# Literature Review

## Introduction

This project investigates the use of atomic force microscopy AFM as a method of detecting the progression of diabetic nephropathy.

### Diabetic Nephropathy

Diabetic nephropathy is a common and serious complication of both type 1 and 2 diabetes resulting in kidney failure due to progressive damage to the nephrons, functional units responsible for filtering the blood. %% source %%

Diabetic nephropathy develops in 30-40% of people with diabetes after 15-20 years, as the disease progresses the damage accumulates and mortality rate rises [1]. Based on the risk factor of the patient treatments range from lifestyle changes and medications, to renal replacement which involves dialysis and transplantation [1].

%% Stats about the number of people with it and dying of it and how that is changing over time %%

%% connecting line from mortality to pathophysiology %%

%% Pathophysiology %% In type 1 diabetes a lack of insulin and in type 2 Insulin resistance cause chronic hyperglycemia a condition where there is too much glucose in the blood. Hyperglycemia causes an increased build up of reactive oxygen species (ROS) this oxidative stress causes inflammation [2]. Inflammation increases production of cytokines, including TGF-, which trigger Epithelial to Mesenchymal Transition (EMT) [3], [4]. EMT is a process where cells which make up structural and functional surfaces ([[epithelial]]) transition into repair/maintenance cells ([[Mesenchymal]]) [5]. In this case tubular epithelial, cells which make up the fine vessels of the kidney that filter blood, transform into myofibroblasts, repair and maintenance cells %% or undergo apoptosis (cell death) %% [6]. This is the underlying mechanism of fibrosis, which induces atrophy and scarring in the tubules %% and results in intraglomerular hypertension %% causing progressive kidney damage [7].

### Diagnosis state of the art

%% #### Current practice %%

The progress of kidney damage is typically monitored by observing degradation of kidney function through elevated albuminuria and decline in effective globular filtration rate (eGFR) based on urine and blood samples respectively. However these tests are limited in their diagnostic accuracy and can only give a rough indication of the state of the kidney [[8]][9].

[!FIGURE] Figure: Prognosis of chronic kidney disease based on uACR and eGFR [10] ![[Diagnosis of diabetic kidney disease - risk factor chart.png]]

%% Biopsey as the gold standard and it’s limitations, sample bias, invasivness %%

Renal biopsies provide a far more direct and precise insight into kidney disease progression and are sensitive enough to catch it at an early stage, however such an invasive procedure is difficult to justify in most cases [10].

%% #### Areas of active development %%

As such effective biomarkers to track the progression of kidney disease especially in its early stages is an area of active research. One biomarker that shows promise is monitoring change in mechanical properties of the kidney as it undergoes fibrosis.

%% Stiffness %%

There are several mechanisms that cause changes to the stiffness of the kidney such as: - f-actin cytoskeleton - cell to cell adhesion - EMT - thickening of cell walls

As myofibroblasts are overproduced their

%% MRI methods %%

### Observing fibrosis with AFM

Recent developments in both understanding of the pathophysiology of kidney disease and the diagnostic application of atomic force microscopy (AFM) technology [11] may provide a novel means of detecting the progression of kidney failure [12]. %% Need to know how easy it is to get hold of affected tubular cells from patients, is this non invasive? %%

Atomic force microscopes use the deflection of a very fine probe on a flexible cantilever to detect contact forces in order of nano newtons. There are several modes of operation,

%% Inter cellular adhesion %%

[1] R. T. Varghese and I. Jialal, “Diabetic Nephropathy,” in *StatPearls*, Treasure Island (FL): StatPearls Publishing, 2025. Available: <http://www.ncbi.nlm.nih.gov/books/NBK534200/>. [Accessed: Jan. 29, 2025]

[2] P. González, P. Lozano, G. Ros, and F. Solano, “Hyperglycemia and Oxidative Stress: An Integral, Updated and Critical Overview of Their Metabolic Interconnections,” *Int. J. Mol. Sci.*, vol. 24, no. 11, Art. no. 11, Jan. 2023, doi: [10.3390/ijms24119352](https://doi.org/10.3390/ijms24119352). Available: <https://www.mdpi.com/1422-0067/24/11/9352>. [Accessed: Jan. 30, 2025]

[3] C. E. Hills, E. Siamantouras, S. W. Smith, P. Cockwell, K.-K. Liu, and P. E. Squires, “TGFβ modulates cell-to-cell communication in early epithelial-to-mesenchymal transition,” *Diabetologia*, vol. 55, no. 3, pp. 812–824, Mar. 2012, doi: [10.1007/s00125-011-2409-9](https://doi.org/10.1007/s00125-011-2409-9). Available: <https://doi.org/10.1007/s00125-011-2409-9>. [Accessed: Jan. 29, 2025]

[4] G. Pizzino *et al.*, “Oxidative Stress: Harms and Benefits for Human Health,” *Oxid Med Cell Longev*, vol. 2017, p. 8416763, 2017, doi: [10.1155/2017/8416763](https://doi.org/10.1155/2017/8416763). Available: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5551541/>. [Accessed: Jan. 30, 2025]

[5] R. Kalluri and R. A. Weinberg, “The basics of epithelial-mesenchymal transition,” *J Clin Invest*, vol. 119, no. 6, pp. 1420–1428, Jun. 2009, doi: [10.1172/JCI39104](https://doi.org/10.1172/JCI39104). Available: <https://www.jci.org/articles/view/39104>. [Accessed: Jan. 29, 2025]

[6] M. Iwano, D. Plieth, T. M. Danoff, C. Xue, H. Okada, and E. G. Neilson, “Evidence that fibroblasts derive from epithelium during tissue fibrosis,” *J Clin Invest*, vol. 110, no. 3, pp. 341–350, Aug. 2002, doi: [10.1172/JCI15518](https://doi.org/10.1172/JCI15518). Available: <https://www.jci.org/articles/view/15518>. [Accessed: Jan. 29, 2025]

[7] W. Metcalfe, “How does early chronic kidney disease progress?: A Background Paper prepared for the UK Consensus Conference on Early Chronic Kidney Disease,” *Nephrology Dialysis Transplantation*, vol. 22, no. suppl\_9, pp. ix26–ix30, Sep. 2007, doi: [10.1093/ndt/gfm446](https://doi.org/10.1093/ndt/gfm446). Available: <https://doi.org/10.1093/ndt/gfm446>. [Accessed: Jan. 29, 2025]

[8] M. P. McTaggart *et al.*, “Diagnostic accuracy of point-of-care tests for detecting albuminuria: a systematic review and meta-analysis,” in *Database of Abstracts of Reviews of Effects (DARE): Quality-assessed Reviews [Internet]*, Centre for Reviews and Dissemination (UK), 2014. Available: <https://www.ncbi.nlm.nih.gov/books/NBK196046/>. [Accessed: Jan. 30, 2025]

[9] E. J. Lamb *et al.*, “Accuracy of glomerular filtration rate estimation using creatinine and cystatin C for identifying and monitoring moderate chronic kidney disease: the eGFR-C study,” *Health Technology Assessment*, vol. 28, no. 35, pp. 1–169, Jul. 2024, doi: [10.3310/HYHN1078](https://doi.org/10.3310/HYHN1078). Available: <https://www.journalslibrary.nihr.ac.uk/hta/HYHN1078>. [Accessed: Jan. 31, 2025]

[10] F. Persson and P. Rossing, “Diagnosis of diabetic kidney disease: state of the art and future perspective,” *Kidney Int Suppl (2011)*, vol. 8, no. 1, pp. 2–7, Jan. 2018, doi: [10.1016/j.kisu.2017.10.003](https://doi.org/10.1016/j.kisu.2017.10.003). Available: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6336222/>. [Accessed: Jan. 29, 2025]

[11] S. Liu, Y. Han, L. Kong, G. Wang, and Z. Ye, “Atomic force microscopy in disease-related studies: Exploring tissue and cell mechanics,” *Microsc. Res. Tech.*, vol. 87, no. 4, pp. 660–684, 2024, doi: [10.1002/jemt.24471](https://doi.org/10.1002/jemt.24471). Available: <https://onlinelibrary.wiley.com/doi/abs/10.1002/jemt.24471>. [Accessed: Jan. 30, 2025]

[12] E. Siamantouras, C. E. Hills, P. E. Squires, and K.-K. Liu, “Quantifying cellular mechanics and adhesion in renal tubular injury using single cell force spectroscopy,” *Nanomedicine: Nanotechnology, Biology and Medicine*, vol. 12, no. 4, pp. 1013–1021, May 2016, doi: [10.1016/j.nano.2015.12.362](https://doi.org/10.1016/j.nano.2015.12.362). Available: <https://www.sciencedirect.com/science/article/pii/S1549963415006073>. [Accessed: Jan. 29, 2025]