiosis and excessive immune activation (Proctor et al., 2005). This imbalance plays a key role in the progression of oral inflammatory conditions (Johansen et al., 2019).

- CKD patients show an overgrowth of anaerobic pathogens such as Porphyromonas gingivalis and Fusobacterium nucleatum, which drive periodontal inflammation and alveolar bone loss (Craig et al., 2016).
- Increased levels of Candida species in CKD patients predispose them to oral candidiasis, particularly in those with xerostomia and immune suppression (Meurman et al., 2009).
- Microbiome alterations stimulate Toll-like receptor (TLR) signaling, leading to excessive cytokine release and chronic oral inflammation (Brito et al., 2016).

The interplay between microbial dysbiosis and immune dysfunction exacerbates oral inflammatory diseases and further compromises oral health outcomes in CKD patients (Mager et al., 2003).

Clinical Implications and Management Strategies

Given the profound impact of inflammatory mechanisms on the oral mucosa, early detection and targeted management strategies are essential for improving oral health in CKD patients (Meijers et al.,

2010).

- Regular periodontal evaluation can help identify early signs of mucosal inflammation and periodontal disease, allowing for timely intervention (Carrero et al., 2008).
- Anti-inflammatory therapy, including topical corticosteroids and systemic immunomodulators, may help reduce cytokine-mediated tissue destruction (Proctor et al., 2005).
- Antioxidant supplementation, such as vitamin C, vitamin E, and polyphenols, can help counteract oxidative stress and improve mucosal resilience (Dou et al., 2018).
- Probiotic therapy may help restore a healthy oral microbiome, reducing the risk of pathogenic overgrowth and secondary infections (Johansen et al., 2019).
- Salivary substitutes and hydration strategies are crucial for managing xerostomia and improving mucosal lubrication, thereby enhancing oral comfort and reducing inflammation (Meurman et al., 2009).

By addressing these inflammatory and immunological pathways, clinicians can significantly improve the oral health and quality of life of CKD patients while also reducing systemic inflammatory burden (Craig et al., 2016).

The impact of uremic toxins on the oral mucosa in chronic kidney disease (CKD) patients undergoing hemodialysis is a critical yet often overlooked aspect of their overall health. These toxins, including indoxyl sulfate (IS), p-cresyl sulfate (PCS), and advanced glycation end products (AGEs), disrupt immune responses, promote chronic inflammation, and impair oral tissue homeostasis (Stenvinkel et al., 2013). As a result, CKD patients are predisposed to mucosal lesions, delayed wound healing, and increased susceptibility to infections (Meurman et al., 2009).

Key Findings and Clinical Significance

The review highlights several pathophysiological mechanisms underlying oral mucosal damage in CKD patients, emphasizing:

- Systemic immune dysfunction leading to impaired mucosal defense and increased risk of oral infections (Carrero et al., 2008).
- Inflammatory cytokine overexpression (IL-6, TNF-α, IL-1β) contributing to mucosal fragility and tissue degradation (Johansen et al., 2019).
- Endothelial dysfunction and oxidative stress impairing vascular supply and wound healing, leading to persistent ulcers and tissue necrosis (Himmelfarb, 2004).
- Microbial dysbiosis and altered oral microbiome, exacerbating periodontal diseases and mucosal inflammation (Proctor et al., 2005).
- Salivary dysfunction and xerostomia, reducing oral mucosal protection and increasing the risk of opportunistic infections (Meijers et al., 2010).

These findings underscore the urgent need for multidisciplinary oral healthcare strategies to mitigate the deleterious effects of uremic toxins on the oral cavity and overall systemic health of CKD patients (Brito et al., 2016).

Future Research Directions

While significant progress has been made in understanding the pathophysiological links between CKD and oral health, several key areas require further investigation:

- Molecular Mechanisms: Future studies should explore the precise molecular interactions between uremic toxins and oral epithelial cells to identify potential therapeutic targets (Craig et al., 2016).
- Biomarker Development: Identifying salivary and serum biomarkers for early detection of CKD-associated oral mucosal damage could help clinicians implement preventive interventions (Dou et al., 2018).
- Therapeutic Innovations: Research should focus on novel anti-inflammatory and antioxidant therapies, including probiotics, herbal formulations, and targeted cytokine inhibitors, to improve oral health outcomes in CKD patients (Johansen et al., 2019).
- Personalized Dentistry Approaches: Developing personalized treatment plans based on a patient's inflammatory profile, salivary composition, and microbiome diversity may enhance the effectiveness of oral healthcare interventions (Meurman et al., 2009).
- Longitudinal Clinical Studies: More long-term clinical trials are needed to evaluate the efficacy of different oral care protocols in preventing oral mucosal complications in CKD patients (Brito et al., 2016).

Practical Recommendations for Clinicians

To improve oral health outcomes in CKD patients, healthcare providers should integrate preventive and therapeutic strategies tailored to their unique needs. Key recommendations include:

- Routine oral health screenings to detect early signs of mucosal inflammation and infections (Meijers et al., 2010).
- Use of antioxidant and anti-inflammatory treatments to counteract oxidative stress and cytokine-mediated damage (Craig et al., 2016).

- Probiotic and microbiome-targeted therapies to restore oral microbial balance and reduce pathogen overgrowth (Johansen et al., 2019).
- Hydration strategies and salivary substitutes to alleviate xerostomia and improve mucosal lubrication (Meurman et al., 2009).
- Collaborative management between nephrologists and dentists to optimize oral health care in CKD patients (Brito et al., 2016).

CONCLUSION

The classification and pathophysiological mechanisms of uremic toxins provide critical insights into their impact on oral health in CKD patients. By understanding how small water-soluble molecules, protein-bound toxins, and middle molecules influence epithelial integrity, immune responses, and oxidative damage, clinicians can develop more effective preventive and therapeutic strategies. Future research should focus on biomarker identification, personalized treatment approaches, and novel interventions to mitigate oral complications in CKD patients.

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