Prevalence and Determinants of Albuminuria on a Manitoba First Nation.

Submitted by
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Abstract

Both diabetic and non-diabetic end stage renal disease is more common in First Nations people than those in the general population in Canada. A marker of early potentially preventable disease is abnormal urinary albumin creatinine ratio (ACR). A cross sectional study of the prevalence and determinants of albuminuria was carried out in 486 residents of a Plains Ojibwa First Nation in Manitoba in the summer of 2003. Twenty percent of the individuals in the study had albuminuria. (5.3% proteinuria, dipstick protein>1g or ACR ≥30mg/mmol, 14.7% microalbuminuria, MAU, ACR≥2 men or ≥2.8 female and <30mg/mmol) Those with albuminuria were older (42 years vs 36 p<0.0001), male (60% vs 45, p=0.01) non smokers (28% vs 14, p=0.01), had more diabetes (60% vs 21, p<0.0001), higher fasting glucose (10 mmol/L vs 6, p<0.0001), higher systolic (134 mmHg vs 125, p<0.0001) and diastolic blood pressures (80 mmHg vs 76, p=0.001) despite increased use of antihypertensives(32% vs 12 p<0.0001) or ACEI (22% vs 6 p <0.0001) than the non albuminuric population. Only 7.5% of those with albuminuria were aware of kidney disease. In a multivariate logistic regression performed in a backwards conditional fashion, independent risk factors for albuminuria were; female gender [OR 0.407 (95% CI 0.23, 0.771), p=0.002], average fasting glucose [OR 1.2 (95% CI 1.115, 1.29),p <0.0001], years diagnosed with diabetes [OR 1.057 (95% CI 1.004, 1.113), p=0.03], systolic BP [OR 1.02 (95% CI 1.005, 1.035), p=0.009], and BMI [OR 1.042 (95% CI 1.001, 1.085), p=0.04]. The high rate of albuminuria in this FN population suggests a screening and multifaceted intervention and education program in those with hypertension and diabetes is warranted to halt the progression and development of albuminuria and ultimately ESRD.

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Glossary of Acronyms

ACEI – Angiotensin converting enzyme inhibitor

ACR – Albumin to creatinine ratio

AER – Albumin excretion rate

ARB – Angiotensin II receptor blocker

ASA – Acetylsalicylic acid or aspirin

BP – Blood pressure

CHD – Coronary heart disease

CI – Confidence interval

CORR – Canadian Organ Replacement Register

CPS – Compendium of pharmaceuticals and specialties

CRF – Chronic renal failure

CV – Cardiovascular

DM – Diabetes mellitus

ESRD – End stage renal disease

FN – First Nation

FSGS – Focal segmental glomerulosclerosis

GFR – Glomerular filtration rate

GN – glomerulonephritis

GTT – Glucose tolerance test

HDL – High density lipoprotein

HTN – Hypertension

IFG – Impaired fasting glucose

IGT – impaired glucose tolerance.

IHD – Ischemic heart disease

IN – Incipient nephropathy, synonymous with microalbuminuria (albuminuria 20-299mg/day)

JNC7 – The Seventh Report of the Joint National Committee on the Prevention, Detection, Evaluation and Treatment of Blood Pressure

LDL – Low density lipoprotein

MAU – Microalbuminuria (30 to 300 mg albumin per day)

MI – Myocardial infarction

NAU – Normoalbuminuria

NHANES – National Health and Nutrition Examination Survey

ON – Overt nephropathy, synonymous with macroalbuminuria or proteinuria, (albuminuria >300mg/day)

RBC – red blood cells

UAE – Urinary albumin excretion

US – United States of America

UTI – Urinary tract infection

ZKP – Zuni kidney project

Chapter 1 – Introduction

1.1 Description of Problem

Microalbuminuria is recognized as an early indication of renal disease.[1] It is generally utilized clinically to detect early diabetic nephropathy and initiate appropriate interventions to prevent the onset of overt nephropathy and renal failure. [2] Albuminuria is common in the diabetic population, [3-8,2] but it can also be seen in non-diabetic subjects[9] and may indicate the presence of renal diseases in this population. It is postulated that increasing albuminuria, specifically in diabetics predicts progressive loss of function and that reduction in proteinuria correlates with a slowing of progression.[10] It is an important target for screening those at high risk, as well as monitoring disease progression and effects of therapy. It can be detected by an increased albumin-to creatinine ratio on a one time urine sample. [11-13]

Diabetes is a disease characterized by hyperglycemia either due to inadequate insulin (juvenile onset diabetes, type 1 or insulin dependant diabetes (IDDM)) or to relative insulin resistance (adult onset diabetes, type 2 or non-insulin dependant diabetes (NIDDM)).[14] World wide the incidence of diabetes, primarily type 2, and its sequelae, such as diabetic nephropathy have been increasing over the last several decades. Reasons for the increasing incidence of diabetes are several-fold, including the aging population especially in Western countries as well as increasing prevalence of obesity and lack of physical exercise. Diabetic nephropathy is a renal disease characterized by structural changes at the glomerular level due to prolonged exposure to the hyperglycemic diabetic

milieu. [15, 16, 17, 18] Nephropathy is manifest by albuminuria and proteinuria. The prevalence of diabetic nephropathy, is increasing as the number of diabetics increase. It can result in chronic renal failure (CRF) and eventually end-stage renal disease (ESRD) requiring dialysis. The prevalence of CRF and ESRD are increasing world wide primarily due to an increase in diabetic nephropathy but also due to primary renal diseases.[19]

Hematuria is an abnormally high number of red blood cells (RBC) in the urine. It can be present secondary to a variety of renal and non-renal diseases. As an indicator of renal disease it can be associated with albuminuria and frank proteinuria, however it can also be an isolated finding. It is detected by a dipstick urinalysis and confirmed by urine microscopy.[20]

1.2 Population of Interest

While diabetes is increasing in most populations, it is increasing by a greater degree among some minority ethnic groups. The First Nations peoples of North America are particularly prone to diabetes and to diabetic complications including diabetic nephropathy and ESRD. Certain groups such as the Pima Indians in the United States have a very high prevalence of diabetic nephropathy among their diabetic population. [6, 7, 21] While diabetic disease forms the greatest percentage of renal disease among First Nations peoples, non diabetic renal disease is also highly prevalent in the Aboriginal population, and contributes to the burden of disease in this population. [9]

The prevalence of ESRD is also high among the First Nation peoples of Manitoba. In 2003 a survey of all those on dialysis in Winnipeg, Manitoba was undertaken. Of 574 on dialysis in Winnipeg, 155 (27%) were Aboriginal, whereas 14% of the population of Manitoba are Aboriginal[22]. Of those, 65% (101/155) were diabetic and 35% (54/155) were non diabetic.[23] This was likely an under estimate of the population of First Nations people on dialysis in the province of Manitoba because a greater proportion of patients on dialysis in rural Manitoba are of First Nations ancestry, and these were not included in the survey. The province wide prevalence ratio of FN to non FN individuals with diabetic ESRD and non diabetic ESRD was 7.3 and 2.3.[19] The high prevalence of ESRD among the First Nation people of Manitoba make knowledge of the prevalence of early and potentially treatable renal disease particularly important.

1.3 Study Region

Manitoba is a Canadian province of 1.1 million people, of whom 14% identify themselves as Aboriginal.[22] Few studies of the prevalence of microalbuminuria and its determinants have been performed among the Canadian Aboriginal population and none among the First Nations people of Manitoba. This study is the first to identify and analyze the prevalence of albuminuria in a First Nation in the province of Manitoba.

1.4 Rationale

While high rates of ESRD and renal failure are well described among the First Nations (FN) people in Canada, there is a paucity of data on the prevalence and determinants of early renal disease as evidenced by proteinuria and albuminuria. This study was designed to survey the prevalence of albuminuria in a representative population based sample of an Aboriginal population in Manitoba, Canada.

1.5 Objectives

This study had four overall objectives.

1. **Renal disease characteristics**: To determine the prevalence of early renal disease as evidenced by albuminuria and hematuria in a population sample of FN individuals and what traits characterise those individuals.

2. **Renal disease screening**: To determine if screening for albuminuria identifies individuals at risk for renal disease who would otherwise not be identified by hypertension and diabetes screening.

3. **Renal disease awareness:** To determine if First Nation people are aware of their kidney disease so they can actively participate in the treatment and monitoring of it.

4. **Renal disease treatment:** To determine if treatment goals (e.g. blood pressure targets and angiotensin converting enzyme inhibitor (ACEI) use) are achieved among the First Nation people at risk for progressive kidney disease.

Chapter 2 - Review of the Literature

A. Albuminuria

2.1 Definitions of Albuminuria

Standard urine dipstick and 24 hour urine determination measure total proteinuria including albuminuria. A standard urine dipstick measures urinary protein, but is relatively insensitive to protein and only becomes positive after protein excretion is greater than 300 to 500mg/day. Moreover, protein excretion <500mg/day can reflect normal tubular protein secretion, and is not necessarily indicative of a glomerular lesion. Proteinuria >500mg/day in a 24 hour urine or >430mg/L on a spot urine sample is synonymous with macroalbuminuria or overt nephropathy (>300mg albumin/day) which indicates a glomerular lesion or diabetic nephropathy in diabetics.[2]

Albumin is a proportion of the protein filtered by the glomeruli. Since albumin is normally excluded from the urine by the intact glomerulus, identification of early glomerular injury relies on detection of low levels of urinary albumin or microalbuminuria (30-300mg/day) undetectable by conventional methods.[20, 24-26] Assays to detect persistent microalbuminuria (MAU) have therefore been developed and are used clinically to detect early diabetic nephropathy or incipient nephropathy.[27] Assays for microalbuminuria include dipstick techniques for albumin concentration (>17mg/L is consistent with MAU), albumin to creatinine ratio (ACR), albumin excretion rate (AER) and a 24 hour urine for albumin.[2] Table 2.1 outlines the normal and expected values for albuminuria determination based on the three commonly used techniques. The gold

standard for albuminuria has long been the 24 hour urine for albumin, however, alternative methods utilizing a spot urine have become more prevalent due to ease of use.

Transient microalbuminuria can occur with fever, strenuous exercise, heart failure and poor glycemic control,[28] and screening should not be performed under these conditions. Due to day to day variability in MAU, at least two of three urines positive for MAU are suggested to confirm the presence of a true positive.[2] MAU portends the development macroalbuminuira (>300mg/day), overt nephropathy (ON) or proteinuria. (see section 2.4) Overt nephropathy can lead to progressive renal disease, renal failure and dialysis. In addition MAU is a risk factor for cardiovascular disease (see section D)

Table 2.1 Comparison of different measurement techniques for albuminuria

	Albumin to Creatinine Ratio (ACR) [14]	Albumin Excretion Rate (AER)	24 hour urine for albumin
Normal	♂ **<2.0 mg/mmol** ♀ **<2.8 mg/mmol**	**<15 μg/min**	<30 mg/day
Microalbuminuria	♂ **2.0 – 20 mg/mmol** ♀ **2.8 – 28mg/mmol**	**20-200 μg/min**	30-300 mg/day
Macroalbuminuria*	♂ >20 mg/mmol ♀ >28 mg/mmol	20-200 μg/min	30-300 mg/day

*synonymous with proteinuria of >500mg/day or >430mg/L on a spot urine

2.2 Validity of Albumin-Creatinine Ratio

A 24 hour urine is considered the gold standard for MAU determination.[28] It has limited usefulness as a screening test in that it is dependent upon a complete 24 hour collection for reliability which is awkward and time consuming for an individual to collect. The albumin to creatinine ratio (ACR) is a convenient alternative done on a one time urine sample. Concentrations of urine and therefore albumin are dependent on the hydration status of the subject which can vary. These differences are accounted for by normalizing the albumin concentration by the creatinine concentration.

A recent study of 2527 non-diabetic participants, collected a morning urine for albumin/creatinine ratio (ACR) and compared it to the gold standard 24 hour urine specimen for albumin. The area-under-the-curve 0.93, discriminator value 9.9mg/g (SI 1.1mg/mmol), sensitivity 87.6% and specificity of 87.5%. [29] Similar high sensitivity and specificity of the ACR compared to the gold standard has been seen in other populations at cut-off values of 26.8 to 32.5mg/g.(SI 3 to 3.7mg/mmol) [11-13] This was also considered a valid test among the pediatric population, although at a lower cut-off of 20 mg/g.(SI 2.3 mg/mmol) [30]

A study of 314 diabetics performed a 24-hour urine for albumin excretion ratio (AER) directly followed by a spot morning urine for ACR. Fifty-three percent of men and 32% of women had an AER of greater than 20 mg/min. Using cut-off values for ACR of greater than 22.1 mg/g (SI units >=2.5 mg/mmol) for men and 30.9 mg/g (SI units >=3.5 mg/mmol) in women, yielded a sensitivity of 95.7% in men and 93.35% in women. Specificity however ranged from 89.5% to 68.2% and worsened with increasing age. [31] Lower cut-off values for men and women were explained by higher muscle mass in males, which lead to higher creatinine excretion, and therefore a lower ACR for an equivalent albumin excretion.[28] A study that included 218 healthy controls supported different cut-offs for men and women, based on 95 percentiles of the normal distribution, which correspond to an ACR of >17mg/g (SI 1.9 mg/mmol) for men and >25 mg/g (SI 2.8mg/mmol) for women,[32] and are the cut offs accepted by the Canadian Diabetes Association. [14]

A variety of laboratory tests can be utilized to detect the ACR, including test strips[33, 34], immunologicaly based tests with latex bead immunoagglutination and ELISA methods[35, 36], sulphosalicylic acid test[37], Bumintest reagent tablets,[38] lazer turbidimetric method and albumin radioimmunoassay.[39, 40] ACR as measured by a 7 minute clinic or bedside test correlates with a 24-hour timed specimen.

Some of the tests have been automated in small, easy to use analyzers. The Bayer DCA2000 desk top analyzer uses an immunoturbidimetric method for analyzing the albumin component and Benedixt/Behre chemistry measures the creatinine. The DCA analyzer had a specificity and sensitivity at a 30 mg/g (SI 3.4mg/mmol) cutoff of 98% and 71.4%, respectively. The specificity and sensitivity improved at a 20 mg/g (SI 2.3mg/mmol) cutoff to 100% and 92.4%.[41, 42] Timing of spot testing in the morning or the afternoon does not appear to make a significant difference in its predictive ability.[43]

The validity of ACR to predict the 24-hour MAU and hence its use as a screening test in the healthy population has been challenged. In a sub-study of the HUNT trial, 2113 non-diabetic and non-hypertensive individuals submitted 3 morning urines for evaluation. Using a cut-off ACR of >=2.5 mg/mmol, 40 men and 41 women had MAU as defined by 2 of 3 positive morning samples. Comparing this with a 24 hour urine for micoralbuminuria, only 10 (25%) men and 19 (46%) of women had abnormal ACR.[44]

In summary the ACR has been shown to be a good screening test for the presence of MAU in the diabetic population. It is easily performed in the outpatient setting,

without the significant difficulties and drawbacks of performing a 24 hour urine collection. The use of this test in the non-diabetic population is not standard practice, and its sensitivity and specificity for detecting albuminuria and hence renal disease may be controversial in the non-diabetic population. Nevertheless ACR appears to be a useful tool for field study of albuminuria in both diabetic and non-diabetic populations.

B. Epidemiology of Albuminuria in First Nations

2.3 Causes of Albuminuria

Although diabetes is the most common etiology of persistent albuminuria in the Aboriginal,[3-7] Asian[8] or Caucasian[2] populations, it is not the only cause of albuminuria. Albuminuria in non-diabetics occurs in the FN population and in some populations, such as the Zuni, can be more prevalent than diabetic MAU.[9] Causes of MAU other than diabetes include the pre-diabetic state defined as impaired fasting glucose (fasting glucose 5.6-7mmol/L) and insulin resistance. The metabolic syndrome (ie hyperglycemia, insulin resistance, hypertension, dyslipidemia, abdominal obesity) as well as hypertension itself and primary glomerular diseases can also cause MAU.

MAU may be a marker for developing diabetes. In a study by Hoehner, involving 934 non-diabetic Menominee and Chippewa aboriginals, the prevalence of MAU was 15.2%. MAU was highly associated with one or more elements of the metabolic syndrome. The prevalence of subjects with one, two or greater than three traits was

7.4%, 16.6% and 27% respectively. Many of the metabolic parameters are themselves risk factors for diabetes, may predate the diabetic state, and have been associated with albuminuria in the Caucasian population.[45-47]

Hypertension itself can cause albuminuria in the Caucasian population.[48, 49] Children of hypertensive parents can have MAU, suggesting a genetic link, perhaps related to endothelial dysfunction.[50] A study in Pima Indians examined the relationship of blood pressure in non diabetics to the eventual development of albuminuria. Abnormally high ACR were seen more often in the highest tertile of blood pressure, suggesting blood pressure is a causative factor for albuminuria that precedes diabetes.[51]

Other causes of albuminuria aside from diabetes, hypertension or a pre-diabetic metabolic state include glomerular diseases. A study in an Australian aboriginal community followed those with childhood post-streptococcal glomerulonephritis (PSGN) 15 years after the outbreak. Those with prior PSGN had significantly higher MAU and macroalbuminuria rates than Aboriginal children with no clinical or laboratory evidence of PSGN at the time of the outbreak. (32% MAU and 13% macroalbuminuria vs 18% MAU and 4% macroalbuminuriain).[52] Definitive diagnosis of glomerular disease requires a biopsy. Published biopsy series are rare in the Aboriginal population, however a small series of Zuni Indians with non-diabetic renal disease were biopsied. Twenty three of those with nephrotic range proteinuria (>3.0 to 3.5 g/day) revealed the following pathology; 16 had mesangiopathic nephropathy with 11 of those with IgA deposition, 3 cases of membranoproliferative glomerulonephritis, and 2 with focal glomerulosclerosis

without immune deposits. Familial clustering was common, as over 57% of the subjects were related.[53]

MAU is a specific marker for glomerular dysfunction and is primarily utilized clinically to detect those at risk for progression to diabetic nephropathy. It is associated with the metabolic syndrome and endothelial dysfunction. It can also precede diabetes. In addition, it can be present in association with hypertension. MAU is also a marker for non-diabetic glomerular disease which occurs in the Aboriginal community and can be genetic.

2.4 Studies on the Natural History of Albuminuria

Urinary albumin excretion (UAE) greater than 30mg per day is an indicator of early diabetic nephropathy. The natural history of nephropathy has been studied in various Caucasian and Aboriginal groups.

The validity of this cut-off was examined in a study of 599 patients with diabetes, without microalbuminuria, who were followed over an eight year period. They were divided into three groups by quantitative albumin amounts on a 24 hour urine (Group I – 0=10mg/24hrs, II – 10.1 – 20 mg/24 hrs, III – 20.1-30 mg/24 hrs). Progression to definite microalbuminuria defined as greater than 30 mg/24 hrs was 25.3, 47.3 and 85.3% over 8 years, with a decline in GFR of 1.19, 1.64 and 2.52 ml/min/year in each of the groups.[54] This suggests that a cut-off in the 20-30mg/24 hours is appropriate, as at this level decline of renal function is accelerated.

Diabetic nephropathy tends to follow a progressive course. In non-proteinuric diabetics glomerular filtration rate (GFR) tends to increase progressively until the development of MAU, at which point it plateaus. Thereafter overt nephropathy (ON) develops and GFR gradually declines by as much as 35% over 4 years in one study in the Pima Indians. Higher baseline MAU amount predicted decline in GFR.[55]

Studies in the Pima Indians indicated that small elevation in UAE, can occur shortly after the onset of diabetes, and MAU appeared on average 5 years after the onset of diabetes (range 0-24), [51] which predicted the development of overt nephropathy.[56]

In 439 Pima Indians with diabetes, who were followed for a mean of 4.2 years, 59 (13%) of them developed overt nephropathy, 47 (80%) of whom had MAU at baseline (albumin-to-creatinine ratio >30mg/g). Those with MAU at baseline had 9.2 times (95% CI 4.4 to 21.4) the incidenceof developing overt nephropathy than those with baseline normoalbuminuria (NAU, albumin to creatinine ratio <30 mg/g). MAU remained a strong predictor for the development of overt nephropathy even when controlled for age, sex, duration of diabetes, BP, and blood glucose.[21]

On a functional level, glomerular hyperfiltration has been observed in Pima Indians beginning at the onset of diabetes diagnosis and GFR remains elevated until overt nephropathy and macroalbuminuria occurs. Pathologically, the glomeruli in those with microalbuminuria are not distinguishable from those subjects with normoalbuminuria. At the time macroalbuminuria occurs, extensive glomerular sclerosis and mesangial expansion with an increase in glomerular volume and increased glomerular basement membrane thickness is seen. Widening of epithelial cell foot processes also occurs, with a decrease in the total number of podocytes per glomerulus. Functionally this is followed by a rapid decline in GFR.[15, 16] Similar processes have been described in the Caucasian population.[17, 18] Logically interventions aimed in the early microalbuminuric stage,

where structural changes to the kidney are not yet extensive, would have the greatest impact to halt or slow the decline in renal function and prevent ESRD.

Lemley [57] biopsied a small group of 12 Pima Indians with longstanding diabetes (>8 years) and MAU and compared them with a group of 10 individuals who had a relatively short duration of diabetes, (<5 years) and NAU, over a 4 year period. Clinically albumin-to-creatinine ratio increased (84 to 260 p=0.01), with 6 of those with MAU deteriorating to overt nephropathy and macroalbuminuria. GFR decreased by 17%, while ultrastructurally there was basement membrane widening and a significant decline in the filtration surface area and mesangial cells, endothelial cells and podocytes. These changes reduced single nephron ultrafiltration coefficient by 20% and explained the decrease in GFR.

Similar findings were seen in two studies by Myers. [58, 59] In 16 Pima Indians with MAU, progression as determined by worsening albuminuria into the macroalbuminuria range was predicted by a significantly lower number of podocytes (or visceral epithelial cells) (r=-0.49 p=0.05). In a group of 34 Pima Indians with ON, where GFR decreased by 34% over a period of 4 years changes were again noted at the glomerular level. Changes in pore density and ultrafiltration coefficient (Kf) as well as increasingly large glomerular pore sizes, explained the reduction in GFR as well as partially explaining the increasing proteinuria seen with advancing diabetic nephropathy.

Diabetic nephropathy tends to be progressive and appear shortly after the diagnosis of diabetes. Early functional changes lead to progressive change in glomerular structure with decreasing GFR and increasing albuminuria from the microalbuminuric to the macroalbuminuric range.

2.5 Studies of Prevalence of MAU and Nephropathy

Prevalence of MAU and overt nephropathy vary among Caucasian and Aboriginal peoples, with and without diabetes. (See table 2.2)

Microalbuminuria is common among the general population of Caucasians. Of 85, 421 Dutch individuals aged 28 to 75, 40,856 (47.8%) submitted an early morning urine sample. MAU was present in 7.2% of the population. It was independently associated with age, gender, hypertension, diabetes, smoking, and previous myocardial infarction (MI) and stroke. After diabetic and hypertensive individuals were excluded, MAU was still present in 6.6% of the population.[60] In a sub-group of the large HUNT (Nord-Trondelag Health Study) in Norway, 5.1% of 2,113 individuals without known diabetes or hypertension had MAU defined as an ACR $\geq$ 2.5mmol/L in 2 of 3 samples. Diabetes and hypertension respectively were subsequently found in 5.1 and 51% of those with MAU.

MAU is also common in the general US population.[61] Part of the NHANES III (National Health and Nutrition Examination Survey) included 21,137 people older than 6

years, who submitted a single urine sample. Overall, 7.8% had MAU (defined by an ACR ≥30 mg/g and ≤ 300mg/g), while 5.1% without diabetes and hypertension had MAU. Overt proteinuria was present in 1.4% as defined by a urinary albumin concentration of >300mg/L.

Prevalence of albuminuria varies among First Nation groups. The Strong Heart Study of 4549 older (45-75 y.o.) Native Americans from Arizona, Oklahoma and the Dakotas revealed a combined prevalence of MAU and ON of 20 to 48%. Those from Arizona (including Pima), had 28% MAU, while diabetics had 34% MAU. MAU was more prevalent (15%) in non-diabetic Arizona aboriginals than non-diabetic participants elsewhere.[62] In 782 participants who were normoglycemic and normoalbuminuric at baseline, 52 (6.6%) developed MAU and 105 (13.4%) developed diabetes in an average 3.91 year (SD ± 0.95 year) followup.[4]

The Zuni Indians were studied as part of the Zuni Kidney Project (ZKP). A sample of 1483 subjects had a 15.0% (95% CI 13.1-16.9%) prevalence of MAU, age and gender adjusted to the Zuni population. In addition overt nephropathy or macroalbuminuria had an age and gender adjusted prevalence of 4.7% (95% CI 3.6 to 5.8%). There was a higher prevalence of MAU and ON among diabetic [MAU 33.6% (27.6 to39.7%) ON 18.7% (13.7 to 23.7%)] than non-diabetic participants. [MAU 10.8% (9.0 to 12.6%) ON 1.8% (1.0 to 2.5%)], however, due to more non-diabetics in the population, those without diabetes formed the largest number with MAU [3, 9]

The Pima Indians have been estimated to have up to a 13-17% cumulative incidence of developing albuminuria in the first 5 years of diabetes[7, 21] In a random cross-section of 2728 Pima, either MAU or overt nephropathy was present in 20% of the entire population, in 7.8% of those with a normal glucose tolerance test (GTT), in 15% of those with impaired glucose tolerance (IGT) and in 47% in those with diabetes.[6] The lower overall prevalence of MAU and overt nephropathy in this study as compared to the Strong Heart Study was likely entirely due to the lower number of diabetics, which related to the older entry age of the Strong Heart Study. As the Pima study was a large random population sample, it probably represents the truest prevalence of MAU and overt nephropathy for the Pima Indians.

Hoy et al[63] collected data on 400 adult diabetic and 366 non-diabetic Navajo Indians attending medical clinics in the Indian Health Service Hospital in Tuba City, AZ. MAU was present in 15% and overt proteinuria in 2% of the non-diabetic population and in 36% and 18% respectively in those with diabetes. Renal insufficiency was present in 10.6% of diabetics.

Prevalence of MAU is significantly higher among FN peoples than among Caucasian and non-FN people. Much of this is likely attributable to the increased diabetes in this population, but non-diabetic Aboriginals also have more MAU than their non-FN counterparts.

Table 2.2 Studies of albuminuria prevalence

Study	Design	Population	N	Ages	% MAU[1]	% ON[2]	% DM	% HTN
General population								
NHANES III[61]	Population X-sectional Survey	Representative US pop'n	21,137	>6	7.8	1.4	29	16
PREVEND[60]	Population X-Sectional Survey	Dutch, Caucasian	40,856	28-75	7.2		2.6	11
HUNT[44]	Population X-sectional survey, "healthy subjects"	Norwegian Caucasian	2,109	>20	5.1		0%	0%
First Nation population								
Strong Heart[62]	Population X-Sectional Survey	Arizona	1445	45-74	28	20	69	43
		Oklahoma	1443	45-74	15	6	39	45
		Dakotas	1407	45-74	14	6	39	27
ZKP[3, 9]	Population X-sectional Survey	Zuni Indians	1483	5->60	15	4.7	10	31
Pima[6]	Longitudinal study 81% population sampled	Pima and Papago	2728	≥15	13	7.2	30	
Hoy et al.[63]	Medical clinic sample	Navajo	766	>20	29	7.6	52	37

[1] Prevalence of MAU (microalbuminuria)
[2] Prevalence of ON (overt nephropathy or macroalbuminuria)

2.6 Risk factors for progression to Nephropathy

Risk factors for nephropathy in the non-Aboriginal and North American Aboriginal population have been well delineated, however not many Canadian studies, and no studies of the Manitoba Aboriginal population have been preformed.

In 1888 Caucasian type 1 diabetics, duration of diabetes was significantly longer in those with microalbuminuria, and no microalbuminuria was seen prior to 5 years. Blood pressure was also a significant variable; those with microalbuminuria have significantly higher systolic (132 vs 122mmHg $p<0.01$) and diastolic (77 vs 72 mmHg $p<0.01$) blood pressures.[64]

A study of 665 Chippewa Indians with diabetes in the south western U.S., showed 47.9% of this population had proteinuria and 62.6% had hypertension defined as a BP greater than 140/90. Hypertensive patients were more likely to have proteinuria than non-hypertensive patients, (55.2%vs 40%, $p<0.05$) as were those with diabetes for more than 10 years (57%vs 40%, $p<0.05$). This included a detailed analysis of 79 patients, in which UAE, renal function measures and cholesterol were measured. UAE was greater in hypertensive than non hypertensive individuals (606 ± 15600 mg/24hrs vs 101 ± 157 mg/24hrs $p<0.05$) and in those with diabetes for longer than 10 years. (748 ± 1732 mg/24hrs vs 96 ± 171 mg/24 hrs $p<0.05$). Hypercholesterolemia was common (56%), but was not associated with abnormal UAE, although hypertriglyceridemia was.[5]

Relationship of total cholesterol, LDL and apolipoprotein B to MAU has been shown in the Oji-Cree.[65]

The importance of blood pressure on albuminuria and renal disease in diabetics and non-diabetics was shown by Hoy in 1994.[63, 66] Three hundred and sixty six non-diabetics and 400 diabetic Navajos were included and 13.4% of the non-diabetics and 58.4% of the diabetics had hypertension by measurement or treatment. Diabetics had significantly higher blood pressures than age and sex matched non-diabetics. While rates of nephropathy were three times greater in diabetics than non-diabetics, blood pressures correlated with UAE irrespective of their diabetic status. Along with UAE, blood pressure correlated with age and BMI. Blood pressure control was optimal in only 50%.

An increase in blood pressure is often observed after the development of diabetic nephropathy. The hypertension is usually attributed to the renal damage from the diabetes. In Pima Indians elevated blood pressure can occur even before the onset of diabetes and predicts elevated UAE after diabetes onset.[51] Therefore the relationship between renal disease and blood pressure in diabetes is not entirely clear. Although higher blood pressure can be a consequence of diabetic renal damage, higher BP prior to diabetes onset may also contribute to the development of renal damage.[56]

In a group of 456 Pima Indians followed for up to 11.6 years, risk factors for microalbuminuria included; retinopathy, diabetes treatment, increased duration of diabetes, lower body mass index, higher mean blood pressure, HgAIC, and fasting and 2-

hour post-load plasma glucose concentrations. A relationship with cholesterol was found in those with diabetes for more than 10 years.[7] Risk factors for the development of overt nephropathy include; high blood pressure, level of glycemia, duration of diabetes, family history of diabetic nephropathy and type of diabetes treatment.[56]

A large study of 4549 Native Americans associated micro or macroalbuminuria with those who were older and diabetic and was independently associated with duration of diabetes, fasting plasma glucose, systolic blood pressure, fibrinogen levels and degree of Aboriginal ancestry.[62]

Homocysteine level has been associated with a higher incidence of nephropathy [IRR – 1.42 (95% CI 1.09 to 1.84, p=0.01)] in 396 diabetic Pima Indian participants over 40 years old who participated in a longitudinal study between 1982 and 1985, when controlled for age, sex and duration of diabetes. This relationship did not hold true however, when renal function at baseline was taken into account.[67] As homocysteine level increases with renal failure, the increased association between overt nephropathy and homocysteine levels may simply be due to the association of renal failure to ON and not due to a true association with homocysteine levels.

In 782 participants of the Strong Heart Study with normal albuminuria at the beginning, development of abnormal albumin excretion was associated with abnormal albumin to creatinine ratio, diastolic blood pressure, fasting insulin and American Indian heritage in univariate and logistic regression analysis. In separate logistic regression

analysis, abnormal albumin excretion and diabetes were strongly related [OR 3.45 $p<0.001$].[4]

Non-diabetic disease is associated with a strong familial clustering in one biopsy series where over 57% of subjects were related, and many clustered in 4 family groups.[53] Anecdotally familial clustering is common among Manitoba First Nations people with renal disease. Many of the First Nations people currently on dialysis have a family member previously or currently on dialysis.

2.7 Incidence of ESRD

First Nations people in Canada and the US experience high rates of renal disease and ESRD. The Canadian Organ Replacement Register (CORR) tracks all individuals who start dialysis in Canada. There were 23,601 prevalent and 4, 342 incident cases of all forms of ESRD treatment including transplant in 1999. In 2000, 18% were Aboriginal.[68] Several studies have looked at the comparative incidence of ESRD in Canadian First Nation peoples. Young and Kaufert[69] found the age-adjusted incidence of ESRD in 1981 to 1986 to be 2.5 to 4 times that of Caucasians depending upon estimates of the Aboriginal population. Saskatchewan First Nation peoples in the years 1981 to 1990, had an unadjusted incidence of non-diabetic ESRD of 2.56 times the Caucasian population while the incidence of diabetic ESRD was 16.2 times as common.[70, 71] In a Manitoba study, the prevalence ratio of diabetic ESRD and non-diabetic ESRD among First Nations compared to non FN people was 7.3 and 2.3.[19] Not only is ESRD

increased, but mortality from renal disease was also increased in a study in British Columbia.[72]

Similar numbers of Aboriginals in the US were seen, and have been more extensively reported. ESRD is significantly more common in Aboriginal peoples in the U.S. than in Caucasians[73-75]. This incidence varies among the Aboriginal tribes in the U.S. The Pima Indians are probably the best described of all the American Aboriginal groups. They have an incidence of ESRD greater than 23 times that of the general U.S. population, primarily from diabetic nephropathy.[56] Among the Zuni Indians there is a 1.6% prevalence of renal disease and 1% of renal insufficiency. The rate of ESRD is 14 times the rate for US whites.[76] Among the Sioux, the age adjusted rate of ESRD is 13.4 times the US Caucasian population, of which 86% is attributable to diabetes.[77] In an 8 year study, spanning 1986 to 1993, Alaskan Aboriginals had a 3.3 per 1000 incidence of ESRD[78] with a prevalence of 15.7 per 1000 in 1986.[79] In contrast, the Cherokee had a rate of 2.5 times that of the Caucasian population, over a the period 1978 to 1988, 88% attributable to diabetes.[80]

Nephropathy and ESRD is the final pathway of untreated albuminuria, especially in diabetics. Given the high prevalence of ESRD in the First Nations population in Canada and the United States, it is a serious health concern that deserves aggressive investigation and treatment.

C. Studies of Treatment of Albuminuria

While ESRD is a common outcome of albuminuria, it is not inevitable, and this has been shown in a study in Alaska First Nation people with decline in ESRD rates over an 8 year period after intervention efforts.[78]. Progression can be halted by aggressive blood pressure control, (to <130/80)[81] as well as therapy with drugs targeting the renin-angiotensin system such as ACEI and ARBs.[82-87] In fact it has been suggested that if ACEI were used routinely in all FNdiabetics at time of diagnosis to reduce nephropathy, costs would be lower than screening for MAU and treating those who screen positive.[88] Good glycemic control in diabetics is also important as has been shown, primarily with type I diabetics, in the DCCT trial [89] and others studies involving both type I and II diabetics.[90] Control of LDL and blood cholesterol has also been suggested as a possible target of intervention, however definitive research as not been done in this area.[91]

While the goals listed above can be difficult to achieve, a combined and integrated diabetes care service using multidisciplinary members can be a route to achieve health outcome goals.[92-94] A study in an Australian aboriginal community utilized a screening strategy to assess the combined renal and cardiac risk factors of hypertension, diabetes with microalbuminuria and overt albuminuria without other risk factors in the population. All subjects who had risk factors received an ACEI and other anti-HTN agents were used as needed to achieve blood pressure goals. Attempts at diabetic and lipid control were also made. An intention-to-treat analysis compared to matched historical controls revealed 50% fewer natural deaths. [95]

D. Non renal risks of Albuminuria

Screening for MAU was initially suggested to prevent the development of nephropathy and ESRD. However many studies in diabetics and non-diabetics [96-102] including new analysis of the HOPE trial have shown a strong independent relationship between increasing microalbuminuria and cardiovascular (CV) outcomes including myocardial infarction (MI), stroke and cardiovascular death.[103] The relationship of albuminuria to coronary heart disease (CHD) was confirmed in American Indians in the Strong Heart Study,[104, 105] and in Australian aboriginals.[106] This relationship extended below the cut-off for Microalbuminuria (≤2 mg/mmol).[107, 108] A recent randomized placebo-controlled trial has shown a non-significant trend to improvement in cardiovascular outcomes with treatment of albuminuria alone.No randomized trial has examined the effect of reducing albuminuria on CV morbidity or death.[109]

E. Awareness of Albuminuria in First Nations

No studies of kidney disease or microalbuminuria awareness in the FN population exist. In an analysis of renal disease awareness among participants in the 4000 participants in the NHANES 1999 to 2000 study in the general population, participants were asked, "Have you ever been told by a doctor or other health professional that you had weak or failing kidneys? (excluding kidney stones, bladder infections or

incontinence)" Overall 2% of the population responded positively to the question. Only 24% of the population with moderate renal dysfunction (GFR 15 to 59 mmol/min) and albuminuria were aware of their renal dysfunction or albuminuria.[110] In the Aboriginal population, awareness of medical conditions is not frequently reported. However, in a study on hypertension, only 50% of Aboriginals in Maine were aware of their condition vs 75% of the general population in a statewide survey.[111]

Awareness of albuminuria is the first step in the ability of a person to engage in treatment and lifestyle changes to prevent progression to nephropathy and eventual ESRD. Therefore it would be important to know how many FN people are aware of their disease.

F. Hematuria in First Nations

Hematuria is very common among various North American Aboriginal groups. Tentori et al[112] surveyed 1469 Zuni Indians over 5 years of age for hematuria. He defined significant hematuria as greater than trace on dipstick or greater and 50 red blood cells (RBC) per micro litre. The prevalence was 33.2 [95% CI 30.7 to 35.6%] and 17.8% [95% CI 15.8 to 19.8]. Hematuria of greater than a trace was more common in females than males. Risk factors for hematuria included; diabetes and alcohol use for greater than 10 years in males but not females.

Work done by Hoy et al[63] shows that hematuria, defined as ≥ small by dipstick, occurred in 20% of 766 Navajo of a hospital clinic sample. Hematuria was present equally in diabetics and non-diabetics. It was associated with albuminuria.

Some of the hematuria in diabetics is likely attributable to underlying diabetic nephropathy, since hematuria has been described in up to 30% of Caucasians with clinical diabetic nephropathy. Biopsy studies have shown 63% diabetic nephropathy in diabetics with hematuria and red cell casts.[113]

Some of the hematuria is undoubtedly non-renal in origin, especially in females. It is also likely that other glomerular diseases account for a portion of the hematuria. In a series of 166 American Native renal biopsies performed from 1971 to 1989, mesangial proliferative glomerulnephritis with mesangial immunoglobulin deposition was described in 68.7% of all biopsies and in 83.8% of all biopsies with a primary glomerulonephritis. Early disease was characterized by microscopic hematuria alone, but five year renal failure rates were estimated at 41%. Mesangial proliferative disease was occasionally clinically characterized by rashes, arthralgias, and/or a history of alcohol abuse.[114] Among the Zuni Indians from the same biopsy series 44 non-diabetic subjects had a biopsy. Eighteen of 21 with asymptomatic microscopic hematuria alone had mesangiopathic glomerulonephritis. Of those 10 stained for IgM deposition and 8 for IgA.[53] Other causes of hematuria included hereditary nephritis and post-streptococcal glomerulonephritis.[115-117]

Chapter 3 – Methods

3.1 Design

Data collection and laboratory determination of a volunteer cross-section of a Plains Ojibwa First Nation community in Manitoba was done in the summer of 2003 under the direction of Drs. Sharon Bruce and Kue Young, with a grant from the Canadian Institute of Health Research (CIHR) and the Manitoba Health Research Council (MHRC) as part of a larger research initiative. The community is situated in southern Manitoba within two hours driving distance of Winnipeg. In the 2001 census it had over 2400 inhabitants, 46% of whom were over the age of 19. The study was approved by the research ethics board of the University of Manitoba. (Appendix I)

3.2 Procedures

After signing the consent form, individuals who volunteered to be part of the study underwent a series of questions, anthropomorphic measures, blood and urine tests. See Appendix II for detailed procedures from Dr. Sharon Bruce's protocol, the procedures are summarized below.

a. Anthropometric Measurements and Blood Pressure Determination

Height was measured in participants by standing them against a metric tape placed vertically against a wall. Participants were asked to remove their footwear prior to

the test and to stand erect, with feet together, heels touching the wall. A set square was placed firmly on their head and height was marked and recorded to the nearest 0.5 cm. Weight was measured with participants in light clothing and without footwear. It was recorded in kilograms to the nearest 0.1 kg.[118]

Blood pressures were taken using a mercury manometer using optimal bladder size proportional to the arm circumference. The participants resting, with arms bare and anticubital fossa at the heart level. Systolic (Korotkoff phase I sound) and Diastolic (Korotkoff phase IV sound) was noted.[119] Participants with blood pressures ≥140 systolic or ≥90 diastolic were referred to a primary care provider.

b. Measurement of Glucose.

Fasting venous blood samples were processed on site, stored at -70^{0}C and shipped to the Clinical Chemistry Laboratory at the Health Sciences Centre in Winnipeg, MB for analysis. Glucose levels were determined using the Hexokinase/G6P-DH assay on the BM/Hitachi 917 Analyzer. Participants with fasting plasma glucose (FPG) value ≥ 7.0 mmol/L were asked to return for a repeat fasting blood glucose measurement. If the second FPG value was ≥ 7.0 mmol/L, the participant was referred to a primary care provider for follow-up.

c. Albumin Creatinine Ratio Determination.

Urine samples were collected from males and non-menstruating females and first tested for protein, nitrite, leukocytes and blood by Multistix Reagent strips. Positive tests were repeated and if still positive subjects were referred to a primary care provider. Menstruating females were asked to return at another time.

Samples negative on a test strip were tested for albumin:creatinine ratio (ACR) by the Bayer DCA 2000 Point-of-Care Analyzer. This machine has displayed high levels of reproducibility and has been validated against gold standard measurements. The DCA2000 microalbumin reagent cartridge detects albumin by immunoturbidimetric direct antibody-antigen aggregation and measures creatinine colorimetrically using the Benedict-Behre reaction. The concentrations of both albumin and creatinine were measured in the reagent cartridge; the albumin and creatinine concentrations and the ACR were reported on the display screen.[42] Albumin concentrations greater than 300mg/L were not quantitated, but reported as >300mg/L. Participants with a positive test (>2.8mg/mmol for females and >2.0 mg.mmol for males) were retested over a three month period.[120] Those that were negative on the first determination were not retested.

3.3 Analysis

a. Definitions and Data Coding

Albumin-creatinine ratio (ACR) ≥ 2 mg/mmol for males and ≥2.8 mg/mmol for females was considered in the microalbuminuric range. Definite microalbuminuria was defined as the presence of at least 2 of 3 samples positive for microalbuminuria, as suggested by the Canadian Diabetes Association. [14] Probable microalbuminuria was defined as only 1 sample positive for microalbuminuria in those individuals who did not have the requisite three samples required to make the diagnosis of definite microalbuminuria, or to conclusively rule it out. Individuals with dipstick positive proteinuria (>1g/L) or those with ACR in the macroalbuminuric of proteinuric range (≥30mg/mmol) on at least one sample were considered to have proteinuria. For logistic regression analysis and comparison with the non-albuminuric group all proteinuric and albuminuric groups were combined.

Hematuria was defined as the presence of blood on the unrinalysis done prior to microalbuminuria testing. Microscopic quantitation of red blood cells (RBC) was not performed.

Smoking, years of smoking and cigarettes smoked per day were self-declared at the time of the questionnaire. A pack of cigarettes was defined as 25 cigarettes, and smoking exposure was defined as pack years (packs per day X years smoked).

Individuals were asked if they had a history of hypertension, and based on their history were considered to have a history of hypertension irrespective of their blood pressure (self-declared hypertension). Averages of blood pressures taken in each arm were calculated. Measured hypertension was considered present if either systolic blood pressure was ≥140 mmHg or diastolic pressure was ≥90 mmHg, as defined by the JNC7.[121] Because the treatment goals for diabetics and those with albuminuria was a BP <130/80 mmHg, a separate category was designated for measured blood pressures above this range.[121] A composite category of total exposure to hypertension was defined as individuals with either self-declared HTN or those with a blood pressure ≥140/90.

Diabetics were segregated into two categories, those with self declared diabetes, on oral hypoglycemics or with fasting sugars ≥7.0mmol/L were considered definite diabetics. Those with fasting sugars ≥ 5.6 mmol/L but below 7.0 mmol/L were considered to have impaired fasting glucose (dysglycemic), as in the 2003 American Diabetes Association definitions.[122]

Self awareness of kidney disease was based on a single question, asked at the time of the survey. If the answer was positive, an attempt was made to determine the cause of

the kidney disease and the age at which it began. Those with malignant or infectious causes of renal disease were eliminated.

Medication history was asked of all participants. Medication use was segregated into 6 categories, using the Compendium of Pharmaceuticals and Specialties (CPS) as reference:[123] ACEI or ARBs; any antihypertensives, diuretics and ACEI and ARBs were included in this group; oral or hypoglycemics or insulin; lipid lowering drugs; ASA and antiplatelet agents; Nitroglycerine.

Weight in kilograms and height in centimetres was collected and BMI (kg/m^2) was calculated for each subject.

b. Statistical Analysis and Analysis plan

Statistical analysis was carried out using SPSS 12.0.0 (4 Sept 2003) for Windows™ developed by Apache Software Foundation. Normally distributed continuous variables were reported as mean and standard deviation. Median and range were reported for the overall study group. Categorical values were reported as percent. Missing values of continuous values were imputed as the mean value of the entire group, for the following variables: weight, height, BMI, average systolic and diastolic blood pressure. Pack years were imputed by the average pack years for smokers only.

Baseline characteristics of the three albuminuric groups (definite and probable MAU and definite proteinuria) were compared. Proteinuric and albuminuric groups were combined in subsequent analysis. The determinants of albuminuria were modeled using logistic regression. Those with albuminuria were stratified and compared according to diabetic status. The association between albuminuria and other cardiorenal risk factors was compared in several ways. First Venn diagrams were used to illustrate the degree of overlap between albuminuria, hypertension and diabetes. Characteristics of those with no, one two and three risk factors were compared. Subjects with hematuria were compared to those without hematuria. Comparison of those with hematuria, with and without albuminuria was carried out to determine differences in hematuria between albuminuric groups. Awareness of diabetes, hypertension and albuminuria was compared. Medication use was compared between the albuminuric and non-albuminuric populations and was considered in a separate analysis, and contrasted with the blood pressure control.

Continuous variables were tested using the Students' t-test for two groups. One way ANOVA was preformed when comparing three or more groups. Tukey's tests were performed if one way ANOVA was significant. Mann-Whitney U test was used where appropriate. In the comparing equal sized groups, (proteinuria, definite and probable albuminuria), equal variances were assumed; however in comparing smaller groups to the larger population, equal variances were not assumed. Binary or categorical variables were tested using the Pearson Chi-squared test and Fisher's Exact test as appropriate.

Frequencies were reported in comparisons where the expected value was five or less, but were considered invalid for statistical purposes and the p value was not quoted.

Binary logistic regression was preformed to test determinants of albuminuria compared to the non-albuminuric population. Univariate analysis of all the candidate determinants was preformed first. Results were quoted as the Odds ratio with the 95% confidence limits and the p value. Multivariate binary logistic regression was preformed in a backward conditional fashion with the removal p value set at 0.1 to choose the final multivariate model. The final multivariate model included those that were entered and not excluded during the backward conditional logistic regression.

c. Communication of Results

Subjects received their albuminuria results at the time of testing in 2003 and were asked to communicate those to their doctor. A further letter was sent out by this investigator upon analysis of these results in those subjects with any degree of albuminuria and diabetes. (Appendix III)

Chapter 4 – Results

4.1 Characteristics of Study Sample

The study sample included 486 (20%) of a possible 2445 residents on a Manitoba First Nation who volunteered to participate in this cross-sectional health survey. A total of 485 subjects gave a sample for blood glucose determination. One subject registered did not participate further in the study, 473 subjects completed at least one question of the survey and the anthropomorphic measurements and 474 had at least one urine to assess for albuminuria. However 6 subject's urines were ineligible due to detection of hematuria, leaving 468 available for albuminuria analysis, these subjects were excluded from the analysis of albuminuria.

Table 4.1a gives the mean, standard deviation, median and range of the baseline statistics of the population for the continuous variables, while Table 4.1b gives the baseline characteristics for the categorical variables in percent. The average age of the population was 38 years with a range of 18 to 81 years, as of January 1, 2003, an arbitrary point between the collection intervals. The study sample greater than 20 years old was compared to the 2001 census figures and was not representative of the general population. (See table 4.2) The main difference appeared to be the proportion of the elderly (≥65 y.o.) in the survey sample was lower in the study sample than the census figures for the community.

Fifty three percent of the population was female. Current smokers made up 74% of the population with 82% having smoked at one time. Three pipe smokers were also

cigarette smokers and so were included as smokers. Three of 4 cigar smokers were also cigarette smokers, and one individual with only exposure to cigars was considered a non-smoker for the analysis. Overall pack-years of smoking were 6.4, with some individuals smoking as many as 70 pack-years.

A high 41% of the population was either diabetic or dysglycemic. Diabetics made up 29% of the population, while dysglycemics consisted of 12%. Individuals were on average morbidly obese (defined as BMI >30) with an average body mass index (BMI) of 31.5 kg/m2.

Two hundred and two individuals (42%) had either self-declared or blood pressure greater or equal to 140/90 by measurement. Those who declared themselves hypertensive made up 27% of the population. Those with measured blood pressures ≥140/90 made up 29%. Other co-morbidities were not available, but ischemic heart disease (IHD) prevalence was inferred by the use of nitroglycerine and was present in 6 (2%) individuals who declared their medication history.

Albuminuia was present in 95 (20%) of the population. This was broken down into proteinuria 25 (5.3%), definite microalbuminuria 29 (6.1%) and probable microalbuminuria in 29 individuals or 6.1% of the population. Hematuria was present in a total of 21 individuals, or 4.4% of the total population.

Missing values are listed in Table 4.3. The data for most variables were essentially complete with $\leq 5\%$ variables missing. Smoking and family history variables were missing in 8-17% of the individuals. Medication information was missing in almost 40% of the study population. Three subjects were prescribed medications but admitted to taking them; they were considered not to be on any medications. Missing values of continuous values were imputed as the mean value of the entire group, for the following variables: weight, height, BMI, average systolic and diastolic blood pressure. Pack years were imputed by the average pack years for smokers only.

Table 4.1a Characteristics of continuous variables of the study sample

	Mean (SD)	Median (Range)
Age at Jan 1, 2003[1]	38 (12)	36 (18, 81)
Years smoked	13 (11)	11 (0, 55)
Pack Years of Smoking	6.4 (9)	3.2 (0, 70)
Average Systolic BP[2]	127 (17)	124 (86, 200)
Average Diastolic BP[2]	77 (11)	74 (36, 128)
Weight[3]	89 (20)	86 (43, 160)
Height[4]	168 (9)	167 (141,192)
Body Mass Index[5]	31.5 (7)	30.8 (18, 56)
Average FBG[6]	6.9 (3)	5.4 (3.4, 20.6)

[1]Age in years; [2]blood pressures in mmHg, [3]Weight in Kilograms, [4]Height in cm, [5]Body Mass Index (BMI) in kg/m2, [6]Average FBG (fasting blood glucose) in mmol/L.

Table 4.1b Characteristics of categorical variables of the study sample

	Count	Percent
Female	255/485	53
Ever a Smoker[1]	393/479	82
Current Smoker[1]	350/474	74
Both DM	201/485	41
Definite Diabetic[2]	141/485	29
Dysglycemics[3]	60/485	12
Self Declared and BP≥140/90	202/478	42
Self-Declared Hypertension	122/460	27
BP≥140/90	137/473	29
Any Albuminuria	95/468	20
Proteinuria	25/468	5.3
Definite MAU[4]	29/468	6.1
Probable MAU[5]	41/468	8.6
Hematuria[6]	21/477	4.4
IHD[7]	6/293	2

[1]Smoking is self-declared; [2]Definite diabetic is on oral hypoglycemics, self declared or has a fasting glucose .≥7.0 mmol/L, [3]Dysglycemics were not definite diabetics, but had a fasting sugar ≥5.8mmol/L and <7.0; [4]Definite MAU defined as either one sample with proteinuria or 2 or more samples with microalbuminuria. [5]Probable MAU defined as only 1 sample with MAU without 2 negative samples. (Note 2 with 1/3 samples positive removed) Hematuria was a positive dipstick for Hemoglobin. [7]IHD inferred by those on nitroglycerine

Table 4.2 Comparison of study sample to 2001 census data

Age range (years)	20-24	25-44	45-54	55-64	65-84	
Study sample	66 (15.9%)	269 (60.5)	73 (16.5)	27 (6.1)	8 (1.8)	
2001 Census	75 (16.9%)	251 (56.7)	63 (14.3)	33 (7.6)	20 (5.5)	
$(0-E)^2/E$	1.08	1.29	1.6	1.09	7.2	$X^2=12.3$ $p<0.05$

Table 4.3 Frequencies of missing values

	Missing	
	Count	Percent
AGE	1	.2
Pack Years	82	17
Year of DM diagnosis	10	2.1
Number of relatives with DM	65	13
Average Systolic BP	13	2.7
Average Diastolic BP	13	2.7
Weight	16	3.3
Height	16	3.3
BMI	16	3.3
Average Fasting Glucose	1	.2
Years of smoking	39	8.0
Sex	1	.2
Ever Smoker	7	1.4
Current Smoker	12	2.5
Family history of DM	65	13
Measured or self-declared HTN	8	1.6
Self-declared HTN	26	5.3
BP ≥140/90	13	2.7
BP ≥130/80	13	2.7
IHD	193	40
On ACEI	193	40
On Anti-HTN	193	40
≥ 2 Anti HTN	193	40
Number of Anti HTN	193	40
On Hypoglycemics	193	40
On Lipid lowering meds	193	40
On ASA	193	40

4.2 Comparing Proteinuric and Albuminuric Groups.

Table 4.4 shows the number of urine tests performed for each diagnosis of the three categories of albuminuria. A total of 349 (75%) of the population only had one urine test, and a further 101 (22%) had 2 tests. One positive test was sufficient to make a diagnosis of proteinuria, but two of three positive or negative tests are required to definitively diagnose MAU, given the variability of the ACR. Therefore 125 (26%) subjects had an adequate number of urine samples to definitively rule albuminuria in or out, with the remainder of the subjects [343 (74%)] not having an adequate number of urine samples taken to make a definitive determination of their albuminuria status.

Tables 4.5a and 4.5b respectively compare the continuous and categorical variables of the individuals with proteinuria, definite microalbuminuria and probable microalbuminuria. In general the three groups are very homogeneous. However the fasting glucose of those with proteinuria is significantly higher than those with probable MAU. There were also more diabetics and no dysglycemics in the proteinuria group compared to either of the other groups.

Medication treatment characteristics of the two groups are given in Tables 4.5c. Due to the small number of subjects in each of the groups on medications, these comparisons are not statistically valid, except to reveal equal number of those on hypoglycemic medications in each group.

Given the relatively small number of subjects in each of the albuminuric groups compared to the non-albuminuric population and their similarity in most parameters, the groups were combined in subsequent analysis.

Table 4.4 Albuminuria category by number of tests done

Number of Urine tests done	Albuminuria Category				
	Normo-albuminuria	Probable Micro-albuminuria	Definite Micro-albuminuria	Proteinuria	Totals
1	321 (69%)	22 (4.7%)	0	6 (1.3%)	349 (75%)
2	48 (10%)	19 (4.0%)	20 (4.2%)	14 (3%)	101 (22%)
3	4 (0.8%)	0	9 (1.9%)	5 (1.1%)	18 (3.8%)
Totals	373 (80%)	41(8.8%)	29 (6.2%)	25 (5.3%)	468

Table 4.5a Characteristics of the three albuminuria categories (continuous variables)

	Albuminuria			
	Proteinuria n=25 Mean (SD)	Definite n=29 Mean (SD)	Probable n=41 Mean (SD)	P value
Age[1]	45 (14)	41 (12)	41 (13)	0.4
Years smoked	12(11)	13 (11)	15 (16)	0.6
Pack-years	5.1 (6)	6.5 (8.3)	9.4 (15)	0.3
Average Systolic BP[2]	138 (20)	135 (21)	131 (16)	0.3
Average Diastolic BP[2]	82 (12)	79 (10)	79 (13)	0.5
No. of Antihypertensives *	0.6 (0.9)	0.2 (0.6)	0.5 (.9)	0.5
Weight[3]	88 (14)	95 (15)	94 (17)	0.2
Height[4]	167 (10)	169 (9)	168 (7)	0.4
Body Mass Index[5]	32 (6)	33 (5)	33 (6)	0.6
Average Fasting Glucose[6]	11.6* (4.8)	9.3 (4.4)	8.6 (4.4)	0.03
Years Dx with diabetes	7.1 (7)	3.2 (6.2)	3.5 (6.5)	0.052

Statistics by one way ANOVA, [1]Age in years; [2]blood pressures in mmHg, [3]Weight in Kilograms, [4]Height in cm, [5]Body Mass Index (BMI) in kg/m2, [6]Average FBG (fasting blood glucose) in mmol/L.

*Proteinuria group sig higher glucose than probable MAU group by Tukey (p=0.02), no difference between the other groups

Table 4.5b Characteristics of the three albuminuria categories (categorical variables)

	Albuminuria			
	Proteinuria n=25 %	Definite MAU n=29 %	Probable MAU n=41 %	P value
Female	36	31	49	0.3
Ever Smoker	80	72	68	0.5
Current Smoker	68	68	62	0.8
Declared or Measured HTN	72	66	70	0.9
Self-Declared Htn	48	34	47	0.5
BP ≥140/90	56	48	43	0.6
BP ≥130/80	68	72	63	0.4
IHD*[1]	4	0	3.0	**
Hematuria	16	10	2	**
Definite DM and dysglycemics	84	79	61	0.08
Definite Diabetics	84	55	49	0.01
Dysglycemics	0	28	12	**
Family Hx of DM	87	72	91	0.1

Statistics by pearson Chi-square, [1]IHD determined by those on Nitrates, **groups to small to compare statistically

Table 4.5c Treatment characteristics of three albuminuria categories (Categorical Variables)

	Albuminuria			
	Proteinuria n=24 %	Definite MAU n=13 %	Probable MAU n=30 %	P value
Any Antihypertensives	33	15	37	**
>2 Antihypertensives	20	8	10	**
ACEI/ARB	25	8	23	**
Lipid Lowering drugs	8	8	3.0	**
ASA	8	8	3.0	**
Hypoglycemics	67	46	47	0.3

Statistics by pearson Chi-square. **groups to small to compare statistically

4.3 Albuminuric vs Non Albuminuric Population

The populations with and without albuminuria are compared in Tables 4.6a and 4.6b. Those with albuminuria tended to be significantly older (42 vs 36 years $p<0.0001$) and albuminuria progressively increased with age. (Fig 4.1) More subjects with albuminuria were male (60% vs 45%, $p=0.01$). Interestingly fewer were ever smokers, (72 vs 84% $p=0.007$) however neither years of smoking nor pack-years of smoker were significantly different in either population.

More subjects with albuminuria were hypertensive by any measure and almost 70% had been told they were hypertensive or had hypertension by measurement vs only 35% of those without albuminuria ($p<0.0001$). In keeping with this, blood pressures were significantly higher in the albuminuric group than those without albuminuria (134/80 vs 125/76, $p\leq0.001$). Optimal blood pressure in those with albuminuria is <130/80, but this was achieved in only 32% of those with albuminuria, while 50% of those without albuminuria had a blood pressure <130/80.

The albuminuric population were significantly heavier and had a higher BMI as well. (Fig 4.2) This increased weight and BMI may be related to the increased number of diabetic and dysglycemic subjects (72% vs 33%, $p<0.0001$), in the albuminuric group. Those with albuminuria also had a longer duration of diabetes and a significantly higher average fasting glucose (10mmol/L vs 6 mmol/L $p<0.0001$). While almost 50% of those

with any degree of albuminuria were diabetic, 42% of the diabetics in the study were albuminuric.

There were a similar proportion of subjects in the group with albuminuria with IHD, as determined by nitrate use (3 vs 1.8%). Hematuria was more prevalent in the albuminuric group. (8.2 vs 2.9% p=0.03)

Figure 4.3 compares the proportion of those with albuminuria to diabetic category. Proportion of those with albuminuria or any form of MAU increased with diabetic category. ($p<0.0001$) Proteinuric groups were too small in number to compare statistically. Comparing individual groups, there were significantly more subjects with any form of albuminuria in the Diabetic category than in either the dysglycemic or the normoglycemic categories (DM vs dysglycemic 42% vs 21 $p<0.001$, DM vs normoglycemic 42% vs 9.4 $p<0.0001$). There were also significantly more with any form of MAU in the DM group vs the normal group (27% vs. 7.9, $p<0.0001$)

Table 4.7 compares the characteristics of those with albuminuria in the three diabetic categories. There was a significant difference in age between the diabetic classes ($p<0.0001$). Age progressively and significantly increased from non diabetics (33 y.o.) to dysglycemics (44 y.o., $p<0.05$ vs nondiabetics) to diabetics (46 y.o.$p<0.05$ vs dysglycemics, $p<0.0001$ vs normoglycemics). While there was no difference in categorical hypertension, the average systolic and diastolic blood pressure was increased in the diabetics vs the non diabetics (sBP 138 vs 125 $p<0.01$, dBP 82 vs 75 $p<05$) Table

7a through 7c explore characteristics of those with and without albuminuria in the three diabetics categories. Those with no diabetes have a significantly higher combined category of self declared and measured hypertension (Alb vs non-alb 54 vs 25 p=0.004), however no significant difference in actual blood pressure or medication use was seen. Those with dysglycemia had a higher proportion of blood pressures ≥140/90 (alb vs non-alb 58 vs 23% p=0.03). Those with diabetes where less likely to be female, had a higher systolic blood pressure and had a higher fasting glucose

Table 4.6a Characteristics of those with albuminuria vs non albuminuria (continous variables)

	Albuminuria		
	Yes n= 95 Mean (SD)	No N= 373 Mean (SD)	P Value
Age	42 (13)	36 (12)	<0.0001
Years smoked	14 (13)	13 (11)	0.4
Pack-years	8 (13)	6 (8)	0.2
Average Systolic BP[1]	134 (19)	125 (15)	<0.0001
Average Diastolic BP[1]	80 (12)	76 (10)	0.001
No. of Antihypertensives*	0.5 (0.8)	.16 (.5)	<0.0001
Weight[2]	93 (16)	87 (21)	0.01
Height[3]	168 (9)	168 (9)	.5
Body Mass Index[4]	33 (6)	31 (7)	0.03
Average Fasting Glucose[5]	10 (5)	6 (3)	<0.0001
Years Dx with diabetes	4 (7)	1 (4)	<0.0001

Statistics by Student's t-test and *Mann-Whitney U test
[1]BP in mmHg, [2]Weight in kg, [3]Height in cm, [4]BMI in kg/m^2, [5]Average fasting glucose in mmol/L

Table 4.6b Characteristics of those with albuminuria vs non albuminuria (categorical variables)

	Albuminuria		
	Yes n=95 %	No n= 373 %	p value
Female	40	55	0.01
Ever Smoker	72	84	0.007
Current Smoker	65	76	0.04
Declared or Measured HTN	70	35	<0.0001
Self-Declared Htn	44	22	<0.0001
BP ≥140/90	48	24	<0.0001
BP ≥130/80	68	51	0.004
IHD[1]	3	1.8	0.6
Hematuria	8.4	2.9	0.001
Definite DM and dysglycemics	72	33	<0.0001
Definite Diabetics	60	21	<0.0001
Dysglycemics	13	12	0.8
Family Hx of DM	85	82	0.6

Statistics by pearson Chi-square and *Fisher's exact test.
[1]IHD determined by those on Nitrates

Table 4.7 Comparison of albuminuria by diabetic categories.

	Albuminurics			
	DM n=57 Mean (SD) or %	**Dysglycemic** n=12 Mean (SD) or %	**Non DM** n=26 Mean (SD) or %	p
Age[1]	46 (11) a+ c*	44 (11) b*	33 (12)	<0.0001
Female	46%	33%	31%	0.4
Ever Smoker	71%	67%	77%	0.8
Curr Smoker	65%	58%	69%	0.8
Pack-years	9.0 (14)	6.6 (10)	4.4 (5.4)	0.3
Measured or previous HTN	79%	58%	54%	0.06
BP ≥ 140/90	54%	58%	31%	0.1
BP ≥ 130/80	71%	83%	50%	0.07
Average Systolic BP[2]	138 (19) a&	135 (23)	125 (13)	0.01
Average Diastolic BP[2]	82 (12) a*	80 (11)	75 (9.4)	0.03
On any Antihypertensives	38%	25%	17%	
ACEI/ARB	26%	25%	5.6%	
Weight[3]	93 (14)	97 (12)	90 (22)	0.5
Body Mass Index[4]	33 (4.8)	34 (4.4)	32 (7.8)	0.3
Average Fasting Glucose[5]	12 (3.8) a+ c+	6.0 (0.2)	5.0 (0.5)	<0.0001
Years Dx with diabetes	7.4 (7.3) a+ c+	0	0	<0.0001
Relatives with DM	2.5 (1.8) a*	1.6 (1.8)	1.3 (1.2)	0.02

Statistics by one way ANOVA and Tukey's for continuous variables and Chi-Squared for categorical determinants, not valid and p value not stated if minimum expected value <5, [1]Age in years; [2]blood pressures in mmHg, [3]Weight in Kilograms, [4]Body Mass Index (BMI) in kg/m2, [5]Average FBG (fasting blood glucose) in mmol/L.

a. significance difference between non DM and DM
b. significance difference between non DM and Dysglycemic
c. significant difference between DM and Dysglycemic

* $p<0.05$, &$p<0.01$, @$p<0.001$, + $p<0.0001$

Table 4.7a Comparison of albuminuria in Non-diabetics.

	Non Diabetics		
	Albumin n=26 Mean (SD) or %	non-Albumin n=251 Mean (SD) or %	p
Age[1]	33 (12)	33 (10)	0.8
Female	31%	51%	0.07
Ever Smoker*	77%	85%	.4
Curr Smoker	69%	77%	0.5
Pack-years	4.4 (5.4)	5.3 (5.9)	0.4
Measured or previous HTN	54%	25%	0.004
BP ≥ 140/90	31%	19	0.2
BP ≥ 130/80	50%	44%	0.7
Average Systolic BP[2]	125 (13)	122 (14)	0.3
Average Diastolic BP[2]	75 (9.4)	74 (10)	0.9
On any Antihypertensives*	17%	5%	0.09
ACEI/ARB*	5.6%	2%	0.4
Weight[3]	90 (22)	84 (20)	0.2
Body Mass Index[4]	32 (7.8)	30 (6.9)	0.3
Average Fasting Glucose[5]	5.0 (0.5)	5 (0.4)	0.7
Relatives with DM	1.3 (1.2)	1.6 (1.3)	0.3

Statistics by Student's t test for continuous variables and Chi-Squared for categorical determinants, * Statistics by Fisher's exact test. [1]Age in years; [2]blood pressures in mmHg, [3]Weight in Kilograms, [4]Body Mass Index (BMI) in kg/m2, [5]Average FBG (fasting blood glucose) in mmol/L

Table 4.7b Comparison of albuminuria in dysglycemics

	Dysglycemics		
	Albumin n=12 Mean (SD) or %	non-Albumin n=44 Mean (SD) or %	p
Age[1]	44 (11)	39 (13)	0.2
Female	33%	54%	0.2
Ever Smoker	67%	86%	0.2
Curr Smoker	58%	73%	0.5
Pack-years	6.6 (10)	7.1 (9.6)	0.9
Measured or previous HTN	58%	39%	0.4
BP ≥ 140/90*	58%	23%	0.03
BP ≥ 130/80*	83%	60%	0.2
Average Systolic BP[2]	135 (23)	126 (13)	0.07
Average Diastolic BP[2]	80 (11)	76 (8.7)	0.2
On any Antihypertensives*	25%	9%	0.4
ACEI/ARB*	25%	5%	0.3
Weight[3]	97 (12)	95 (20)	0.7
Body Mass Index[4]	34 (4.4)	34 (6.7)	0.9
Average Fasting Glucose[5]	6.0 (0.2)	6 (0.3)	0.8
Years Dx with diabetes	0	0	
Relatives with DM	1.6 (1.8)	2 (1.7)	0.5

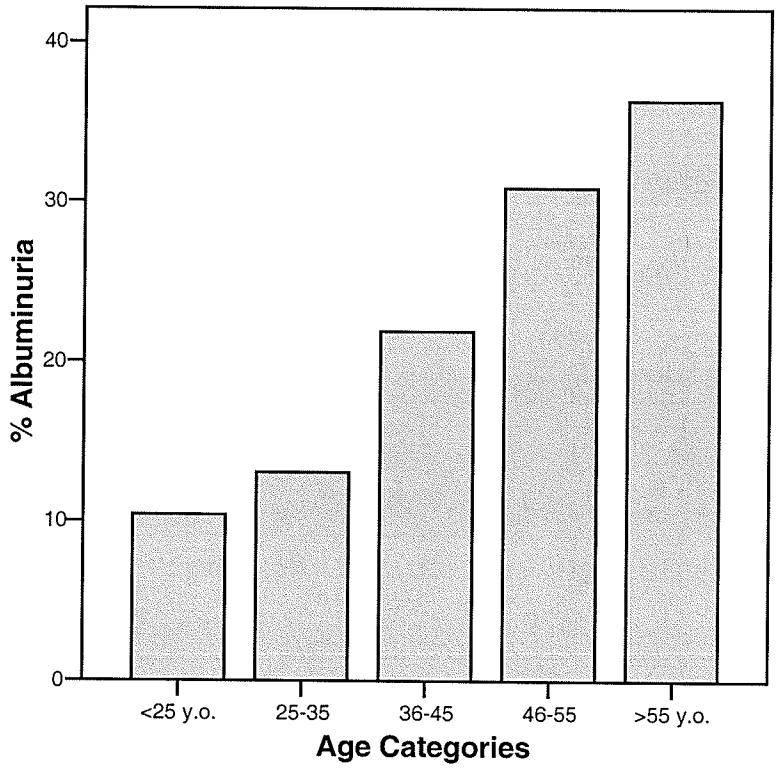
Statistics by Student's t test for continuous variables and Chi-Squared for categorical determinants,* statistics by Fisher's exact test. [1]Age in years; [2]blood pressures in mmHg, [3]Weight in Kilograms, [4]Body Mass Index (BMI) in kg/m2, [5]Average FBG (fasting blood glucose) in mmol/L.

Table 4.7c Comparison of albuminuria in diabetics.

	Diabetics		
	Albumin n=57 Mean (SD) or %	non-Albumin n=78 Mean (SD) or %	P
Age[1]	46 (11)	43 (12)	0.1
Female	46%	60%	0.03
Ever Smoker	71%	81%	0.3
Curr Smoker	65%	72%	0.4
Pack-years	9.0 (14)	8 (10)	0.7
Measured or previous HTN	79%	66%	0.1
BP ≥ 140/90	54%	42%	0.2
BP ≥ 130/80	71%	68%	0.7
Average Systolic BP[2]	138 (19)	132 (15)	0.047
Average Diastolic BP[2]	82 (12)	79 (10)	0.09
On any Antihypertensives	38%	26%	0.2
ACEI/ARB	26%	15%	0.2
Weight[3]	93 (14)	92 (22)	0.8
Body Mass Index[4]	33 (4.8)	34 (7.3)	0.7
Average Fasting Glucose[5]	12 (3.8)	9.9 (3.5)	<0.0001
Years Dx with diabetes	7.4 (7.3)	5 (6.8)	0.06
Relatives with DM	2.5 (1.8)	2.2 (1.2)	0.4

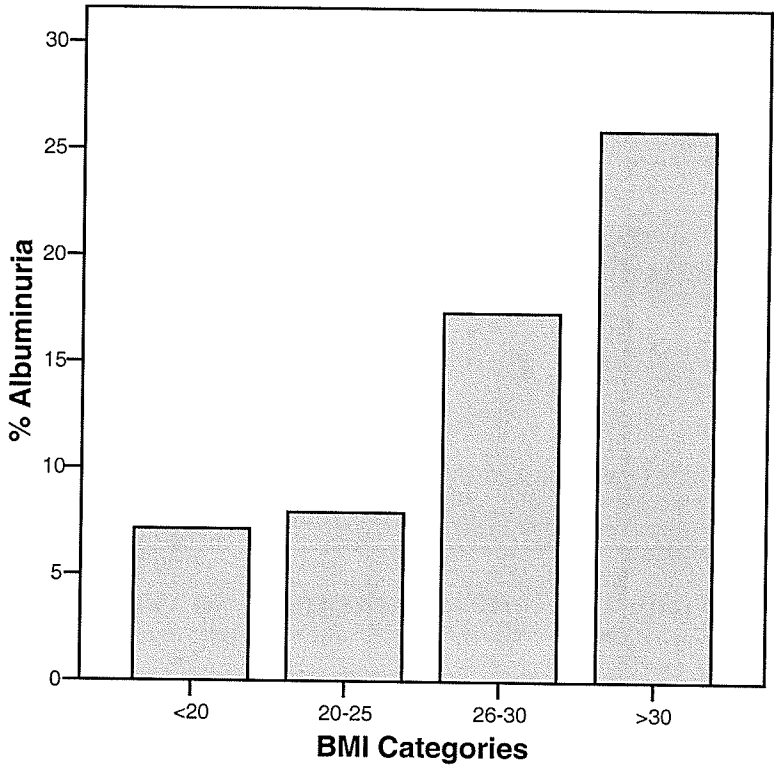
Statistics by Student's t test for continuous variables and Chi-Squared for categorical determinants, * statistics by Fisher exact test. [1]Age in years; [2]blood pressures in mmHg, [3]Weight in Kilograms, [4]Body Mass Index (BMI) in kg/m2, [5]Average FBG (fasting blood glucose) in mmol/L.

Fig 4.1 Percent albuminuria by age categories



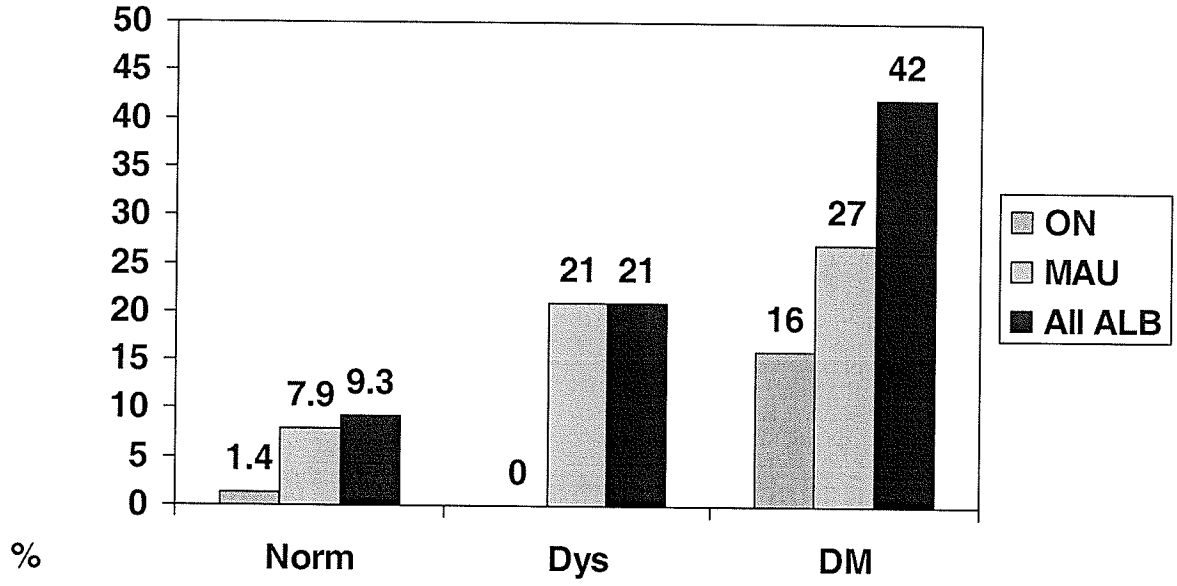
p<0.0001 by Pearson chi-square

Fig 4.2 Percent albuminuria by BMI categories



P=0.02 by Pearson Chi-square

Fig 4.3 Percent albuminuria by Diabetic categories



All alb -- P<0.0001 DM vs normal and p<0.01 DM vs normoglycemia

MAU -- p<0.0001 DM vs nromoglycemia

4.4 Logistic Regression

Odds ratios and 95% CI are listed in Table 4.8b for both univariate and multivariate logistic regression. Multivariate logistic regression was performed in a backwards conditional fashion, the terms entered into the analysis are listed in Table 4.7a, and the final model terms are identified in Table 4.8b. The r^2 value of the final model was 0.26.

Univariate analysis indicated odds of having MAU increased 4% for each year increase in age. Age was not significant in the final multivariate model. When both fasting glucose and years of diabetes were removed from the model and age was included, age became significant suggesting high multicolinearity between the diabetic factors and age. (model not shown) Females had a lower association with MAU than males, which remained significant in the multivariate model.

Smokers were less associated with albuminuria than non-smokers and smoking appeared protective in univariate analysis, however, it did not achieve significance in the multivariate model.

There were 7 diabetes factors. The two factors looking at number of family members with diabetes and family history of diabetes did not achieve significance in the univariate model. The presence of definite diabetes as defined by self-declared diabetes

or by a fasting glucose ≥7 mmol/L was seven times more likely to be associated with albuminuria than the in normal population. Dysglycemic, those with impaired glucose tolerance and a fasting sugar >5.6 but <7mmol/L were also significantly associated with albuminuria. For each increase in average fasting glucose, albuminuria increase by 27% in the univariate model, and 20% when controlled for gender, years diagnosed with DM, systolic blood pressure and BMI. Length of time of diabetes was also a significant predictor of albuminuria and confirms the natural history of albuminuria (see discussion) Neither categorical variable of definite diabetes nor dysglycemia were significant in the multivariate regression, likely due to high multicoliniarity with years of diabetes (ie exposure time) and average fasting glucose (i.e. diabetes control).

Six factors examined the effect of various aspects of blood pressure on albuminuria. All were significant in the univariate analysis, but systolic blood pressure was independently associated with albuminuria in the multivariate model and risk of albuminuria increased by 2% for every mmHg of increase systolic blood pressure. (1.02 (1.005, 1.035), p= 0.009)

Lastly, weight and BMI were both significant alone, but BMI was an independent predictor of albuminuria in the multivariate analysis, after accounting for average fasting glucose, gender, years diagnosed with DM and systolic blood pressure. (1.042 (1.001, 1.085), p= 0.04)

Table 4.8a Factors inserted into the initial backwards conditional regression

Age Gender Ever Smoker Current smoker Pack-years	Definite diabetics and Dysglycemics Average glucose Years Diagnosed with DM	Self-declared HTN Systolic BP Diastolic BP	Hematuria Weight BMI

Table 4.8b Univariate and multivariate logistic regression

	Univariate Odds ratio[1] (95%CI), p value	Multivariate Odds ratio[1] (95%CI), p value
Age, years[1]	1.040 (1.021,1.059), <0.0001	
Sex:	Male = 1 (referent) Female = 0.560 (0.354, 0.885), 0.013	Male = 1 Female = 0.407 (0.23, 0.771), 0.002
Ever smoker	non-smoker = 1 (referent) Evr smoke = 0.485 (0.285,0.825), 0.008	
Current smoker	non-smoker = 1 (referent) Curr smoker = 0.587 (0.36, 0.955), 0.032	
Years smoking[1]	1.008 (0.988, 1.029), 0.417	
Pack years[1]	1.015 (0.991, 1.04), 0.215	
Definite or dysglycemic	Normoglycemic = 1 (referent) DM/dys = 5.329 (3.235, 8.778), <0.0001	
Definite DM	Non- DM = 1 DM = 7.718 (4.412, 13.5), <0.0001	
Dysglycemic	Non – Dysglycemic = 1 Dysglycemic = 3.291 (1.768, 6.128), <0.0001	
Ave fasting glucose[1], mmol/L	1.27 (1.192, 1.352), <0.0001	1.2 (1.115, 1.29), <0.0001
Years Dx with DM[1]	1.127 (1.078, 1.179), <0.0001	1.057 (1.004, 1.113), 0.03
Family Hx of DM	No Family Hx DM = 1 Family Hx = 1.148 (0.596, 2.213), 0.68	
Number of family with DM[1]	1.121 (0.957, 1.313), 0.156	
Self declared or Measured HTN	Non-HTN = 1 HTN = 4.11(2.53, 6.69), <0.0001	
Self declared HTN	Non-HTN = 1 HTN = 2.749 (1.69, 4.47), <0.0001	
BP≥140/90	BP<140/90 = 1.0 BP≥140/90 = 2.86 (1.79, 4.56), <0.0001	
BP ≥130/80	BP<130/90 = 1.0 BP ≥130/80=1.91(1.86, 3.07), 0.008	
Systolic BP[1], mmHg	1.032 (1.019, 1.046), <0.0001	1.02 (1.005, 1.035), 0.009
Diastolic BP[1], mmHg	1.034 (1.013, 1.055), 0.002	
Weight[1], Kg	1.014 (1.003, 1.025), 0.001	
BMI[1]	1.036 (1.004, 1.070), 0.026	1.042 (1.001, 1.085), 0.04
Hematuria	No Hematuria=1.0 Hematuria = 3.079 (1.201, 7.877), 0.019	

[1]Per unit change for Continuous variables

4.5 Treatment Characteristics

Medication treatment characteristics of those with albuminuria versus those without are shown in Table 4.9. Medication information was only available for 287 (59%) of the individuals in the study. More of those with albuminuria were on antihypertensives (31.9% vs 11.5% $p<0.0001$) and a slightly higher number of antihypertensives (0.5 medications vs 0.16), than those without albuminuria, likely reflecting the higher percentage of albuminurics with hypertension. Drugs targeting the renin-angiotensin system, appropriate care for those with albuminuria, were more prevalent in the albuminuric group (21.7% vs 6% $p<0.0001$).

Hypertension was more prevalent in the albuminuria group (table 4.6b, 70 vs 35% $p<0.0001$). Figure 4.4 shows the relative penetration of blood pressure medication in those deemed hypertensive by self-declaration or measurement. Those with albuminuria were significantly more likely to be on antihypertensive treatment (42% vs 25% $p<0.05$). ACEI or ARB use was higher in those with albuminuria, but not significantly. (29% vs 15% $p=0.06$)

Medications for diabetes were also more prevalent among those with albuminuria (53.6% vs 16.5% $p<0.0001$), once again likely reflecting the higher prevalence of diabetes in the albuminuric population and appropriate medical care in this group. There

were no differences between the groups with regards to use of lipid lowering drugs or ASA.

The blood pressures of those on ACEI or ARBs or any antihypertensives are shown in Table 4.10. Despite the use of antihypertensives or ACEI/ARBs, blood pressures of those on these medications in the entire study sample were significantly higher than those not on the medications. (On antihypertensives vs no antihypertensives 139/83 vs 128/76 $p<0.0001$, On ACEI/ARBs vs no ACEI/ARBs 137/82 vs 129/77 $p<0.05$) Of those with albuminuria, neither antihypertensive nor ACEI/ARBs use revealed a significantly different blood pressure from those not on medications. (On antihypertensives vs no antihypertensives 140/83 vs 134/80 p=NS, On ACEI/ARBs vs no ACEI/ARBs 138/80 vs 135/81 p=NS)

Table 4.9 Medication treatment characteristics of those with albuminuria vs non albuminuria (categorical variables)

	Albuminuria		
	Yes n=69 %	No n=218 %	p Value
Any Antihypertensives	32	12	<0.0001
>2 Antihypertensives*	43	32	0.5
No. of Antihypertensives+	0.5 (0.8)	.16 (.5)	<0.0001
ACEI/ARB	22	6	<0.0001
Lipid Lowering drugs	5.8	3.2	0.3
ASA	5.8	3.2	0.3
Hypoglycemics	53.6	16.5	<0.0001

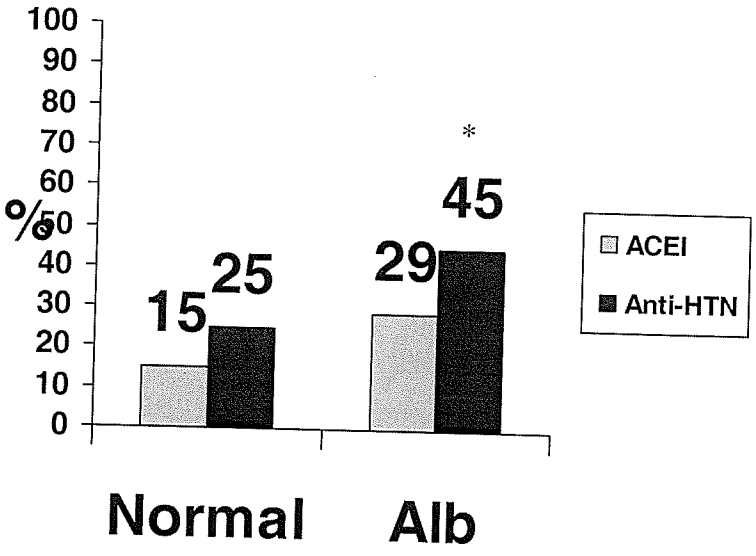
Statistics by pearson Chi-square and *Fisher's exact test

+ expressed as mean and (SD), statistics by Mann-Whitney U test

Table 4.10 Blood pressure control in those on antihypertensives

	Entire sample			Albuminurics		
	Anti-hypertensives n=46	No Anti-hypertensives n= 243	p	Anti-hypertensives n=21	No Anti-hypertensive n=46s	p
Systolic	139	128	<0.0001	140	134	0.3
Diastolic	83	76	<0.0001	83	80	0.5
	Ace/ARB n=28	No ACEI/ARB n=261	P	Ace/ARB n=15	No ACEI/ARB n=53	P
Systolic	137	129	0.02	138	135	0.6
Diastolic	82	77	0.03	80	81	0.8

Fig 4.4 Proportion of Hypertensive subjects on Antihypertensives and ACEI/ARB



* $p<0.05$

4.6 Risk Factor Distribution.

Figure 4.5 shows the relationship between albuminuria, definite diabetes and self declared or measured hypertension. Individuals were included in the analysis if they had information on at least 2 of the target risk factors. At least 54% of the population had at least one or more readily identifiable risk factor; 20% had albuminuria, 29% had diabetes and 42% had self-identified hypertension or had a blood pressure $\geq$ 140/90. Of those at risk, 126 (27%) had only one risk, 89 (19%) had two risks and 44 (9%) had all three risks. Four percent had albuminuria alone as a risk factor without hypertension or accompanying diabetes. Of those 17 individuals, two (11%) had proteinuria and 7 (39%) had definite microalbuminuria.

Differences between those with one, two or three risk factors and no risk factors are shown in Table 4.11. There was a significant and progressive increase in age at each interval between no, one and two risk factors. Those with three risk factors were older than those with one or no risk factors. Average systolic and diastolic blood pressures were significantly greater between each of the risk factor groups and those with no risk factors. Blood pressures were not significantly different between any of the risk factor groups individually, except those with three versus one risk factor had significantly higher systolic blood pressures. BMI's were also increased in those with any number of risk factors compared to those with no risk factors. Fasting blood glucose increased

significantly with each increase in the number of risk factors. Smoking ironically decreased as the number of risk factors increased.

Those with albuminuria and one, two or three risk factors are explored in table 4.12. Those with Three and two risk factors in total are significantly older than those with only albuminuria as a risk factor. Despite a greater percentage on antihypertensives, the average systolic is significantly higher than with only one or two risk factors.

Table 4.13, compares those with only one risk factor to those with no risk factors. As expected, those with hypertension had higher systolic and diastolic blood pressures those with no risk factors and those with only albuminuria and diabetes. Those with diabetes had higher blood sugars than all the other categories. Those with isolated albuminuria were not readily distinguishable from those with no risk factors by these characteristics, except for a lower prevalence of smoking ($p=0.002$, analysis not shown).

Figure 4.5 Relationship of albuminuria, definite diabetic status and self declared or measured HTN

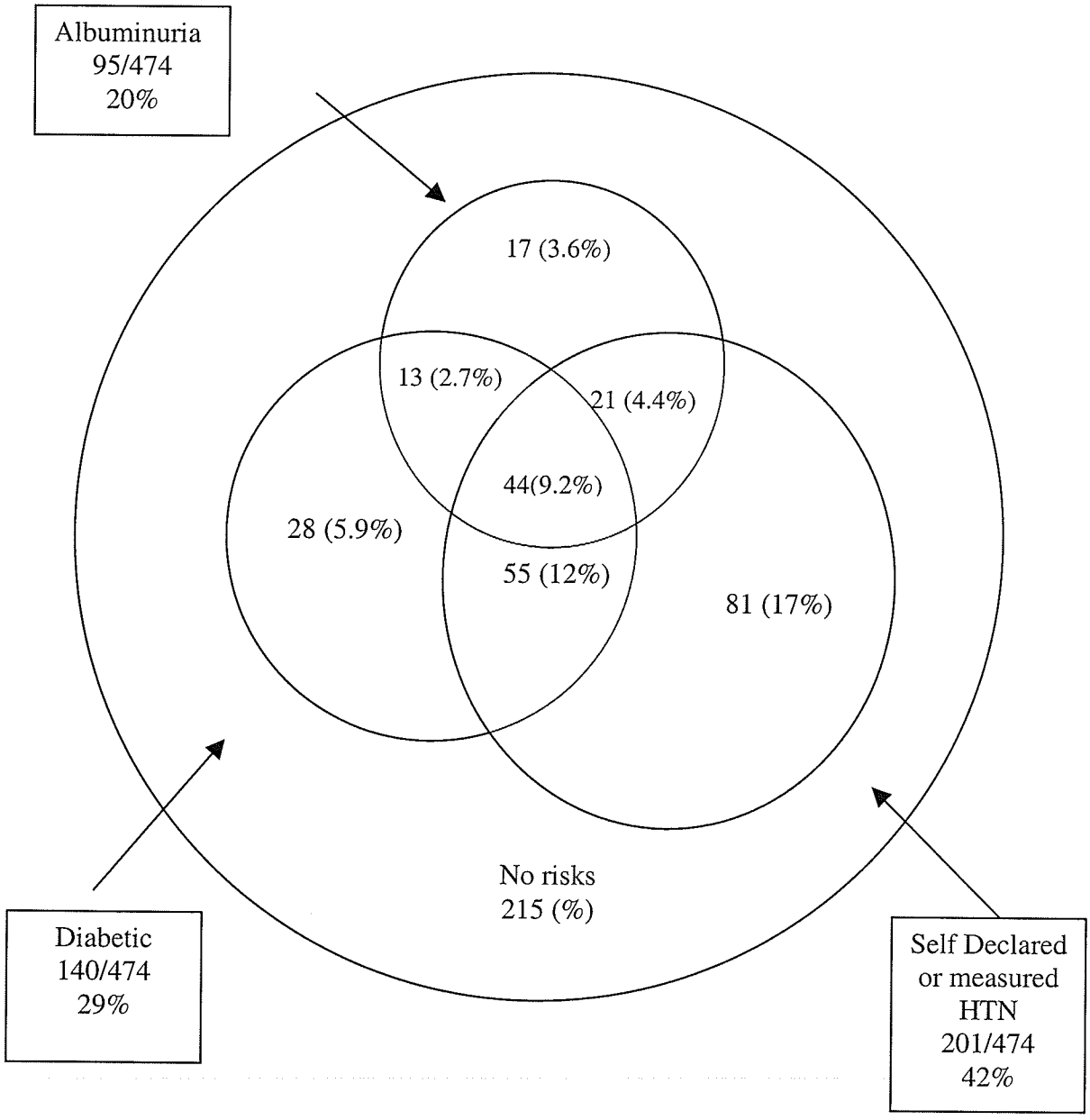


Table 4.11 Comparison of those with no, one, two or three risk factors

	Risk factors				
	Three n=44 Mean (SD) or %	**Two** n=89 Mean (SD) or %	**One** n=126 Mean (SD) or %	**None** n=215 Mean (SD) or %	p
Age[1]	46 (10)$^{c+,\ e@}$	45 (10)$^{b+,d+}$	38 (11)$^{a+}$	33 (10)	<0.0001
Female	39%	61%	52%	51%	0.2
Ever Smoker	72%	76%	82%	87%	0.05
Curr Smoker	67%	68%	74%	77%	0.3
Years smoked	15 (14)	15 (14)	14 (11)	11 (9.2)	0.05
Pack-years	9 (15)	7.4 (9.7)	6.7 (8.7)	5.4 (5.9)	0.05
Albuminuria	100%	40%	14%	0	
ON	36%	8.2%	1.6%	0	
Average Systolic BP[2]	143 (19)$^{c+,\ e+,f*}$	136 (16)$^{b+,d+}$	130 (16)$^{a+}$	118 (10)	<0.0001
Average Diastolic BP[2]	84 (13)$^{c+,\ e*}$	80 (10)$^{b+}$	79 (10)$^{a+}$	72 (6.7)	<0.0001
Any anti-Hypertensives	48%	29%	10%	1.8%	<0.0001
ACEI	34%	17%	5.2%	0	
Weight[3]	95 (13)^{c*}	92 (20)$^{b\&}$	89 (21)	85 (20)	0.001
Body Mass Index[4]	33 (4.6)^{c*}	34 (6.5)$^{b+}$	32 (7)	30 (7)	<0.0001
Average Fasting Glucose[5]	12 (3.8)$^{c+,\ e+,\ f*}$	9.8 (4.4)$^{b+,\ d+}$	6.2 (2.4)$^{a@}$	5.1 (0.5)	<0.0001
Years Dx with diabetes	7.1 (8)$^{c+,\ e+,\ f@}$	4.7 (6.7)$^{b+,\ d+}$	1.1 (4)	0	<0.0001

Statistics by one way ANOVA and tukey's for continuous variables and Chi-Squared for categorical determinants, not valid and p value not stated if minimum expected value <5 [1]Age in years; [2]blood pressures in mmHg, [3]Weight in Kilograms, [4]Body Mass Index (BMI) in kg/m2, [5]Average FBG (fasting blood glucose) in mmol/L.

a. significance difference between no risks and one risk
b. significance difference between no risks and two risks
c. significant difference between no risks and three risks
d. significant difference between one risk and two risks
e. significant difference between one risk and three risks
f. significant difference between two risks and three risks

* $p<0.05$, &$p<0.01$, @$p<0.001$, + $p<0.0001$

Table 4.12 Comparison of those with Albuminuria with, one, two or three risk factors

	Risk factors			
	Three n=44 Mean (SD) or %	**Two** n=33 Mean (SD) or %	**One** n=17 Mean (SD) or %	p
Age[1]	46 (10) [b&],	43 (15) [a*]	33 (11)	0.002
Female	39%	50%	24%	0.2
Ever Smoker	72%	79%	59%	0.3
Curr Smoker	67%	69%	53%	0.5
Years smoked	15 (14)	15 (13)	8.5 (10.8)	0.3
Pack-years	9 (15)	7 (7.9)	4.4 (8.9)	0.4
Average Systolic BP[2]	143 (19)[b+,c@]	132 (16)[a*]	118 (7.9)	<0.0001
Average Diastolic BP[2]	84 (13)[b&,c*]	78 (9.7)	73 (7.4)	0.001
Any anti-Hypertensives	48%	17	0	
ACEI	34%	8.7	0	
Weight[3]	95 (13)	92 (17)	90 (20)	0.5
Body Mass Index[4]	33 (4.6)	33 (6.5)	31 (6.8)	0.4
Average Fasting Glucose[5]	12 (3.8)[b+,c@]	8.7 (5)[a*]	5.3 (0.6)	<0.0001
Years Dx with diabetes	7.1 (8)[b+]	3.1 (5.5)[c*]	0	<0.0001

Statistics by one way ANOVA and tukey's for continuous variables and Chi-Squared for categorical determinants, not valid and p value not stated if minimum expected value <5 [1]Age in years; [2]blood pressures in mmHg, [3]Weight in Kilograms, [4]Body Mass Index (BMI) in kg/m2, [5]Average FBG (fasting blood glucose) in mmol/L.

a. significance difference between one risk and two risks
b. significance difference between one risk and three risks
c. significant difference between two risks and three risks

* $p<0.05$, &$p<0.01$, @$p<0.001$, + $p<0.0001$

Table 4.13 Comparison of those with no risks vs one risk categories.

	Risk factors				
	DM only n=28 Mean (SD) or %	**Alb only** n=17 Mean (SD) or %	**HTN only** n=81 Mean (SD) or %	**None** n=219 Mean (SD) or %	p
Age[1]	38 (9.3)	33 (11)	39 (12) c+	33 (10)	<0.0001
Female	57%	24%	56%	51%	0.1
Ever Smoker	96%	59%	81%	87%	0.005
Curr Smoker	86%	53%	74%	78%	0.07
Pack-years	9 (8.3)	4.6 (8.7)	6.4 (8.3)	5.6 (6.2)	0.046
Average Systolic BP[2]	121 (8.6)	118 (7.9)	136 (16) e+,c+,f+	118 (10)	<0.0001
Average Diastolic BP[2]	73 (7.1)	73 (7.4)	83 (13) e+,c+,f+	72 (6.8)	<0.0001
On any Antihypertensives	4.8%	0%	15%	1.8%	
Weight[3]	88 (21)	90 (20)	99 (22)	85 (20)	0.4
Body Mass Index[4]	32 (8.3)	31 (6.8)	32 (6.7)	30 (7.1)	0.2
Average Fasting Glucose[5]	9.6 (3.8) a+,d+,e+	5.3 (0.6)	5.2 (0.6)	5.1 (0.5)	<0.0001
Years Dx with diabetes	5.1 (7.1) a+,d+,e+	0	0	0	<0.0001
Relatives with DM	2.4 (1.0)	1.3 (1.5)	1.7 (1.4)	1.7 (1.4)	0.06

Statistics by one way ANOVA and tukey's for continuous variables and Chi-Squared for categorical determinants not valid and p value not stated if minimum expected value <5, [1]Age in years; [2]blood pressures in mmHg, [3]Weight in Kilograms, [4]Body Mass Index (BMI) in kg/m2, [5]Average FBG (fasting blood glucose) in mmol/L.

a. significance difference between no risks and DM
b. significance difference between no risks and Alb
c. significant difference between no risks and HTN
d. significant difference between DM and Alb
e. significant difference between DM and HTN
f. significant difference between Alb and HTN

* p<0.05, &p <0.01, @p<0.001, + p<0.0001

4.7 Hematuria

Twenty one subjects had hematuria on at least one occasion. Tables 4.14a and 4.14b contain the univariate analysis of the continuous and categorical variables respectively. There is an association with diabetes and dysglycemia (76 vs 39% p= 0.001), primarily due to the presence of definite diabetes as dysglycemia was not significantly associated. Albuminuria was also associated with hematuria. (42 vs 19 p=0.01). Additional significant associations with higher average glucose and more years diagnosed with diabetes, go along with the relationship of hematuria to diabetes. Increased BMI also was associated with hematuria (35 vs 31 p=0.03)

More of those with hematuria had albuminuria than those without hematuria, (42 vs 19 p=0.01). Table 4.15a and 4.15b characterise those with hematuria in which we know the albuminuria status. Six of those with hematuria never had an albuminuria test and therefore only 15 subjects remain. Given the small numbers the groups do not differ significantly in any of the determinants except that 100% of those with hematuria and no accompanying albuminuria are female.

Table 4.14a Characteristics of those with hematuria vs those without (continuous variables)

	Hematuria		
	Yes n=21 Mean (SD)	No n=455 Mean (SD)	p value
Age	41 (9)	37 (12)	0.1
Years smoked	17 (11)	13 (11)	0.06
Pack-years	8 (8)	6 (9)	0.4
Average Systolic BP	134 (21)	127 (16)	0.04
Average Diastolic BP	77 (10)	76 (11)	0.7
Weight	96 (18)	88 (20)	0.09
Height	167 (8)	168 (9)	0.6
Body Mass Index	35 (8)	31 (7)	0.03
Average Fasting Glucose	9.9 (5.7)	6.7 (3.2)	<0.0001
Years Dx with diabetes	4.8 (7)	1.6 (4.5)	0.002

Table 4.14b Characteristics of those with hematuria vs those without (categorical variables)

	Hematuria		
	Yes n=21 %	No n= 455 %	p value
Female	62	51	0.3
Smoker*	86	82	1*
Declared or Measured HTN	57	41	0.2
Self-Declared Htn	39	26	0.2
BP >140/90	38	29	0.3
BP >130/80	65	54	0.3
Albuminuria	42	19	0.01
Definite DM and dysglycemics	76	39	0.001
Definite Diabetics	62	27	0.001
Dysglycemics	14	12	1*
Family Hx of DM	83	81	1*

Statistics by Pearson Chi-squared and * Fisher's exact test.

Table 4.15a Characteristics of those with hematuria with and without albuminuria(continuous variables)

	Albuminuria		
	Yes n=8 Mean (SD)	No n=7 Mean (SD)	p value
Age	41 (9)	41 (12)	0.9
Years smoked	14 (12)	17 (12	0.6
Pack-years	4.4 (4.9)	6.8 (7.8)	0.5
Average Systolic BP	131 (19)	136 (21)	0.6
Average Diastolic BP	78 (13)	79 (9)	0.9
Weight	91 (15)	98 (21)	0.5
Body Mass Index	33 (5.6)	38 (9.6)	0.2
Average Fasting Glucose	13 (6.2)	7.6 (3.5)	0.06
Years Dx with diabetes	8.5 (8.4)	3.1 (4.1)	0.2

Table 4.15b Characteristics of those with hematuria with and without albuminuria(categorical variables)

	Albuminuria		
	Yes n=8 %	No n= 7 %	p value
Female	38	100	0.03*
Smoker*	75	86	1*
Declared or Measured HTN	57	40	1*
Self-Declared Htn	75	57	0.6*
BP >140/90	50	43	1*
BP >130/80	63	71	1*
Definite DM and dysglycemics	100	71	0.2*
Definite Diabetics	75	71	1*
Dysglycemics	25	0	0.5*
Family Hx of DM	88	86	1*

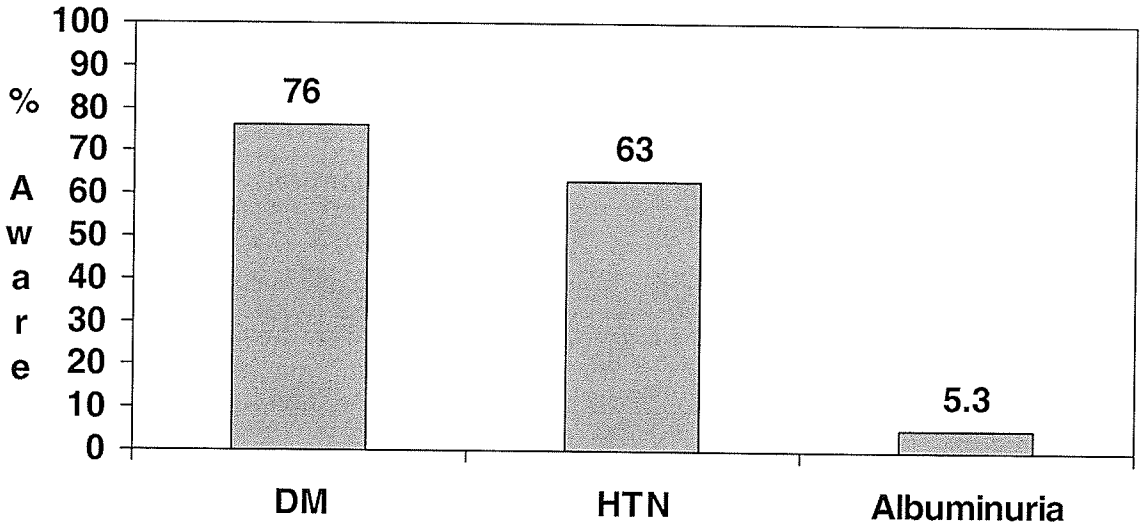
Statistics by Pearson Chi-squared and * Fisher's exact test.

4.8 Awareness of Kidney Disease

A question of kidney disease awareness was asked of all the study participants. Only 10 individuals (2%) of the study population had any personal awareness of kidney disease. Figure 4.6 compares those aware of diabetes, hypertension and albuminuria. Seventy six percent of those with on oral hypoglycemics, previously diagnosed diabetes and hyperglycemia (FBS$\geq$ 7.0mmol/l) were aware of their condition, while hypertension awareness was present in 63% of those with a BP $\geq$ 140/90 or with previously diagnosed hypertension. In contrast, 5 individuals (5.3%) with albuminuria were aware of kidney disease. Awareness of those with more severe disease, proteinuria was 17% (4/24), while awareness of those with definite MAU was 3.4%(1/29). The higher awareness among those with more severe disease suggests the question that was asked had some legitimacy. Only one individual (5%) of those with hematuria was aware of kidney disease.

When asked the form of kidney disease, seven of the ten who indicated that they had kidney disease gave further explanation. Only three indicated some knowledge of underlying renal disease which could be related to a disease associated with albuminuria —"Dr. wants to put me on dialysis", "microalbuminuria" and "scar on one kidney". All three of these individuals had albuminuria, and one had hematuria. Three individuals indicated a prior malignancy of the kidney (none of these had hematuria) and one indicated urinary tract infection, these individuals were not counted in the awareness of renal disease.

Figure 4.6 Awareness of disease states in the Study population.



Chapter 5 – Discussion

The high rates of diabetes and renal complications of diabetes (ESRD) have been well described among the Canadian FN people.[69, 71, 124-126] Significant rates of renal complications (ESRD) among non-diabetic FN people are also seen.[19, 70] Microalbuminuria is well recognized as a significant precursor to either diabetic or non-diabetic renal disease. Microalbuminuria prevalence among North American FN people in the United States has been described. However, this writer is not aware of any published literature regarding population based microalbuminuria screening studies of FN people in Canada.

A. Renal disease Characteristics

5.1 Albuminuria

Independent risk factors for albuminuria in the multiple logistic regression were; female gender [OR 0.407 (95% CI 0.23, 0.771), p=0.002], average fasting glucose [OR 1.2 (95% CI 1.115, 1.29),p <0.0001], years diagnosed with diabetes [OR 1.057 (95% CI 1.004, 1.113), p=0.03], systolic BP [OR 1.02 (95% CI 1.005, 1.035), p=0.009], and BMI [OR 1.042 (95% CI 1.001, 1.085), p=0.04].

Sex – The current study found female gender protective for albuminuria, [OR 0.407 (95% CI 0.23, 0.771), p=0.002], independent of fasting glucose, years with diabetes, systolic blood pressure or BMI. This association was also found in the Strong Heart Study.[62] This contrasts with the NHANES III and Pima Indian non-diabetic data, in which women had significantly more albuminuria than men.[6, 61] The NHANES III

study, however, did not use a lower cut-off for ACR in males, as did the current study. A differential ACR cut-off due to the higher excreted creatinine in males, has been supported by many investigators and is supported by the Canadian Diabetes Association practice guidelines, [14, 28, 31, 32] and may account for the differences between the NHANES and Pima Indian non-diabetic data and the current study. In the Pima diabetic population and in the Zuni Indian population studies, no gender differences were seen.[3, 6, 9] Men with albuminuria tend to have a worse mortality than women,[127] and therefore the increased albuminuria in men is concerning.

Diabetes – Diabetes was associated with albuminuria in two different determinants. There was an association with albuminuria with increasing fasting blood glucose as well as increasing years of diabetes. In the current study, 35% of diabetics and dysglycemics had albuminuria, this proportion climbs to 42% when only definite diabetics are considered. This is 1.5 times more frequent than in general US population in the NHANES III study in which 28.8% of diabetics had albuminuria. It is however very similar to the Pima population in which 47% of the diabetic population has albuminuria and 39% of diabetics and dysglycemics had albuminuria.[6]

In the current study fasting glucose was an independent association with albuminuria [OR 1.2 (95% CI 1.115, 1.29),p <0.0001]. The single fasting glucose performed in this study is unlikely to be sufficient to judge a subject's long term glucose control. More likely the association indicates that fasting glucose is simply a marker for the presence or absence of diabetes. It is more likely that increased years of diabetes [OR

1.057 (95% CI 1.004, 1.113), p=0.03] and exposure to the diabetic milieu is a more important factor in the development of albuminuria

BMI – Increased BMI [OR 1.042 (95% CI 1.001, 1.085), p=0.04] was independently related to increased prevalence of albuminuria in the study sample. Increased BMI has been described as a risk factor for albuminuria and proteinuria.[128] Mechanisms include the hyperfiltration which can lead to a focal segmental glomerulosclerosis (FSGS).[128] While increased BMI has been described in people of First Nations ancestry,[129-131] it has not been previously described as an independent risk factor for microalbuminuria in this population. In fact Nelson et al, described increased albuminuria with lower BMI, despite higher association with type II diabetes, which is associated with increased BMI.[7] This may be due to previous studies focusing on the diabetic population, who tend to have higher weight and thus higher BMI, and thus in these studies, higher BMI is simply a marker for diabetes. In contrast, in this population it was independently related to albuminuria.

Hypertension – Hypertension is well described in the literature as a risk factor for albuminuria.[132-134] In this study systolic, but not diastolic blood pressure was independently related to microalbuminuria in the multiple logistic regression analysis. This may simply have been that systolic blood pressure has a higher association with albuminuria than diastolic blood pressure, as has been shown in other studies.[135]

Forty percent of the general population had a blood pressure ≥140/90, or were self declared hypertensives, which is more than some FN populations.[136] Forty eight percent of those with albuminuria had a blood pressure in the hypertensive range and 67% had a blood pressure above the recommended (≥130/80), for those with albuminuria.[121] Blood pressure is readily treatable and while poor rates of treatment are not unusual in the general[1] and FN population, more efforts to control blood pressure is certainly warranted. (see section D)

Smoking – Smoking has been described in other studies as an independent risk factor for albuminuria and deteriorating renal function.[137-139] There was a very high prevalence of smoking as up to 82% of the study sample smoked at one time and 74% were current smoker at the time of the data collection. This range is high for a Caucasian population. American Indian and Alaskan Natives smoking rates are also lower and have also been described in the 21 to 44% range.[140] A similar high rate of smoking has been described in other Canadian FN populations.[141] Interestingly there were significantly fewer smokers among the population with albuminuria in the univariate analysis, but did not achieve significance in the multiple logistic regression analysis. Among those with albuminuria are many with diabetes and hypertension. They likely have had increased awareness and concern for their health status, and therefore may have been less likely to smoke. In addition they likely would have had more contact with health care professionals, and would undoubtedly have been extensively counselled to stop smoking. Perhaps the anti-smoking counselling would make them less likely to admit current or

past smoking history due to higher awareness of how negatively it is viewed by health care workers.

Age – Age was not included in the final multivariate model, likely due to high multicolinearity with time of diabetes and diabetes itself. It has been found by other authors as a significant risk factor for albuminuria.[61] Age was progressively higher in those with albuminuria compared to non diabetics in dysglycemics and diabetics. While by no means confirmatory, this suggests a possible difference in lead time. As albuminuria is a risk factor for diabetes,[142] those younger individuals with dysglycemia and even without diabetes, may develop diabetes as they age.

The study population was younger than the census population of 2001 and the age group over 65 was not as well represented.

5.2 Hematuria

Hematuria was found in a relatively small number of subjects [21(4.4%)] of the overall population. There was a high association with hematuria and diabetes and microalbuminuria. Most individuals with both albuminuria and hematuria had diabetes, suggesting that diabetic nephropathy can be manifested by hematuria, which has been described in up to 30% of diabetics.[113, 143] Those with hematuria and not albuminuria were all female and primarily diabetic. Non-renal conditions are a possibility, especially in the absence of albuminuria. Additional information such as presence of pyuria and leukocyte esterase was not available, but the hematuria may be related to urinary tract

infection (UTI), to which diabetics and females are more prone.[144] Menstral contamination was possible as well. Alternatively, renal or bladder malignancy was possible.

Primary glomerular diseases may explain the hematuria in the non-diabetic population with hematuria. Primary glomerular diseases may also be present in the diabetic population. [112, 113] Certainly, other glomerular diseases that manifest primarily as hematuria have been described in Canadian and international FN people including; hereditary nephritis[71, 115], IgA nephropathy[145], mesangial proliferative GN[76, 114], and post-streptococcal GN.[52, 146]

Given the high prevalence of diabetes, the simultaneous presence of glomerular diseases manifesting in a small proportion of the diabetics would not be entirely unexpected.

B. Screening for Albuminuria

Albuminuria screening has been considered in the general population based on the NHANES III data, however only 8.3% of this large study had any degree of albuminuria and 11 people would have to be screened to find one with albuminuria.[61, 147] Given that 20% of the FN population in this study has albuminuria the burden of disease is higher than the general population and only 5 people would have to be screened in this FN population to find one with albuminuria. As interventions are available, screening for albuminuria in the FN population would be warranted. Population based screening and treatment programs have been shown to be effective in reducing renal failure deaths and all cause natural deaths in an Australian aboriginal community; targeting the combined renal and cardiovascular risks of hypertension, diabetes with any albuminuria and those with overt albuminuria without other risk factors.[95] While these programs can be complex to initially set up, an integrated approach involving the community, physicians, nurses and allied health workers has been shown to significantly improve diabetic outcomes including glucose control, blood pressure and cholesterol control, in a FN community.[92]

An alternative to widespread albuminuria screening would be to simply treat based on the known and more readily identifiable risk factors of hypertension and diabetes. In this study that approach would have missed 18 individuals or 4% of the entire population, who may be at risk for progressive renal failure or cardiovascular

disease. Kiberd and Jindal[88] argue on an economic basis to use drugs targeting the renin-angiotensin system in all diabetics without screening, however that approach in this population would treat 22 diabetics (21% of diabetics) with good blood pressures and no albuminuria, subjecting them to potential real, if small, risks of a pharmaceutical agent. In addition screening provides prognostic information about renal and cardiac risks which may motivate the patient and the treating physician to achieve intervention goals.

Recommendations in those with Albuminuria and no diabetes or hypertension do not exist. Albuminuria is a risk factor for cardiovascular mortality in diabetics and non-diabetics [96-102, 104, 105] and can precede diabetes.[142] A recent trail in over 800 individuals showed a non-significant trend to improvement in cardiovascular mortality.[148] In addition the HOPE study showed a decreased incidence of new diabetes with ACEI treatment.[149] In the FN population, at high risk for diabetes and CV disease, a randomized placebo controlled trial of ACEI in those with non-diabetic, non-hypertensive albuminuria would be ethical and warranted.

C. Disease Awareness

Only five individuals (5.3%) with albuminuria were aware of their kidney disease. This is significantly worse than the general population, where 24% of those with moderate renal dysfunction and albuminuria were aware of their renal disease. [110] The comparison to those in the general population with renal dysfunction is likely not appropriate as measures of renal function were not available in this study. Awareness of renal disease was also worse than awareness of other disease states in other FN populations, where 50% were aware of their diagnosis of hypertension. [111]

Only three of those who claimed to be aware of kidney disease gave an explanation for their kidney disease that would be consistent with albuminuria or that indicated an awareness of albuminuria and potential progressive renal disease. This suggests either a deficit in personal disease awareness or a lack of information in general about kidney disease. A screening and information program (see section B) could be started and would have several goals. First, general kidney disease education for the population would outline the importance of screening, natural history and the treatments available for albuminuria. Second, a motivated and informed population would be screened. Third, aggressive treatment of albuminuria especially albuminuria associated with hypertension and diabetes could be undertaken.

Patient awareness of albuminuria was low, however 3.7 times more of those with albuminuria were on ACEI/ARBs than those without albuminuria (22 vs 6% $p<0.0001$). As ACEI/ARBs are appropriate agents to treat those with albuminuria, this suggests that physicians may have been aware of the albuminuria and were treating it. Possible health care worker awareness did not translate into patient awareness. Health care worker awareness did not confer protection, as even those on ACEI or on antihypertensives had poor blood pressure control.

D. Treatment of Albuminuria

Treatment of albuminuria is multifaceted, but the mainstays of treatment are good blood pressure control, preferably with a drug targeting the renin-angiotensin system and glucose control.

Rates of treatment of antihypertensive medication were higher in the albuminuric population (32 vs 12% p <0.0001), but were poor overall with only 32% of hypertensives, even those with knowledge of their hypertension, receiving treatment. Rates of antihypertensive use are known to be poor, but were better in other studies of FN people up to 64%.[150] Control of systolic hypertension to <130 mmHg in the study population with albuminuria was 34%, which while far from optimal was better than in other populations, where control was achieved in only 10%.[1]

Treatment of hypertension, particularly hypertension related to diabetes with drugs targeting the renin-angiotensin system, specifically ACEI and ARBs, is a well recognized strategy to prevent and treat its sequele including microalbuminuria.[151, 152 1] Only 22% of those with albuminuria were appropriately treated with ACEI in this study, a proportion that was not different between definite and probable albuminurics and those with proteinuria. Even the few subjects on ACEI or ARBs had an average blood pressure above the recommended (≥130/80) for those with albuminuria and diabetes. Increasing

the penetration of ACEI in the population has been shown to improve the outcome of not only renal disease but mortality. [95]

While not all the albuminuric individuals in the study were diabetic, over 70% were diabetic or had dysglycemia. Therefore controlling diabetes would be an important target of intensive treatment among the FN population to help prevent albuminuria progressive renal disease as has been shown primarily in type I,[89] and to a lesser extent in type II diabetes.[90] Despite 81% of diabetics in this study on treatment with hypoglycemics, the average fasting glucose among diabetics was 11.5mmol/L. Improvement of this parameter alone by diet, exercise and medication, would likely not only reduce albuminuria, but prevent the development of albuminuria in those without evidence of early diabetic nephropathy.

Overall, better control of two readily identifiable and treatable risk factors for albuminuria, namely hypertension and hyperglycemia, would be an important measure in the effort to prevent and treat albuminuria, and prevent progressive renal disease.

E. Limitations of the Study

This study had many limitations. As it was a volunteer sample of subjects, self-selection bias may exist. Those with known disease or those who suspect they may have disease may systematically avoid entering the study, while those who are more compliant and concerned about their health may be more likely to attend. These combined potential selection biases would be additive and may bias towards a healthier sample. The age of the study subjects was not comparable to the 2001 census data, and in fact did not reflect the older (>65 years) category. As more elderly individuals are more prone to health problems and had more albuminuria, this lends credence to the possibility that the volunteer sample was healthier than the general population. The bias toward a healthier study sample means that the true prevalence of albuminuria is likely higher in the general population.

The primary goal of the study was determination of true albuminuria status and its determinants. Unfortunately 43% of those considered to have albuminuria in the study did not a have sufficient urine tests to make a definitive determination of their true status. Undoubtedly some within the population who only had one test positive and were considered to have albuminuria do not truly have albuminuria (false positive) and thus are potentially skewing the sample of those with true micoroalbuminuria. There were significant difficulties in collecting a second urine. By protocol these had to be performed in three months. FN subjects were suspicious of the researchers and had to be

persuaded to return for a second sample. People also moved away after three months or lost interest in the study.

Conversely 321 individuals (69%) within the population considered to be normo-albuminuric also only had one urine test. While this was per protocol, three samples would have been better to confirm the absence of albuminuria and decrease the possibility of false negatives. While from a research point of view this would have provided a greater certainty of the absence of albuminuria, it was not feasible in a study focusing more broadly on all diabetic complications

In addition, differentiation of MAU from macroalbuminuria and overt nephropathy was difficult. In individuals where only a dipstick urine for protein was positive (proteinuria >1g/L) were categorized as having proteinuria, an approach which has been suggested by some authors.[2] Dipstick proteinuria has been shown to correlate with either proteinuria or MAU, however without further quantitation some uncertainty exists into which category low level proteinuria belongs.[153] The analyzer itself did not give accurate readings beyond 300mg/L for albuminuria, thereby possibly misclassifying some individuals with urine albumins greater than that amount. This limitation was overcome by combining the albuminuric categories at the cost of losing the ability to analyze proteinuric versus MAU groups.

The spot urine test itself, although recommended for population screening, correlates at times poorly with a 24 hour or timed urine for MAU. Obtaining a 24 hour or

timed urine in such a large sample would have been an enormous and expensive undertaking, and if not collected properly its accuracy would not have substantially improved upon the present method.

In addition to three spot ACR samples for MAU, a serum creatinine would have provided additional valuable information about renal disease status. In the NHANES III, population study,[147] significant portions of the population were in renal failure. The prevalence of albuminuria did not adequately reflect this as 37% of those with a GFR <30ml/min did not have albuminuria. In the current study the population has more albuminuria and is at higher risk for developing albuminuria and progressive renal failure than the general population given the high prevalence of diabetes and hypertension. Therefore a significant portion would likely have had stages II through IV kidney disease. A serum creatinine would thus provide more prognostic information about the prevalence of renal disease as well as the possibility of renal disease progression than a urine albumin alone.

Hematuria was tested primarily by urine dipstick. Recording the urine nitrate and leukocytes would have helped to rule out urinary tract infection. A subsequent urine microscopy with quantitation RBCs and dysmorphic cells, would have been more informative about the possible etiology of the hematuria and its significance. As some hematuric and indeed albuminuric diseases are hereditary, detailed questions about family members with renal failure would have been useful and perhaps provided additional information in this study.

Self-awareness of kidney disease was detected by one question asked amid a host of other questions about health status. This question was not validated, and may not have been answered due to difficulties in comprehending medical terms or misunderstanding about the word disease. A small qualitative study could have been done with members of the FN who were known to have renal failure or kidney disease. This study could have sought the best culturally appropriate and understandable terms to use. A series of questions using the appropriate terms could be generated and the survey validated in a renal clinic setting with members of the FN. The low frequency of self-awareness in this study is interesting and disturbing, but it is not clear if awareness is truly low, or whether the instrument was inadequate.

Finally, medication information was only available in 59% of the study population. In addition some of the medication histories were based on recall, which may have missed valuable information. In Manitoba all drugs dispensed at a pharmacy are entered into a province-wide DPIN (Drug prescription Information Network) system. An additional request in the consent could have been added to access the DPIN for correlating and confirming medication histories. This would have provided not only accurate drug histories, but also information about doses and medication adherence.

F. Importance and Future Directions

This study has shown a prevalence of albuminuria (combined MAU and proteinuria) among a FN people in Manitoba to be as high as 20%. This is much higher than the 5.1 to 9.2% in the general population, [61;44;60] and similar to the prevalence of many of the First Nations in the United States. [3, 9 62;6] Higher prevalence of disease has been described in some surveys of the Pima Indians where a prevalence as high as 48% has been described. However, this was in an older population with more diabetes than in the current study. The population in this study was younger than the population of the FN at the 2001 census. Given that older individuals tend to have more diabetes and albuminuria, this means the population of the FN likely have an even higher prevalence of albuminuria and diabetes than the study population indicate.

Most of the FN people affected by albuminuria were unaware of their potential for progressive renal disease. Aggressive screening programs for the combined risk factors of diabetes, hypertension and microalbuminuria would help detect those with diabetes, hypertention and albuminuria who should be targets for intervention. While those with albuminuria without other risk factors are at risk for CV mortality, progressive renal failure and diabetes, there is no literature to support treatment of this group. A randomized controlled trial could therefore be ethically and scientifically justified.

As expected, albuminuria was highly correlated with diabetes. Given the natural history of diabetic nephropathy the albuminuria is likely to progress. Future interventions should target not only the high rate of hypertension, but also address the low use of drugs targeting the renin-angiotensin system. Drug therapy alone is not the answer, but interventions targeting the whole person should be undertaken. Interventions such as diet and exercise programs would help not only the high rate of obesity, but would improve diabetes and hypertension control. This would diminish amount of albuminuria, as well as prevent new onset of albuminuria and ultimately renal failure and ESRD.

While much of the discourse in Aboriginal health surrounds diabetes, the presence of significant numbers of people with hematuria, as well as the 4% of those with MAU without other risk factors, confirms the presence of non-diabetic renal disease. Further investigations should be focused on this group; first to help ascertain the cause of their hematuria or albuminuria and second to intervene appropriately. In those with MAU and no other indications to treat, an randomized controlled trial of ACEI or ARB use vs placebo in this otherwise high-risk population

Ongoing longitudinal follow-up of the individuals in this study would help further the understanding of the significance of individual health determinants. In addition, further follow-up would give important information about the natural history of albuminuria in the population. The response to treatment and community intervention strategies could also be assessed.

Appendix I:
Research Ethics Board Approval Letter

UNIVERSITY OF MANITOBA

BANNATYNE CAMPUS
Research Ethics Boards

P126-770 Bannatyne Avenue
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APPROVAL FORM

Principal Investigator: Dr. James Zacharias
Supervisor: Dr. Sharon Bruce

Protocol Reference Number: H2005:230
Date of Approval: October 19, 2005
Date of Expiry: October 19, 2006

Protocol Title: "Prevalence and Determinance of Albuminuria on a Manitoba First Nation Community"

The following is/are approved for use:

- **Proposal (submitted October 18, 2005)**

The above underwent expedited review and was **approved as submitted** on October 19, 2005 by Dr. K. Brown, MD, MBA, Chair, Health Research Ethics Board, Bannatyne Campus, University of Manitoba on behalf of the committee per your received October 18, 2005. The Research Ethics Board is organized and operates according to Health Canada/ICH Good Clinical Practices, Tri-Council Policy Statement, and the applicable laws and regulations of Manitoba. The membership of this Research Ethics Board complies with the membership requirements for Research Ethics Boards defined in Division 5 of the *Food and Drug Regulations.*

This approval is valid for one year only. A study status report must be submitted annually and must accompany your request for re-approval. Any significant changes of the protocol and informed consent form should be reported to the Chair for consideration in advance of implementation of such changes. The REB must be notified regarding discontinuation or study closure.

This approval is for the ethics of human use only. For the logistics of performing the study, approval should be sought form the relevant institution, if required.

Sincerely yours,

Ken Brown, MD, MBA
Chair, Health Research Ethics Board
Faculty of Medicine

Please quote the above protocol reference number on all correspondence.
Inquiries should be directed to REB Secretary
Telephone: (204) 789-3883 / Fax: (204) 789-3414

Appendix II:
Methods of Sample collection from Dr. S. Bruce

PROTOCOL FOR MEASUREMENT OF GLUCOSE AND INSULIN

Fasting venous blood samples will be processed on site at the health centres/nursing stations and stored at -70°C. Approximately every two weeks, samples will be packed in dry ice and shipped to the Clinical Chemistry Laboratory at the Health Sciences Centre, Winnipeg for analysis. Glucose levels will be determined using the Hexokinase/G6P-DH assay on the BM/Hitachi 917 Analyzer. Participants with fasting plasma glucose (FPG) value $\geq$ 7.0 mmol/L will be asked to return for a repeat fasting blood glucose measurement. If the second FPG value is $\geq$ 7.0 mmol/L, the participant will be referred to a primary care provider for follow-up. Insulin concentration will be determined using an immunoassay (MEIA – Abbot Axsym) for quantitative measurement of human insulin in serum. Hemoglobin A1c will be measured using the DCA2000 Analyzer.

PROTOCOL FOR DETERMINING THE PRESENCE OF NEPHROPATHY THROUGH MEASUREMENT OF ALBUMIN:CREATININE RATIO

Urine albumin:creatinine ratio (ACR) will be determined using the Bayer DCA 2000 Point-of-Care Analyzer. This machine has displayed high levels of reproducibility and has been validated against gold standard measurements (Collins et al, 2001; Parsons et al, 1999). The DCA2000 microalbumin reagent cartridge contains all the reagents required for measurement of albumin and creatinine. The concentrations of both albumin and

creatinine are measured in the reagent cartridge; the albumin and creatinine concentrations and the ACR are reported on the display screen.

Procedure:

1. Upon arrival to the health centre/nursing station, female participants will be asked if they are menstruating. If yes, the test will be re-scheduled.
2. Urine samples will be collected.
3. Urine samples will be tested with Multistix Reagent strips for presence of protein, nitrite, leukocytes and blood.
4. If participant's sample is positive for any of these elements, they will be asked to return on another day and provide another sample. If urine sample tests positive for any of these elements on a second visit, participant will be referred to a primary care provider.
5. Samples negative for protein, nitrite, leukocytes and blood will be loaded into DCA2000 Analyzer.
6. Quantitative albumin and creatinine results and the ACR ratio will be recorded at completion of test (7 minutes).
7. Participants who have a positive results (> 2.8 mg/mmol for females and > 2.0 mg/mmol for males, will be re-tested for confirmation in two out of three measurements over a 3 month period. Participants who have a positive result in two out of three measurements will undergo a timed urine collection.
8. Timed urine specimens will be processed on site, frozen and shipped to the Clinical Chemistry Lab, Health Sciences Centre, Winnipeg for analysis.

Interpretation of timed urine as follows: <20 μg/min – normal; 20-200 μg/min – microalbuminuria; > 200 μg/min – macroalbuminuria. Participants with levels >20 μg/min will be referred for follow-up.

Source: Meltzer S, Leiter L, Daneman D et al. 1998 clinical practice guidelines for the management of diabetes in Canada. CMAJ 1998;159 (8 Suppl):S1-29.

PROTOCOL FOR BLOOD PRESSURE MEASUREMENT BY SPHYGMOMANOMETER

1. Measurements will be taken with a mercury manometer with mercury column at eye level.
2. Choose a cuff with an appropriate bladder width matched to the size of the arm. The optimal bladder width equals the arm circumference/2.5, with an acceptable range of 80% to 100% of the arm circumference.
3. Place the cuff so that the lower edge is 3 cm above the elbow crease and the bladder is centered over the brachial artery. The participant should be resting comfortably for 5 min in the seated position with back support. The arm should be bare and supported with the antecubital fossa at heart level. There should be no talking, and the participant's legs should not be crossed. At least two measurements should be taken in the same arm with the patient in the same position.

4. Increase the pressure rapidly to 30 mmHg above the level at which the radial pulse is extinguished.
5. Place the bell or diaphragm of the stethoscope gently and steadily over the brachial artery.
6. Open the control valve so that the rate of deflation of the cuff is approximately 2 mmHg/heart beat.
7. Read the systolic level – the first appearance of a clear tapping sound (phase I Korotkoff)- and the diastolic level - the point at which the sounds disappear (phase V Korotkoff). Record the blood pressure to the closest 2 mmHg on the manometer, as well as the arm used, and note whether the participant was supine, sitting or standing. Record the participant's heart rate.
8. If Korotkoff sounds persist as the level approaches 0 mmHg, then the point of muffling of the sound is used (phase IV) to indicate the diastolic pressure.
9. In the care of arrhythmia, additional readings may be required to estimate the average systolic and diastolic pressure. Isolated extra beats should be ignored. Note the rhythm and pulse rate.
10. Leaving the cuff partially inflated for too long will fill the venous system and make the sounds difficult to hear. To avoid venous congestion, it is recommended that at least 1 min should elapse between readings.
11. Blood pressure should be taken at least once in both arms, and if an arm has a consistently higher pressure, then that arm should be clearly noted and subsequently used for blood pressure measurement and interpretation.

12. Participants will be referred for follow-up if on two separate occasions their systolic blood pressure is ≥ 140 mmHg or diastolic blood pressure is ≥ 90mmHg.

Source: Zarnke KB, Levine M, McAlister A, et al. The 2000 Canadian recommendations for the management of hypertension: Part two – Diagnosis and assessment of people with high blood pressure. Can J Cardiol 2001;17:1249-63.

PROTOCOL FOR ANTHROPOMETRIC MEASUREMENTS

Height – A metric wall tape will be placed vertically against a wall. Participants will be instructed to stand erect, without footwear, arms hanging by the sides, feet together with the heels and back in contact with the wall. Participants will then be instructed to look straight ahead, stand as tall as possible, and take a deep breath while the measurement is taken. A set square will be place on the head, depressing the hair to make firm contact, and the field worker will mark height at the level of the lower border of the square on the wall. The distance from the floor to the pencil mark will be recorded to the nearest 0.5 cm.

Weight – A beam scale will be placed on a flat surface. Participants, wearing light clothing (shorts and t-shirt/blouse) will be instructed to remove footwear and step on the scale. Weight in kilograms will be recorded by the field worker to the nearest 0.1 kg.

Waist (Abdomen) Girth – Participants, wearing light clothing, will be instructed to stand erect with arms hanging loosely at their sides. An inelastic tape measure will be held by the field worker between his/her thumbs and index fingers with the second fingers stabilizing and leveling the tape. The tape will be placed horizontally at the level of noticeable waist narrowing. An assistant may be needed to help position the tape in a horizontal plane in obese people. In some participants waist narrowing may be difficult to identify. In that case, an indeterminate waist can be approximated by taking the girth at the estimated lateral level of the twelfth or lower floating rib. Tension will be applied to the tape sufficient to maintain its positions but not to cause indentation of the skin surface. The measurement will be taken at the end of a normal expiration. The measurement will be recorded to the nearest 0.5 cm.

Hip (Buttocks) Circumference: Participants, wearing light clothing, will be instructed to stand erect with arms hanging loosely at their sides and feet together. The field worker will squat at the side of the participant so that the level of the maximum extension of the buttocks can be seen. The tape measure is placed around the buttocks in a horizontal plane at this level without compressing the skin. An assistant may be required to help position the tape horizontally. The measurement is recorded to the nearest 0.5 cm.

Source: Canadian Society for Exercise Physiology (CSEP). The Canadian physical activity, fitness and lifestyle appraisal. Ottawa: CSEP 1996.

Appendix III:
Sample letter to all those with diabetes and Definite and Probable Microalbuminuria

Dear Study Subject

Thank you for participating in a study on diabetes and kidney disease in 2003. You have already been informed of the overall study conclusions. This letter is to inform you that during the study you had at least one abnormal urine tests for microalbuminuria. (a small but abnormal amount of protein in the urine). This can sometimes be transiently increased related to very high sugars or infections, but may also be an early warning of kidney disease. Fortunately it is treatable. It does not mean you will end up on dialysis. Your doctor may have already checked this and either found you no longer have microalbuminuria or that you still have it and is treating you. To be sure, please show your doctor this letter. Your doctor can then recheck the urine test. If you still have microalbuminuria, treatment can be started to help your kidney stay healthy. In addition there are other things you can do improve your kidney and general health. Please ask you doctor about them. . Please make sure you visit your doctor regularly, your doctor knows the details of your health the best and can make suggestions for your specific needs.

If you or a doctor has further general questions about the kidney, the Manitoba Renal program has a website www.mrp.ca or your doctor can refer you to a nephrologist.

Sincerely

James Zacharias, MD, FRCPC, Nephrologist

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