

## Mast Cells: A New Target for Diabetic Nephropathy

Jonathan J Kopel<sup>1\*</sup>, Gregory L Brower<sup>1</sup>

1. Texas Tech University Health Sciences Center

\*Corresponding Author

### Abstract

Diabetes remains a mounting health burden as more patients with chronic and uncontrolled diabetes develop progressively worse complications requiring extensive medical and surgical interventions. In many instances, chronically uncontrolled diabetes can injure the kidneys leading to diabetic nephropathy (DN). Among diabetics, DN patients have a worse prognosis and survival with the risk of developing many chronic kidney diseases and end-stage renal disease (ESRD), which increases the demand for dialysis and surgical intervention. Despite several available pharmacological treatments, most fail to improve survival among DN patients. As a result, new pharmaceutical regimens for managing DN are critically needed. In recent years, pharmaceutical therapies targeting mast cells in DN have shown great potential to reduce renal inflammation and induce remodeling of damaged kidney structures. Further double-blind clinical trials are needed to evaluate the efficacy and safety of mast cell stabilizers among DN patients.

**Keywords:** Mast Cells, kidney, cardiovascular, diabetic nephropathy, and mast cell stabilizers

### Discussion

Diabetes remains a mounting health burden as more patients with chronic and uncontrolled diabetes develop progressively worse complications. In many instances, chronically uncontrolled diabetes can injure the kidneys leading to diabetic nephropathy (DN), which classically presents with proteinuria and reduction in glomerular filtration rate. Among diabetics, DN patients have a worse prognosis and survival with many succumbing to cardiac, cerebrovascular, or hypoglycemic complications.<sup>1,2</sup> Furthermore, DN is a major cause of chronic kidney disease and end-stage renal disease (ESRD), which increases the demand for dialysis and surgical intervention.<sup>3</sup> Although kidney transplantation remains a viable option, many DN patients have post-operative complications, including cardiovascular disease events, associated with kidney transplant procedures.<sup>4,5</sup> Therefore, current therapeutic guidelines for DN emphasize improving glycemic control and lowering blood pressure through angiotensin-converting enzyme (ACE) inhibitors.<sup>6</sup> However, these pharmacological agents fail to improve survival among DN patients.<sup>7,8</sup> As a result, new pharmaceutical regimens for managing

DN are critically needed.<sup>9,10</sup> Specifically, investigations into pharmaceutical therapies targeted at the immune system may provide new treatments options for DN.<sup>11</sup>

Recently, mast cells have become an emerging target for DN treatment.<sup>12</sup> Mast cells are bone marrow-derived cells that modulate the innate immune response and contribute to several chronic inflammatory and renal diseases.<sup>13-15</sup> Mast cells exhibit unique phenotypes at different tissues and organs contributing to their function and structural integrity.<sup>14</sup> Furthermore, mast cells contain a variety of stimulatory and inhibitory receptors, which can be activated with either immunoglobulin E (IgE) or other signaling molecules.<sup>16</sup> Specifically, IgE-bound mast cells crosslink and activate mast cell degranulation releasing several proinflammatory mediators involved in the pathogenesis of asthma and other pulmonary diseases.<sup>16</sup> Under normal physiological conditions, mast cells remain stable except in chronic inflammatory processes, fibrotic disorders, and wound healing, where mast cell hyperplasia infiltrates surrounding tissues and organs.<sup>16</sup> In recent years, several clinical studies showed increased mast cell proliferation in the renal interstitium of DN patients, which correlated with the progressive decline in renal function.<sup>15,17,18</sup> Once activated, mast cell degranulation releases proteases and cytokines, such as tryptase, chymase, and tumor necrosis factor-beta (TGF- $\beta$ ), into the tubular interstitium promoting renal inflammation and fibrosis in the onset and progression of DN.<sup>15,18</sup> Among the many pathophysiological processes in DN, tubulointerstitial fibrosis is the major factor leading to an irreversible loss of renal function in DN, which predicts the progression and prognosis of DN.<sup>19</sup> Current models suggest chronic inflammatory processes mediated by high glucose levels increase mast cell activity and the synthesis and release of TGF- $\beta$ , tumor necrosis factor-alpha (TNF- $\alpha$ ), and renin, which initiate fibrotic processes in surrounding tissues. Therefore, pharmacological therapies targeting mast cells, known as mast cell stabilizers, may improve the symptom severity and progression of DN.<sup>11</sup>

Although the pharmacological mechanism of mast cell stabilizers remains elusive, current theories suggest tachykinin antagonism, decreased TNF- $\alpha$ , and G-protein signaling may mediate mast cell stabilizer interactions.<sup>16</sup> Currently, two mast cell stabilizers, Ketotifen and Tranilast, have shown promise reducing the progression of DN. Ketotifen is a cyproheptadine analog with antihistamine properties and has mast stabilizer properties similar to first-generation mast cell stabilizers, such as Cromolyn Sodium.<sup>16</sup> A mouse model examining Ketotifen in DN showed improvement in renal collagen, urinary protein, creatinine, and urea clearance.<sup>20</sup> Specifically, Ketotifen improved renal function by reducing renal lipid peroxidation.<sup>20</sup> Furthermore, a small clinical trial in 48 diabetic patients treated with Ketotifen showed an improved lipid profile (triglycerides, low and high-density lipoproteins), decreased interleukin-6, and a decreased risk of cardiovascular disease.<sup>21</sup> Tranilast is an antifibrotic agent that inhibits TGF- $\beta$  release from fibroblasts and macrophages, which reduced collagen synthesis fibrosis in DN.<sup>22</sup> Follow up studies after one year showed Tranilast slowed the decline in renal function in early and advanced DN by reducing renal fibrosis, mast cell infiltration in the kidney, as well as urinary protein and type IV collagen excretion and accumulation.<sup>22-24</sup> However, the studies included small sample sizes (less than 10 patients) and elderly patients.<sup>22-24</sup> Therefore, these small clinical trials fail to establish whether Ketotifen is an effective alternative for treating diabetic nephropathy. Larger sample sizes and long periods of observation are required to determine the full therapeutic effect and potential side effects of Tranilast.<sup>22,23</sup>

Overall, pharmaceutical therapies targeting immune cells in DN have the potential to reduce renal inflammation and induce remodeling of damaged kidney structures. However, further double-blind clinical trials are needed to evaluate the efficacy and safety of mast cell

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stabilizers among DN patients. Despite the effectiveness of mast cell stabilizers, several challenges to develop targeted mast cell stabilizer therapy limit its widespread application in the clinic.<sup>16</sup> However, an increasing number of clinically approved drugs, such as statins and calcium channel blockers, exhibit mast stabilizing properties.<sup>16</sup> For example, recent studies examining tyrosine kinase inhibitors, which are effective chemotherapy agents against several cancers, demonstrated mast cell stabilizing properties, which suggests the potential of new drug candidates targeting receptors and enzymes on mast cells involved in specific cancers.<sup>16</sup> In summary, mast cells remain viable targets for the treatment and management of DN and other pathological conditions.

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### **Declaration of Interest**

The author reports no conflict of interest.

### **Contribution**

Each author contributed equally to the research, writing, and creative development of this review.

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