NFS498 Proposal Outline

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| Requirements  * 5 pages, double spaced, excluding references * Research area & why it is important * Research question * Methods/approach to solving research question |

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| Introduction Flow Diabetes (importance/interest in topic) 🡪 complications 🡪 kidney disease 🡪 present knowledge/lit review 🡪 potential biomarker VDBP 🡪 VDBP and vit D metabolism 🡪 unclear whether cause or consequence 🡪 aims of study |

There has been an increased incidence of vitamin D deficiency in T2DM patients around the world (cite). As well, recent studies have shown that the presence of vitamin D deficiency in diabetes is independently associated with the presence of diabetic nephropathy (DN) (1), which is a leading cause of end-stage renal disease (ESRD) (2).

Currently, microalbuminuria is considered to be the first detectable stage of DN (3). However, studies such as The United Kingdom Prospective Diabetes Study (UKPDS) and the U.S. National Health and Nutrition Examination Survey (NHANES) have demonstrated high prevalence rates of renal disease early in T2DM (4,5). This suggests the pathogenic process leading to DN starts before the clinical detection of T2DM. [Talk about **renal reserve**?] In order for the early implementation of preventative strategies to decrease the burdens of DN, identification of metabolic risk factors sensitive to early renal decline need to be characterized. However, there is little information available regarding this in populations at high risk for T2DM.

One potential marker for DN is urinary vitamin D binding protein (VDBP). Diabetic subjects have significantly more urinary VDBP compared to normal subjects, and the amount has been shown to increase with severity of the disease (6,7).

[Paragraph about vitamin D pathway, notes below]

However, it is unclear whether the appearance of VDBP in the urine is a cause or consequence of T2DM. [Details, notes below]

The aim of this study is to examine whether vitamin D deficiency precedes and potentiates the progression of DN, or progressive renal decline characterized by urinary excretion of VDBP contributes to vitamin D deficiency in patients at high risk for T2DM. [Hypothesis] [Implications of findings]

## Present knowledge (see table on last page for lit review summary)

* T1DM study suggest that VDBP loss in urine can explain low vitamin D levels in diabetics (6)
* Other studies agree that there is more VDBP present in disease state vs control
* Rats with T2DM demonstrated excessive excretion of VDBP complex (cite)
* Starch resistant to digestion (high-amylose maize) prevented excretion of VDBP complex in T1DM rats

### Vitamin D Pathway

* 88% of 25(OH)D in circulation is bound to VDBP (8)
* VDBP + 25(OH)D complex 🡪 freely cross glomerulus 🡪 transported to proximal tubule 🡪 VDBP + 25(OH)D reabsorbed by megalin 🡪 1α-hydroxylase from proximal tubule epithelial cells converts 25(OH)D to 1,25(OH)2D
  + Renal reabsorption of VDBP complex is mediated through megalin endocytosis. This determines whether 25(OH)D becomes activated 1,25(OH)2D or returned to circulation

### Gaps in knowledge

* Quality of VDBP as a biomarker is uncertain
* VDBP as a cause for vitamin D deficiency in diabetes is uncertain
* Uncertain whether VDBP loss in urine is cause or consequence of diabetes (this can be examined using a longitudinal study)

## Project focus & hypothesis

1. Determine whether VDBP loss in urine is a cause or consequence of T2DM
   1. Vitamin D deficiency precedes and potentiates the progression of diabetic nephropathy
      1. Evidence: angiotensin-1 receptor antagonists and activated vitamin D analogue 🡺 improves diabetic nephropathy (9)
      2. Evidence against: 2001-2006 National Health and Nutrition Examination Survey reported high levels of vitamin D deficiency in diabetic adults, with and without nephropathy
   2. Progressive renal decline (characterized by increased VDBP excretion) contributes to vitamin D deficiency
2. Examine the potential mechanism of vitamin D deficiency in T2DM as relating to urinary loss of VDBP

### Hypothesis

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### Contribution and implications of finding

1. If VDBP is cause of T2DM, it can be used as an early detection biomarker (non-invasive, easy, cheap detection)

# **Design**

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| * What is going to be done? * Why are we using this approach? |

# **Experimental work & data collection**

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| * What is the analytical procedure being used? * What are the steps taken to ensure reliability, precision, and accuracy? * N=? * Animals/humans? * Time frame for sample acquisition and analysis? |

* PROMISE cohort: subjects are at high risk for T2DM
* Longitudinal study with follow-ups every 3 years (9 year mark)

# **Data analysis**

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| * Method used to process data |

Statistical analysis will be performed using SAS (version 9.3; SAS Institute Inc., Cary, NC) and R statistical software (version…).

# **Time allocation**

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| October 2015 | Receive urinary data |
| 13 November 2015 | Submit proposal + presentation |
| October 2015 – February 2016 | Data analysis |
| February 2016 – March 2016 | Write final manuscript |
| April 2016 | Submit manuscript + presentation |

*Table 1* Summary of Existing Literature

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| **Study** | **Author** | **Population** | **Main Findings** | **Limitations** |
| Enhanced excretion of vitamin D binding protein in type 1 diabetes: a role in vitamin D deficiency? | Thrailkill KM et al. (2011) | 155 subjects with T1DM and controls, aged 14-40 yrs | The loss of VDBP in T1DM could contribute mechanistically to vitamin D deficiencies. |  |
| Dietary resistant starch prevents urinary excretion of vitamin D metabolites and maintains circulating 25-hydroxycholecalciferol concentration in Zucker Diabetic Fatty Rats | Koh GY et al. (2014) | 24 rats split into three groups (lean control, AIN-93G diet, and AIN-93G diet with resistant starch) | Vitamin D balance can be maintained by dietary resistant starch through nephroprotective mechanisms. This is independent of vitamin D supplementation and megalin expression. |  |
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**References**

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