

**PREVALENCE AND ASSOCIATED RISK FACTORS FOR THE
DEVELOPMENT OF ALBUMINURIA (MICROALBUMINURIA
AND MACROALBUMINURIA) IN PATIENTS WITH TYPE 2
DIABETES ATTENDING THE NATIONAL CENTER OF
DIABETES, ENDOCRINOLOGY AND GENETIC (NCDEG) IN
JORDAN**

By

Zainab Al Hasan

Supervisor

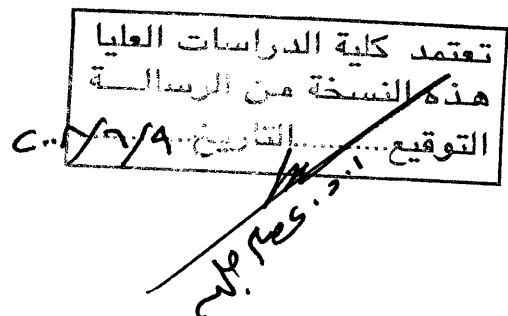
Dr. Nabil Akash M.D

**This Thesis was Submitted in Partial Fulfillment of the Requirements for the
Master's Degree in Diabetology**

Faculty of Graduate Studies

The University of Jordan

June, 2008



COMMITTEE DECISION

This Thesis (Prevalence and Associated Risk Factors for the Development of Albuminuria (Microalbuminuria and Macroalbuminuria) in Patients with Type 2 Diabetes Attending the National Center of Diabetes, Endocrinology and Genetic (NCDEG) in Jordan) was Successfully Defended and Approved on 3/6/2008.

Examination Committee

Dr. Nabil Akash, (Supervisor)
Assist. Prof. of Internal Medicine & Nephrology
(Royal Medical Services, King Hussein Medical Center)

Signature

العبد الطيب
نابيل أحمد الكاش
مستشار أمراض الكلى

Dr. Riyadh Said. (Member)
Prof. of Internal Medicine & Nephrology
(Jordan Hospital)

Riyad Said

Dr. Ayman Wahbeh. (Member)
Assist. Prof. of Internal Medicine & Nephrology
(Jordan University)

Ayman Wahbeh

Dr. Nabil Issah. (Member)
Prof. of Internal Medicine & Endocrinology
(Damascus University, Syria)

Nabil Issah

تعتمد كلية الدراسات العليا
هذه النسخة من الرسالة
التوقيع..... التاريخ 3/6/08

DEDECATION

*To the greatest man in my life, who supports my ambitious and lights my
road.....To my father.*

*To the symbol of love, who inundates me with mercy and
care To my mother.*

*To the lovely angles, who are filling my life with beautiful
smiles.....To my brothers and sisters.*

*To my husband and my children
for their everlasting love, support and trust in me during the hard times.*

ACKNOLEGEMENT

My sincere and grateful thanks go to Prof. Kamel Al-Ajlouni who taught me that desperate and success can never meet.

My deep thanks and indebtedness are expressed to my supervisor Dr. Nabil Akash whose guidance, fruitful suggestions and valuable help made the completion for this work possible

My Special gratitude goes also to Prof. Riyad Said & Dr. Ayman Wahbeh for their Valuable Comments in clarifying many aspects related to my work

My extended thanks go to Dr Yousef S. Khader for his help in statistical analysis

Words of thanks and appreciation are further extended to all staff in the National Center of Diabetes, Endocrinology and Genetics.

TABLE OF CONTENTS

Subject	Page
Committee Decision.....	ii
Dedication.....	iii
Acknowledgement.....	iv
List of contents	v
List of Tables.....	vi
List of Figures.....	vii
List of Abbreviation	viii
Abstract (in English)	x
Introduction.....	1
Natural history of the diabetes nephropathy.....	4
Pathogenesis.....	5
Screening and Diagnosis of albuminuria.....	8
Literature Review.....	10
Study Objectives.....	30
Methodology.....	31
Statistical analysis	36
Ethical consideration.....	36
Results.....	37
Discussion.....	46
Conclusion and Recommendations.....	52
Data Sheet for Type 2 DM.....	54
References.....	56
Abstract in Arabic.....	66

LIST OF TABLES

NUMBER	TABLE CAPTION	PAGE
1	Definition of Abnormalities in Albumin Excretion.	9
2	Comparison of the Prevalence of Microalbuminuria and Macroalbuminuria in Type 2 Diabetes in Different Population Based Studies.	19
3	Sociodemographic and Anthropometric Characteristics of the Participants.	37
4	Clinical and Biochemical Characteristics of the Participants.	38
5	Prevalence of Diabetic Microalbuminuria and Macroalbuminuria According to Sociodemographic and Anthropometric Characteristics.	41
6	Prevalence of Diabetic Microalbuminuria and Macroalbuminuria According to Clinical and Biochemical Characteristics.	42
7	Logistic Regression Analysis Factors Associated with Microalbuminuria.	44
8	Logistic Regression Analysis Factors Associated with Macroalbuminuria.	45

LIST OF FIGURES

NUMBER	FIGURE CAPTION	PAGE
1	Potential Interactions Between Metabolic and Haemodynamic Pathways in Mediating Diabetic Renal Disease.	6
2	The Anti-Diabetic Treatment Modalities Used By the Participants.	39
3	The Anti-Hypertensive Treatment Modalities Used By the Participants.	40

List of Abbreviation or Symbols

ADA, American Diabetes Association

ACEI, Angiotensin converting enzyme Inhibitors

AGE, Advanced Glycation Endproducts

ARBs, Angiotensin Receptor Blockers

BMI, Body Mass Index

DBP, Diastolic Blood Pressure

DCCT, Diabetes Control and Complication Trail

DHCCB, Dihydropyridine ca-channel blockers

DM, Diabetes Mellitus

DNP, Diabetes Nephropathy

DR, Diabetes Retinopathy

ESRD, End Stage Renal Disease

FBS, Fasting Blood Sugar

GFR, Glomerular Filtration Rate

HbA 1c, Glycosylated Hemoglobin

HDL, High density lipoprotein

LDL, Low density Lipoprotein

MA, Microalbuminuria

MAA, Macroalbuminuria

NDCCB, Non dihydropyridine ca-channel blocker

NIDDM, Non –Insulin- Dependent Diabetes Mellitus

OHD, Oral Hypoglycemic Drugs

PKC, Protein kinase C

SBP, Systolic Blood Pressure

TGF β , Transforming growth factor β

UKPDS, United Kingdom Prospective Diabetes Study

VEGF, Vascular endothelial growth factor

WHO, World Health Organization

**PREVALENCE AND ASSOCIATED RISK FACTORS FOR THE
DEVELOPMENT OF ALBUMINURIA (MICROALBUMINURIA
AND MACROALBUMINURIA) IN PATIENTS WITH TYPE 2
DIABETES ATTENDING THE NATIONAL CENTER OF
DIADETES, ENDOCRINOLOGY AND GENETIC (NCDEG) IN
JORDAN.**

**By
Zainab Al Hasan**

**Supervisor
Dr. Nabil Akash**

ABSTRACT

To investigate the prevalence of diabetic albuminuria (microalbuminuria and macroalbuminuria) among patients with type 2 diabetes mellitus (DM) attending the National Center of Diabetes, Endocrinology, and Genetics (NCDEG) among the study group. The second objective of the study is to determine if there is any association between diabetes albuminuria (micro-and macroalbuminuria) and a number of independent variables, including glycemic control, hypertension, duration of diabetes mellitus (DM), serum lipids, body mass index, smoking, age, gender and the presence of retinopathy.

A cross-sectional study was carried out at the National Center for Diabetes, Endocrinology, and Genetics (NCDEG)-Jordan. A total of 869 diabetic patients aged 30 years and above with type 2 diabetes mellitus who attended the clinic at the NCDEG from 1st September 2007 till 10th January 2008 were included.

At least two out of three random morning spot urine samples were collected in a three months period to determine the urinary albumin- creatinine ratio (ACR). Microalbuminuria is defined as an ACR of 30-299 mg/g and macroalbuminuria is defined as an ACR $\geq$ 300 mg/g according to the definition proposed by the American Diabetes Association (ADA). Sociodemographic, clinical, and laboratory data were obtained from the medical records of patients. Statistical analysis was carried out using the Statistical Package for Social Sciences (SPSS, version 11.5).

Of the 880 patients recruited, 5(0.6%) were excluded due to the presence of urinary tract infections and 6 (0.7%) for the presence of congestive heart failure, leaving 869 patients for evaluation. There were 56.0% male and 44% female. The mean age and duration of diabetes were 57.8 years and 9.5 years respectively. About 62.4% were managed by oral hypoglycemic agents alone, 4.3% by insulin alone, 31.7% were on

combination of oral hypoglycemic agents and insulin, 1.6% were on diet alone. The mean value for HbA1c was 7.71%.

The overall prevalence of albuminuria among participants was found to be 34.6%. Microalbuminuria was found in 29.3%, while macroalbuminuria was found in 5.3%.

Multivariate logistic regression analysis identified HbA1c, SBP, DBP and presence of retinopathy as independent risk factors for microalbuminuria and SBP, male sex and presence of retinopathy as independent risk factors for macroalbuminuria.

Albuminuria is highly prevalent among Jordanians with type 2 diabetes. This calls for early and universal screening of urinary albumin and measures that target tight glycemic, optimal blood pressure control and use of renin-angiotensin system blockade are urgently needed.

INTRODUCTION

Diabetes mellitus (DM) is considered to be a major health problem that is predicted to turn into global epidemic ⁽¹⁾, affecting around 171 million people worldwide and the World Health Organization predicts that this number will rise to 366 million by 2030⁽²⁾.

In Jordan ,the reported prevalence of diabetes among adult Jordanians in 1998 was 13.4%⁽³⁾, while in a recent study in Jordan, the age standardized prevalence of DM was 17.1%; confirming that the prevalence of DM in Jordan is also increasing⁽⁴⁾.

Among all the complications of diabetes mellitus, nephropathy is the diabetes specific complication with the greatest mortality ⁽⁵⁾ .Although in the past the risk of renal complication was thought to be considerably lower among patients with type 2 diabetes than among those with type 1 diabetes ⁽⁶⁾, there is an increasing body of evidence that the risk of nephropathy with progression to ESRD was similar in the two groups ⁽⁷⁾.

It was not surprising that more ESRD patients emerged among type 2 diabetes because of increasingly greater prevalence of type 2 diabetes and due to better survival of diabetic patients with renal failure ⁽⁷⁾. Nephropathy associated with type 2 diabetes is the most frequent cause of (ESRD) in the United States, Europe, and Japan⁽⁸⁾ .In Jordan, DM was the cause of ESRD in 10.5% of patients on haemodialysis in 1992 ⁽⁹⁾and was the cause of 29.2% of such cases in 2003⁽¹⁰⁾.Although the magnitude of the disease has been better defined in developed countries, the situation is particularly serious in the developing countries, where resources of health care budgets are limited⁽¹¹⁾.One of the initial markers of this condition is microalbuminuria, which indicates an increased risk of deteriorating renal function and mortality ⁽¹²⁾.Microalbuminuria is also a well established marker of increased cardiovascular disease risk⁽¹³⁾. Without specific interventions, 20-40% of type2 diabetic patients with

microalbuminuria progress to macroalbuminuria (overt nephropathy), but by 20 years after the onset of overt nephropathy, only~ 20% will have progressed to end-stage renal disease (ESRD) ⁽¹⁴⁾.

Macroalbuminuria is a strong and independent predictor of increased cardiovascular morbidity and mortality and its presence predicts loss of kidney function ⁽¹⁵⁾.

Diabetic retinopathy can be found in more than 90% of type 1 diabetic patients with nephropathy ⁽¹⁶⁾. However the relationship between albuminuria and diabetic retinopathy (DR) was less predictable in type 2 diabetes ⁽¹⁶⁾. A study showed that the albuminuric patients with type 2 diabetes without DR had a prevalence of biopsies with normal glomerular structure or non-diabetic kidney diseases of approximately 30%. In other words, the type 2 diabetic patients with albuminuria without DR had a high incidence of non-diabetic glomerular disease. ⁽¹⁷⁾

Several studies showed that there is a significant association between diabetic nephropathy and variables, such as glycemic control, hypertension, hyperlipidemia, smoking, obesity, and duration of DM ^(12, 18, 19, 20, 21, 22, 23).

Diabetic nephropathy could be reduced, and its progression to ESRD significantly delayed with better overall management of the underlying DM ^(20, 21). A better understanding of the prevalence of albuminuria and risk factors associated with albuminuria was required for further development of preventable strategies for DN in Jordanian patients diagnosed with type 2 diabetes ,especially that the prevalence of diabetes and IFG is high in Jordan and is also increasing ⁽⁴⁾.

To date, no available data documenting the prevalence of albuminuria among type 2 diabetes in Jordan.

Natural History of Diabetic Nephropathy

Histopathological changes start early ,at the beginning of metabolic dysfunction ,with progression of structural changes through clinically silent phases, culminating eventually in ESRD.The interplay between structural changes and functional consequences occurs throughout the course of nephropathy ⁽²⁴⁾.

Five distinct clinical and histological stages are recognized

Stage I: Glomerular hypertrophy and hyperfiltration.

The earliest stage is one of glomerular hypertrophy (some times with basement membrane thickening), and hyperfiltration .The glomerular filtration rate (GFR) is increased, and on ultrasound the kidneys are enlarged ⁽²⁴⁾.

Stage II: Clinically Silent: Normoalbuminuria.

The increased GFR continues throughout this second stage, which remains clinically silent .Structural changes developed in stage I continue to progress. Sequential kidney biopsies over the course of the illness show progressive thickening of the glomerular basement membrane and increase in the fractional volumes of mesangial regions. Diabetic subjects with duration of about 5 years demonstrate a 25-30% increased thickness of basement membrane compared to normal ⁽²⁵⁾. Albumin excretion and blood pressure are normal, but basement membrane thickening in the glomerular occlusion start to occur ⁽²⁵⁾.

Stage III: Incipient Nephropathy.

This stage is defined by the permanent increase in urinary albumin excretion (microalbuminuria), with type1 diabetes provides an early warning that renal function

may deteriorate to overt proteinuria in the future. The onset of this stage is usually 6-15 years following the diagnosis of diabetes .

Stage IV: Overt nephropathy.

This stage is defined by persistent proteinuria ($\geq 300\text{mg}/24\text{hrs}$). Early in the course of overt diabetic nephropathy, GFR values may be accompanied by a normal serum creatinine level, but without intervention, GFR falls by about $1\text{ml}/\text{min}/\text{month}$ ⁽²⁴⁾.

Stage V: End stage renal failure with uremia.

This stage is the consequence when attempts to arrest or postpone progression of renal insufficiency fail. Strategies to combat uremia and planning the timing for renal replacement therapy are the main principles in the treatment at this stage of nephropathy ⁽²⁴⁾.

Pathogenesis

The pathophysiology of renal microvascular complications in diabetes mellitus consists of an intensive interplay of metabolic and functional/haemodynamic factors **Figure 1**.

Together with genetic factor, this results in the development of microvascular complications ⁽²⁶⁾.

Because diabetes is a state of chronic hyperglycemia, it is probable that glucose-dependent processes are involved in diabetic nephropathy. For example, the chronic effects of glucose in inducing tissue injury may occur via the generation of advanced glycated proteins (AGE), which is a spontaneous non-enzymatic reaction between glucose and lipids and protein. AGE, accumulate in the kidney, particularly in people with diabetes or declining renal function, or both ⁽²⁷⁾.

Another glucose-dependent pathway, known as the polyol pathway has been implicated in the pathogenesis of diabetic nephropathy. To further explore this pathway, inhibitors of the enzyme aldose reductase have been given to both rodents and man with conflicting results. The activity of the enzyme protein kinase C has been reported to be increased in various diabetic tissues including the glomerulus ⁽²⁶⁾.

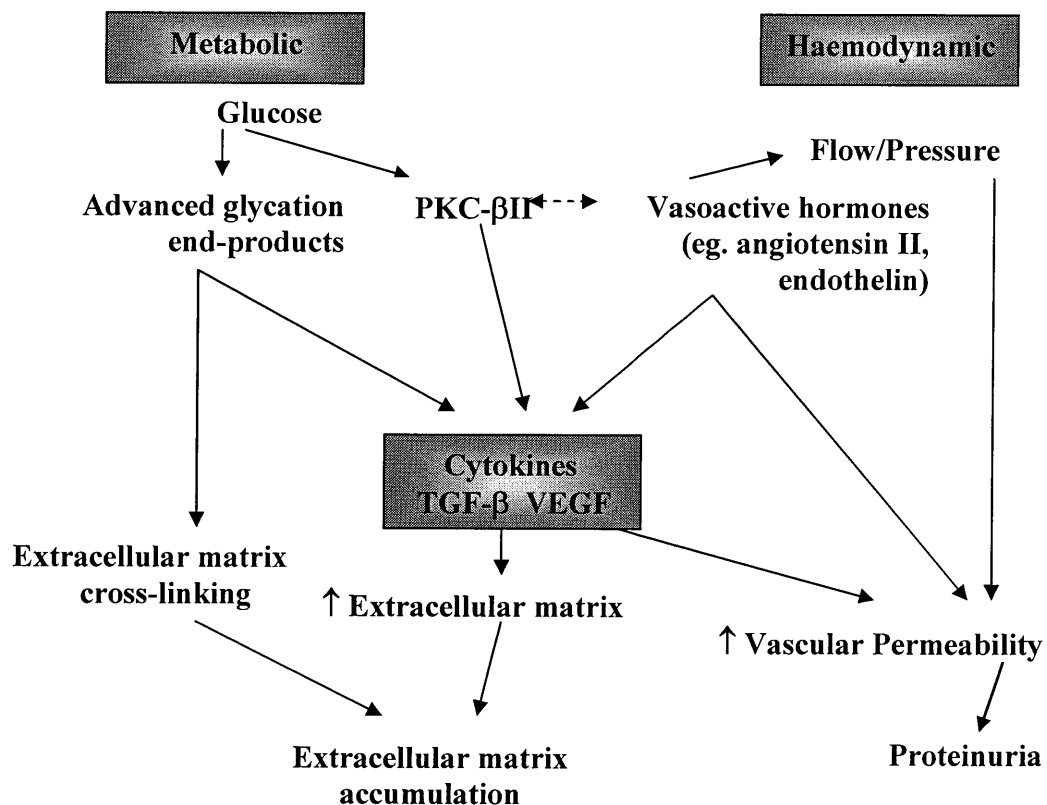


Figure 1: Schema Outlining Potential Interactions Between Metabolic and Haemodynamic Pathways in Mediating Diabetic Renal Disease. Adapted from Cooper ME. Pathogenesis, Prevention and Treatment of Diabetic Nephropathy. Lancet 1998; 352:213-219

TGF β=Transforming growth factor β ; VGEF=Vascular Endothelial Growth Factor; PKC=Protein Kinase C

Diabetic nephropathy is commonly associated with systemic hypertension.

Micropuncture studies have shown that in animal models of diabetes there is an elevation

of the intraglomerular pressure, even in the absence of systemic hypertension. These renal haemodynamic changes may be partly related to the actions of vasoactive hormones such as angiotensin II in diabetes and endothelin. Whether these hormone pathways are altered in diabetes or their actions are amplified in the context of hyperglycemia remains to be clarified ⁽²⁷⁾.

Diabetes nephropathy involves not only a range of renal functional abnormalities but also pathological changes, the hallmark being extracellular matrix accumulation. It has been postulated that the pro-sclerotic cytokine, transforming growth factor (TGF)- β , which is stimulated by glucose, AGE and vasoactive hormones such as angiotensin II and endothelin, plays a pivotal part in the development of diabetic nephropathy. It is likely that TGF- β plays an important part in mediating the interaction between metabolic and haemodynamic factors leading to extracellular matrix accumulation in the diabetic kidney ^(25, 27).

Genetic factors

The risk of nephropathy is strongly determined by genetics. Familial clustering of diabetic nephropathy, high rates of hypertension and cardiovascular events among the relatives of patients with type 2 diabetes that have nephropathy, and higher-than-normal blood-pressure levels and rates of albuminuria among the offspring of these patients have all been described. The risk of nephropathy has been linked to specific Chromosomal sites ⁽⁷⁾. The genes involved have not been identified. At least among whites, the presence of the insertion or deletion polymorphism of the angiotensin-converting enzyme (ACE) gene is not a major predictor of renal risk, although it apparently influences progression. Several genes or gene products have been linked to diabetic nephropathy. A

polymorphism of the $\beta 3$ subunit of the G protein at position 825 is related to obesity and hypertension. The G $\beta 3$ 825T allele is more frequent among patients with type 2 diabetes with progression to end-stage renal disease than among non-diabetic patients ⁽⁷⁾.

Screening and Diagnosis of albuminuria

Before the onset of overt or clinical albuminuria, there is a preclinical stage of diabetic nephropathy (also called incipient diabetic nephropathy) characterized by microalbuminuria ⁽¹⁴⁾. Testing for the presence of microalbuminuria should be performed at diagnosis in patients with type 2 diabetes ⁽²⁸⁾. Microalbuminuria rarely occurs within short duration of type 1 diabetes; therefore, screening in individuals with type 1 diabetes should begin 5 years after diagnosis. Some evidence suggests that the prepubertal duration of diabetes may be important in the development of microvascular complications; therefore clinical judgment should be exercised when individualizing these recommendations ⁽²⁹⁾. Because of the difficulty in precise dating of the onset of type 2 diabetes, such screening should begin at the time of diagnosis ⁽²⁹⁾. After the initial screening and in the absence of previously demonstrated microalbuminuria, a test for the presence of microalbuminuria should be performed annually. Screening and diagnosis for microalbuminuria can be performed by three methods **Table 1:** 1) measurement of the albumin-to-creatinine ratio in a random spot collection; 2) 24-h collection with creatinine, allowing the simultaneous measurement of creatinine clearance; and 3) timed (e.g., 4-h or overnight) collection ^(14, 28). The first method is often found to be the easiest to carry out in an office setting, generally provides accurate information, and is therefore preferred ⁽²⁸⁾. Twenty-four-hour and timed urine collections are cumbersome and prone to errors related to collecting samples or recording of time ⁽²⁹⁾. Microalbuminuria is said to be present if urinary albumin excretion is 30-299 mg/24 h

(equivalent to 20-199 $\mu\text{g}/\text{min}$ on a timed specimen or 30-299 mg/g creatinine on a random sample) and macroalbuminuria is $\geq 300\text{mg}/24\text{h}$ (equivalent to ≥ 200 $\mu\text{g}/\text{min}$ on a timed specimen or ≥ 300 mg/g creatinine on a random sample ^(14, 29). Because of marked day-to-day variability in urinary albumin excretion, two of three specimens collected within a 3- to 6-month period should be abnormal before considering a patient to have crossed one of these diagnostic thresholds ⁽¹⁴⁾.

Table 1 Definition of abnormalities in albumin excretion			
Category	Spot collection ($\mu\text{g}/\text{mg}$ creatinine)	24-h collection ($\text{mg}/24\text{h}$)	Timed collection ($\mu\text{g}/\text{min}$)
Normal	<30	<30	<20
Microalbuminuria	30-299	30-299	20-199
Clinical albuminuria	≥ 300	≥ 300	≥ 200

Adapted from American Diabetes Association .Nephropathy in diabetes. Diabetes care 2004; 27 Suppl. 1:S79-S83

Literature Review

Literature from western countries

In the Wisconsin Epidemiological Study of Diabetic Retinopathy WESDR, a large geographically defined population study of both type 1 and type 2 diabetic patients ;aimed to examine the prevalence of microalbuminuria and its relationships to blood pressure and other risk factors in individuals diagnosed with diabetes at ≥ 30 year of age either taking insulin (n=435) or not taking insulin (n=363), who were participants in this study during 1984-1986. The frequency of microalbuminuria was 29.2% in those individuals taking insulin and 22% in those not taking insulin. Microalbuminuria was significantly associated with the male sex, older age, higher systolic blood pressure, higher glycosylated hemoglobin, use of insulin, higher recent alcohol consumption and a history of cardiovascular disease ⁽³⁰⁾.

In Sweden a large cross sectional-study was done by Cederholm et al (2002) on 9135 type 1 and 31,037 type 2 diabetic patients, showed that the frequency of microalbuminuria was 14.8% in type 1 and 15.5% in type 2 diabetic patients and it was independently associated with HbA1c level, diabetes duration, systolic Bp, BMI, smoking and triglycerides in both types of diabetic patients, and with HDL-cholesterol in type 2 patients ⁽²³⁾

A prospective cohort study carried out in United Kingdom (UK) on 246 NIDDM Patients. The median age of the cohort was 68 years, and the median duration of diabetes was 7 years. Results of the study showed that the prevalence of microalbuminuria, macroalbuminuria were 15% and 4% respectively ⁽³¹⁾.

Another study in Hungary performed by Molnar et al. (2000) on 200 patients with type 2 diabetes; aimed at defining the prevalence of microalbuminuria (MA) and macroalbuminuria (MAA), their relationship with other diabetic complications and with some known

cardiovascular risk factors. The prevalence of normoalbuminuria NA, MA, MAA were 33%, 27.5% and 38.5% respectively. Significant positive correlation with serum triglyceride, serum uric acid and serum creatinine was noticed. Diabetic non-proliferative retinopathy was detected in 27% of NA patients while 51% of MAA patients were without retinopathy. This study also demonstrated that 56% of NA patients, 57% of MA patients and 93% of MAA patients had macroangiopathy⁽³²⁾.

In Italy, population-based cohort study was performed in 1574 NIDDM subjects to determine the prevalence of micro and macroalbuminuria in NIDDM and their relationship with some known and putative risk factors. The study results showed that the prevalence of microalbuminuria, macroalbuminuria and hypertension were 32.1%, 17.6% and 67% respectively. Both micro- and macroalbuminuric diabetic subjects had significantly longer duration of diabetes, higher levels of systolic blood pressure, fasting plasma glucose, HbA1c, triglycerides and uric acid. Only in macroalbuminuric subjects, levels of apolipoprotein B and HDL cholesterol were respectively, higher and lower than in normo- and microalbuminuria subjects⁽³³⁾.

In Spain, a cross sectional study was done in a Canarian population of type 2 diabetic patients (n=288), 179 unselected patients referred by their family physicians, and 109 from their diabetic clinic. The overall prevalence of micro- and macroalbuminuria were 28.5% and 11.8% respectively. The study also demonstrated the prevalence of diabetic retinopathy, diabetic polyneuropathy, cerebrovascular disease, and coronary heart disease were 31.5%, 21%, 8.1% and 20.2% respectively. The albumin excretion rate was significantly correlated with plasma creatinine levels, diastolic blood pressure, total cholesterol and the presence of coronary heart disease and diabetic retinopathy⁽³⁴⁾.

In Denmark (Parving HH et al) (n=370 NIDDM patients), 139 were females and 224 were males. This prospective study conducted to evaluate the prevalence and causes of persistent albuminuria (greater than 300mg/24hr). Fifty patients (7 women) suffered from persistent albuminuria (13.8%). The prevalence of albuminuria was significantly higher in males (19%) than in females (5%).⁽³⁵⁾

In Australian Diabetes, Obesity and Lifestyle Study (Aus Diab), performed on 11,247 Australian adults aged 25 years and older; to determine the prevalence of and risk factors associated with albuminuria. The prevalence of albuminuria among patients with diabetes (type 1 and type 2) was 25.3% (21% microalbuminuria, 4.3% macroalbuminuria). This was significantly associated with age, duration of diabetes, systolic blood pressure, current smoking, Body mass index and glycated hemoglobin level⁽³⁶⁾.

Another study in Polynesian Western Samoans in Australia (1995), conducted on 162 NIDDM or impaired glucose tolerance (IGT) patients. This population based study aimed to assess the prevalence of diabetic retinopathy and nephropathy and to define associated risk factors. The prevalence of microalbuminuria among newly diagnosed and known diabetic patients was 22%, 17.2% respectively⁽³⁷⁾.

A cross-sectional study was carried out on 557 European type 2 diabetic patients. The aim was to find out the prevalence of micro- and macroalbuminuria, arterial hypertension, retinopathy and large vessel disease on those patients. Results of the study have revealed a high prevalence of microalbuminuria (27%) and macroalbuminuria (14%). The prevalence of macroalbuminuria was significantly higher in males (20%) than in females (6%), while the prevalence of microalbuminuria was almost identical in males (26%) and females (29%). The prevalence of arterial hypertension and retinopathy increased with increased albuminuria.

Prevalence of coronary heart disease, was more frequent in patients with macroalbuminuria (46%) compared to patients with microalbuminuria .Foot ulcers were more frequent in micro and macroalbuminuric patients⁽³⁸⁾.

A population-based controlled cross-sectional study in Finland was performed by Wirta OR et al. (1995) on 188 type 2 diabetic patients .In a recent onset diabetes (< than 1 year), the prevalence of microalbuminuria and macroalbuminuria were 29% and 4% respectively .But in patients with a long term diabetes(5-25 years) the prevalence of microalbuminuria and macroalbuminuria were 27 % and 7% respectively⁽³⁹⁾.

Literature from Africa

A cross sectional study evaluated 91 patients with Type 1 and 153 patients with Type 2 diabetes patients to determine the prevalence of microalbuminuria among African diabetes patients in Dar es Salaam, Tanzania. Results of the study showed that in type 1 patient prevalence of microalbuminuria was 12% and macroalbuminuria 1%. Among Type 2 patients, 9.8% had microalbuminuria, and 7.2% had macroalbuminuria. Type 2 patients with abnormal albumin excretion rate (AER) had significantly longer diabetes duration than those with normal (AER).Systolic and diastolic blood pressure among Type 2 patients with abnormal albumin excretion rate were significantly higher than in those with normal albumin excretion rate. The study also demonstrated that no significant differences in body mass index, glycaemic control, and cholesterol levels was found among patients with normal compared with those with elevated albumin excretion rate either in Type 1 or Type 2 patients⁽⁴⁰⁾.

In a study done in Jos Nigeria by Agaba et al; to investigate the prevalence of microalbuminuria in newly diagnosed type 2 diabetic patients and its clinical correlates. Out of a total of 99 patients recruited, only 65 completed the study .Microalbuminuria was present in 32 (49.2%) of the patients, and was significantly associated with mean arterial pressure, systemic hypertension and diabetic retinopathy ⁽⁴⁰⁾.

A cross-sectional analytical study performed by Dasmahapatra et al(1994) on 116 African-American subjects with NIDDM ; reported an overall prevalence of 50% of nephropathy ;31% had incipient and 19% had overt nephropathy ⁽⁴²⁾ .

Another study in Cameroon performed by Sobngwi et al (1999) on 64 non-proteinuric diabetic patients (9 IDDM and 55 NIDDM) aged 19-70 years, reported an overall prevalence of 53.1% of microalbuminuria ⁽⁴³⁾

Literature from Asia

A Cross-sectional large multicenter study in Asia involving 6,801 hypertensive type 2 diabetic patients to determine the prevalence of microalbuminuria and macroalbuminuria and to characterize the predictive factors in those subjects .Results of the study showed high prevalence of microalbuminuria(39.8%) and macroalbuminuria(18.8%).

The predictive factors for the presence of microalbuminuria were age, BMI, systolic blood pressure and ethnic origin. The highlighted predictive factors for the presence of macroalbuminuria were age, sex, ethnic origin, BMI, duration of diabetes, presence of diabetes complications, intake of calcium channel blocker, diastolic and systolic blood pressure .The high prevalence (58.6%) of microalbuminuria and macroalbuminuria observed in these patients is alarming and indicates an impending pandemic of diabetic cardiovascular and renal diseases in Asia with its potential consequences ⁽⁴⁴⁾.

A population-based cross sectional study took place in Shanghai downtown in 2007 to determine the prevalence and risk factors associated with albuminuria .The relationship between diabetic retinopathy (DR) and albuminuria were also evaluated among the 1039 Chinese patients diagnosed with type 2 diabetes aged over 30. The results showed that the overall high prevalence of albuminuria was 49.6%. , 41.4% with microalbuminuria and 8.2% with macroalbuminuria. Microalbuminuria was significantly associated with systolic blood pressure, gender and waist circumference. Macroalbuminuria was significantly associated with systolic blood pressure and duration of diabetes. The percentage of DR in the macroalbuminuric group (59.2%) was significantly higher than that in the normalalbuminuria group (16.1%) and microalbuminuria group (24.6%) (16).

A study took place in Hong Kong in four primary care clinics (n=1262).A total of 13.4% of the patients had microalbuminuria .Having the condition was significantly associated with advanced age, female sex, poor glycemic control, and coexisting hypertension .No significant association with ever smoking was found⁽⁴⁵⁾.

In a study done in a large diabetes centre in Southern India ,1425 type 2 diabetic patients were examined to determine to prevalence and risk factors for microalbuminuria among those patients .Results of the study showed overall prevalence of microalbuminuria was 36.6%and the prevalence of microalbuminuria increased with increase in duration of diabetes⁽⁴⁵⁾.

Another study done by Unnikrishnan R et al on 1,719 Urban South Indian populations with type 2 diabetes (2007).Microalbuminuria was detected in 26.9% and overt nephropathy present in 2.2% of the patients⁽⁴⁷⁾.

A cross-sectional multicenter study was performed in Pakistan by Ahmedani et al (2003) on 2100 subjects with type 2 diabetes. The overall prevalence of microalbuminuria was 34% and this was significantly related to age, diastolic blood pressure, serum LDL and retinopathy ⁽⁴⁸⁾

A cross-sectional study conducted in Iran by Manaviat et al on 590 patients suffering from type 2 (2004); to evaluate the incidence of microalbuminuria, macroalbuminuria and their relation to diabetic retinopathy and other risk factors. The overall prevalence of retinopathy was 39.3% .The prevalence of microalbuminuria was 25.9% while 14.5% of the patients revealed to have macroalbuminuria, also this study showed that diabetic retinopathy and renal involvement were highly positively correlated ($p=0.001$).⁽⁴⁹⁾

Literature from Arab countries

A study performed in Sultanate of Oman (n=261) to evaluate the prevalence and predictors of microalbuminuria in type 2 diabetes at the Sultan Qaboos University Hospital. Microalbuminuria was detected in 70 patients (27%).In this study significant predictors of microalbuminuria included HbA1c, creatinine, and the presence of hypertension ⁽⁵⁰⁾.

A study done at a large diabetic clinic in Riyadh, enrolled 184 patients with NIDDM; to investigate the prevalence of microalbuminuria among Saudi Arabian with NIDDM .The results showed 76 subjects (41.3%) had microalbuminuria and its presence is closely related to glycemic control ⁽⁵¹⁾.

Another study conducted in Saudi Arabia at King Abdulaziz University Hospital, to estimate the prevalence of microalbuminuria in type 2 diabetic patients (n=331). Microalbuminuria was diagnosed in 151 patients out of the total numbers of the patients included in the study (45.6%) ⁽⁵²⁾.

In United Arab Emirates (UAE) a cross sectional survey was carried out on 513 diabetic patients to assess the prevalence of microalbuminuria using the single Micral-Test II strips. MA was found in 61% of the sample ⁽⁵³⁾.

A large population-based cross sectional study took place in Egypt (n=6052); showed that the prevalence of albuminuria in people with previously undiagnosed diabetes was 22%, where as those with diagnosed disease was 21% ⁽⁵⁴⁾.

Table 2 Comparison of the Prevalence of Microalbuminuria and Macroalbuminuria in Type 2 Diabetes in Different Population-Based Studies ^{(16, 30, 31, 33, 34, 39, 47).}

Site	Author	Year	No of Subjects	Prevalence of microalbuminuria (criteria)	Prevalence of macroalbuminuria (criteria)
Wisconsin, USA	Klein et al ³⁰	1993	798	25.9% (30-299 mg/L)	16% (>300mg/L)
Oxford, UK	Neil et al ³¹	1993	246	15% (>40mg/L)	4% (>200mg/L)
Italy	Bruno et al ³³	1996	1574	32.1% (20-200µg/min)	17.6% (>200µg/min)
Western Samoa	Collins et al ³⁷	1995	162	Newly detected diabetes :22% Self reported:17.2% (30-299 µg/ml)	Newly diagnosed: 3.9% Self reported:6.3% (≥ 300 µg/ml)
Finland	Wirta et al ³⁹	1995	188	Newly diagnosed:29% Self reported:27% (30-300 mg/24hours)	Newly diagnosed:4% Self reported:7% (>300mg/24hours)
China	Lu B et al ¹⁶	2006	1018	41.1% (30-299mg/g)	8.2 % (≥300mg/g)
South India	Unnikrishnan ⁴⁷ R et al	2007	1,716	26.9% (30-299 µg / mg)	2.2% (≥300 µg / mg)

Risk factors

Glycaemic control

Clinical trials have consistently demonstrated that low HbA_{1c} level is associated with decreased risk for clinical and structural manifestation of diabetic nephropathy in type 1 and type 2 diabetic patients.

In the Diabetes Control and Complication Trial (DCCT) study, which was the largest randomized comprehensive diabetes study ever conducted on type 1 diabetes from 1983-1993. The DCCT involved 1441 volunteers with type 1 DM. Volunteers had diabetes for at least 1 year but no longer than 15 years, intensive treatment reduced the incidence of microalbuminuria by 39%⁽⁵⁵⁾.

The United Kingdom Prospective Diabetes Study (UKPDS) a large multicenter randomized control clinical trial 1977-1999, was another outstanding study, demonstrated that an intensive treatment policy in type 2 diabetes, with the goal of meticulous glycemic control, could decrease clinical diabetic complications. UKPDS screened 3867 newly diagnosed with type 2 DM⁽²⁰⁾. After three months of diet treatment. Patients with a mean of two fasting plasma glucose concentration of 6.1-15 mmol/ liter were randomly assigned to an intensive glycemic control group, using various pharmacologic agents, a sulfonylurea, chlorpropamide, glibenclamide or Glipizide, or with insulin, and conventional glycemic control. The control group attempted control with diet alone, adding pharmacologic therapy when symptoms developed or fasting plasma glucose exceeded 270mg/dl. After 10 years of follow up, the intensive treatment policy achieved a median HbA_{1c} of 7.0% versus 7.9% in the conventional treatment policy group. The target fasting blood glucose concentration was 108mg/dl (6mmol/L) or less. The risk reduction for the development of microalbuminuria was 30% in

as follows: an HbA_{1c} level less than 6.5%, FBS less than 110mg/dl, and 2 hours postprandial blood glucose concentration less than 180mg/dl.

Gilbert RE et al, also reported that the rate of increase in urinary albumin excretion, from normal to microalbuminuria to macroalbuminuria, varied directly with the HbA_{1c} value in patients with type 2 or type 1 diabetes. In patients with type 2 diabetes, the yearly rate of increase in albumin excretion was approximately 25% in those with mean HbA_{1c} value of 8%, compared with 50% in those with a mean HbA_{1c} of 12%⁽⁵⁸⁾.

Hypertension

High blood pressure is an established risk factor for the development and progression of diabetic nephropathy⁽⁵⁹⁾. Thus systemic control of blood pressure is known to reduce urinary albumin excretion and deterioration of renal function in type 1 and type 2 patients⁽⁶⁰⁾. The UKPDS (the largest and the longest study of type 2 patients), showed that blood pressure control reduces the risk for both retinopathy and nephropathy. The hypertension and diabetes study^(21, 61) was part of the UKPDS study in which 1148 patients with type 2 diabetes and coexisting hypertension from 20 hospital clinics in England, Scotland, and Northern Ireland were studied. The mean age for patients was 56 years; with mean blood pressure at entry 160/94mmHg. Seven hundred fifty-eight patients were allocated to tight control of blood pressure and 390 patients to less tight control, with a median follow up of 8.4 years. The tight control subjects were given an angiotensin converting enzyme inhibitor (captopril) and 358 were given a β -blocker (atenolol) as the main treatment; 390 patients were allocated a less tight control of blood pressure, aiming for blood pressure less than 180/105mmHg but avoiding treatment with angiotensin converting enzyme inhibitor, or β -blockers. The tight

control group averaged 144/82 mmHg and the control group averaged 154/87 mmHg .At eight to nine years ,patients with lower blood pressure had an overall 24% reduction in diabetes-related end points .Tight control also resulted in a 37% reduction in risk of microvascular disease and 29% reduction in the risk for the development of microalbuminuria .This trial showed that both drugs were equally effective in lowering blood pressure and there was no significant differences in the incidence of microalbuminuria or proteinuria.

In a study of 1,204 subjects with hypertension and normoalbuminuric type 2 diabetes, Ruggenti et al,compared trandolapril alone ,trandolapril plus verapamil ,verapamil alone ,and placebo in preventing the appearance of microalbuminuria.Trandolapril alone and in combination with verapamil were much more effective in preventing the appearance of microalbuminuria than verapamil alone or placebo. This benefit occurred even though the levels of blood pressure control achieved were identical in all groups, suggesting that inhibition of the renin angiotensin system provided protection in addition to that resulting from lowering of blood pressure ⁽⁶²⁾.

In the normotensive ABCD study, 480 type 2 diabetic patients with baseline blood pressures of <140/90 were randomly assigned to placebo (moderate control) or to either enalapril or nisoldipine and a target diastolic blood pressure of 10 mmHg below the baseline level (intensive control). The mean blood pressures for the moderate and intensive control groups were 137/81 and 128/75 mmHg, respectively. Nearly one-half of patients initially given placebo eventually required antihypertensive medications. At follow-up at five years, intensive control resulted in a lower incidence of stroke and decreased progression of

The United Kingdom Prospective Diabetes study (UKPDS)⁽⁶⁶⁾, described the development and progression of nephropathy in type 2 diabetes during a long follow-up period >15 years. At diagnosis of DM 7.3% of patients had microalbuminuria or worse rising to 17.3% after 5 years, 24.9% after 10 years and 28% after 15 years. Another study (n=133) of newly diagnosed patients with type 2 diabetes, and 144 control subjects were followed for 10 years prospective study reported that in the diabetes patients the cumulative incidence of micro-and macroalbuminuria increased sharply after 5 years but markedly less in control subjects⁽⁶⁸⁾. These correspond to the results of other reports^(69,70). Other studies produced no evidence of risk association between albuminuria and diabetes duration^(22,32).

Serum lipids

So far, there have been no large trials analyzing whether the treatment of dyslipidemia could prevent the development of diabetic nephropathy or the decline of renal function⁽²⁹⁾. However, there is some experimental studies⁽²⁹⁾ have reported that lipids may induce both glomerular and tubulointerstitial injury through mediators such as cytokines, reactive oxygen species and chemokines.

Gall M et al found that the concentration of serum cholesterol was associated with increased risk of developing incipient or overt nephropathy in a cohort lasting nearly six years⁽²²⁾. In contrast a study done in Southern India (2001), showed no significant association between serum triglyceride and cholesterol values and microalbuminuria⁽⁴⁶⁾.

Other study done in Hungary⁽³²⁾, reported that serum triglyceride level were significantly associated with urinary albumin excretion but there was no association with serum cholesterol and HDL levels. Similarly, a study done in Italy⁽³³⁾, showed that serum

triglyceride levels were significantly associated with the degree of albuminuria, while HDL cholesterol was found to have negative correlation with it.

In the Diabetes Atherosclerosis Intervention study (n=314), all but three patients with type 2 diabetes had either normoalbuminuria (214 patients) or microalbuminuria (97patients) prior to being randomly assigned to fenofibrate or placebo, worsening of proteinuria was significantly less with active therapy .Most prominently, the rate of progression from normoalbuminuria excretion to microalbuminuria at three years was significantly lower with fenofibrate ⁽⁷¹⁾.

Body Mass Index

The relationship between microalbuminuria and BMI was significant in a cross-sectional study (2003) that included 9135 type 1 and 31,037 type 2 diabetic patients ⁽²³⁾.High BMI was independently associated with established microalbuminuria in several studies^(23,32).

Obesity have been demonstrated to cause increased release of inflammatory cytokines from adipose tissue and liver ,which may cause progression of renal dysfunction from low-grade inflammation in patients with microalbuminuria ⁽⁷²⁾.Marked decreases in proteinuria may be observed in obese diabetics who lose weight .This was illustrated in randomized trial of 30 over weight patients (BMI>27kg/m²) with proteinuric nephropathy ,14 of whom had type 2 diabetes; proteinuria significantly decreased at five months among dieters versus the non-dieters control group. A mean weight loss of 4% was observed in the diet group⁽⁷³⁾.But there are some studies ^(22,34,40,44,52,69) that are inconsistent with these finding such as the study that was held by Lutale JJK , ⁽⁴⁰⁾ which reported no significant association between microalbuminuria and BMI. On the other hand Ramirez and colleagues ⁽⁷⁴⁾ noted that, among

a sample of persons from Singapore, the relationship between proteinuria and BMI was J-shaped because those with a BMI of 18 kg/m² or less (and those with a BMI of ≥ 25 kg/m²) were more likely to have proteinuria than those with BMI of 18.01 to 22.99 kg/m².

Smoking

Smoking has been identified as a strong predictor of renal injury in type 1 diabetes. Chase et al (1991)-359 young Type 1 diabetics were studied. The authors found abnormal albumin excretion ratio (AER) risk to be increased 2.8 times in smokers than nonsmokers. The progression rate of albuminuria in the smoking patients also was greater than in the nonsmokers and cessation of smoking has been associated with reduction in AER⁽⁷⁵⁾. Some studies revealed that in type 2 diabetes the risk of albuminuria is higher in smokers and former smokers, than in non-smokers^(23, 48). In a study done by Molnar M et al, showed that more smoker patients found in micro and macroalbuminuric groups, than in normoalbuminuric group⁽³²⁾.

However a population-based study (n=1267) in Denmark showed a positive association between smoking and albuminuria⁽⁶⁹⁾. Other subsequent study had failed to demonstrate an association between the risk of development of incipient and overt diabetic nephropathy and cigarette smoking⁽²²⁾.

Age

In DEMAND (Developing Education on Microalbuminuria for Awareness of renal and cardiovascular risk in Diabetes) multicenter study (n=1841) showed that patients with microalbuminuria were significantly older than those without microalbuminuria⁽⁷⁶⁾.

Varghese et al (2000), reported that age is statistically significant with the development ⁽⁴⁶⁾ of microalbuminuria. Nelson RG also assured that the albuminuria is significantly related to age in Pima Indian ⁽⁷⁷⁾. MAPS (The Microalbuminuria Prevalence Study) conducted in hypertensive type 2 diabetic patients in Hong Kong showed that the prevalence of macroalbuminuria are higher in patients older than 75 years ⁽⁷⁸⁾. Another study done by Pablos et al ⁽³⁴⁾, revealed no significant association between age and albuminuria.

Gender

For unknown reasons, gender also plays a role in influencing the occurrence of nephropathy. A study conducted by Anderson AR et al (1983), demonstrated a male preponderance of 5:1 ⁽⁷⁹⁾. Also a study done by Cederholm J et al, showed that microalbuminuria independently associated with male gender ⁽²³⁾. In a study among Pakistani diabetics, showed the same result ⁽⁴⁸⁾. On the other hand Varghese et al (2001), reported that gender had no significant association with microalbuminuria ⁽⁴⁶⁾.

Diabetic retinopathy

Numerous cross-sectional studies reported the strong association between retinopathy and albuminuria ^(16, 43, 49, 80). Also one of the prospective studies in type 2 diabetes showed that diabetic retinopathy was a predictor for later development of nephropathy ⁽²²⁾. Retinopathy is probably a risk marker and not a risk factor in itself, since these microvascular complications (diabetic nephropathy and diabetic retinopathy) share common determinants ⁽²⁹⁾. Even patients who have microalbuminuria were at high risk of developing retinopathy ⁽¹⁶⁾. In a study done by Parving et al, to assess the prevalence and the causes of persistent albuminuria

showed that 27 patients out of 35 (77%) revealed diffuse and/or nodular diabetic glomerulosclerosis by kidney biopsies, while the remaining eight patients (23%) had a variety of non-diabetic glomerulopathies .Diabetic retinopathy was present in 15 of 27 patients (56%) with diabetic glomerulosclerosis. This study concluded that the presence of diabetic retinopathy strongly suggests that a diabetic glomerulopathy is the cause of albuminuria and albuminuric non-insulin dependent diabetic patients without retinopathy require further evaluation, that is, kidney biopsy⁽³⁵⁾.

Objectives

1. To determine the prevalence of albuminuria (micro-and macroalbuminuria) among patients diagnosed with type 2 diabetes mellitus (DM) attending the National Center of Diabetes, Endocrinology, and Genetics (NCDEG).
2. To determine if there is any association between diabetic albuminuria (micro-and macroalbuminuria) and a number of independent variables, including, glycemic control ,hypertension , duration of diabetes mellitus(DM), serum lipids, body mass index ,smoking, age , gender and the presence of retinopathy.

Methods

A cross-sectional study was conducted at the National Center for Diabetes, Endocrinology and Genetics (NCDEG). The center was established in Amman in 1998 as one of the centers attached to the Higher Council for Science and Technology. The center is considered to be the only specialized national center for diabetes, endocrinology and genetics in Jordan. The patients come to the center from all over the country, either directly, or referred from other clinics in the kingdom.

A systematic sample of 869 patients who are diagnosed as having type 2 diabetes according to the criteria proposed by American Diabetes Association aged 30 years and above who regularly attended the diabetic clinic at NCDEG in Jordan starting from 1st of September 2007 and continued until 10th of January 2008. Every third type 2 diabetics were selected. The patients attended the out patient clinic every 1-3 months as part of the routine follow- up. A Patient who exercises excessively within 24 hours, presence of acute febrile illness, congestive heart failure, pregnancy and pyuria and hematuria were excluded from the study. The sample size was 869 diabetic patients, sufficient to provide 95% assurance that the margin of error in estimating the prevalence of albuminuria (microalbuminuria and macroalbuminuria) would not exceed 3%, assuming the most conservative estimate of the prevalence is 50%.

Data collection

Relevant sociodemographic, clinical and laboratory data were obtained from the medical records of patients including: age, gender, duration of DM, smoking, systolic and diastolic blood pressure, use of antihypertensive drugs, height, weight, current oral hypoglycemic drugs (OHD), HbA_{1C} level, fundoscopic examination and lipid profile ; serum(HDL)

Albuminuria

Urinary ACR will be classified into subgroups as normoalbuminuria ($<30\text{mg/g}$), microalbuminuria ($30\text{-}299\text{ mg/g}$) and macroalbuminuria ($\geq 300\text{mg/g}$) according to screening protocol proposed by American Diabetes Association (ADA) ⁽²⁸⁾. Because of the marked day-to-day variability in albumin excretion; at least two of three urine collections should be done in a three months period before designate a patient as having abnormal test. The fresh random morning spot urine should be examined by the strip test (Combur 9 Test) for leucocytes, nitrites and blood. Patients with positive nitrites, which is indicative of significant bacteriuria, and patients with erythrocytes and/or leucocytes equal or above 5 cells count per microliter, which are indicative of hematuria or/and pyuria, to be excluded from the analysed patients.

Duration

Duration of diabetes was defined as the time period between the ages at diagnosis and the age at the time of examination.

Body Mass Index

Body Mass Index (BMI) to be defined as, ratio of weight in kilograms to square height in meter squared [Kg/m^2]. Being overweight to be classified as having a BMI of 25.0 to 29.9, and obesity to be classified as having a BMI of ≥ 30 as defined by the WHO ⁽⁸²⁾.

Smoking

Past smoker, one who had smoked ≥ 100 cigarette during his/her life time and currently does not smoke at all. Current smoking was defined as regular smoking of at least one cigarette per day for at least one month before enrollment ⁽⁸³⁾.

HbA1c

Was defined as controlled diabetes if glycosylated hemoglobin (HbA1c) level was below 7% according to the ADA guidelines ⁽⁸⁴⁾.

Hypertension

Was deemed present if the patient was diagnosed with hypertension by the physicians , current use of blood pressure-lowering medications, or blood pressure values of ≥ 130 mmHg systolic or ≥ 80 mmHg diastolic ⁽⁸⁵⁾.

Diabetic retinopathy

Was defined as any degree or type of retinopathy detected by direct ophthalmoscopy carried out by an ophthalmologist or a physician in the Centre. The International clinical DR severity scale adopted by American Academy of Ophthalmology (AAO) ⁽⁸⁶⁾, and International Council of Ophthalmology (ICO) ⁽⁸⁶⁾, were used to classify patients into Non-Proliferative DR (NPDR), and Proliferative Diabetic Retinopathy (PDR).

Lipid

Lipid levels were considered abnormal according to ADA criteria, 2004 ⁽⁸⁸⁾.

Hypercholesterolemia refers to a total cholesterol level ≥ 200 mg/dl.

HDL was considered low when the level was < 40 mg/dl in males or < 50 mg/dl in females.

LDL was considered high when the level was $\geq 100\text{mg/dl}$.

Hypertriglyceridemia refers to a level $\geq 150\text{mg/dl}$.

Dyslipidemia is defined as the presence of one or more of the previous abnormalities in serum lipid. Patients receiving medications for any of the above conditions were classified as having the condition.

Laboratory and biochemical analysis

Urinary albumin was measured using commercially available immunoturbidometric assay by COBAS INTEGRA system. Human albumin forms a precipitate with a specific antiserum which is determined turbidimetrically at 340nm. Urinary creatinine and serum creatinine were measured by modified kinetic Jaffé reaction. Urinary ACR was calculated from urinary albumin divided by urinary creatinine. Glycosylated hemoglobin (HbA1c) analyzed by using a high-performance liquid chromatography (HPLC) method (Bio-Rad). The information concerning HbA1c is adopted from the tests made in the lab of NCDGE using this method; 10 ml of venous blood was drawn from each patient. Blood was usually taken from cubital fossa and/or dorsum of the hand veins, using disposable syringes. It was used to be injected in the plain tube. Lipid, total cholesterol, triglyceride, High density lipoprotein (HDL) and low density lipoprotein (LDL) were assayed by the automated spectrophotometer, enzymatic colorimetric method, COBAS INTEGRA using commercial kits supplied by Roche Diagnostics.

Statistical Analysis

Statistical analysis carried out using Statistical Package for Social Sciences (SPSS, version 11.5) under guidance and supervision of Dr.Yousef Al-gaud. Initially, the data were examined for data entry errors and outlying values. Detected errors were corrected as appropriate. Descriptive statistics were obtained, such as mean values for continuous variables and proportions for categorical variables. The prevalence for the different types of albuminuria was expressed as percentages, with 95% confidence interval. Association between albuminuria and a number of variables were assessed for statistical significance using Chi square tests for categorical variable, and on independent T-test, for continuous variables.

Multivariate logistic regression was used to asses the independent effect of a given variable after adjustment for other potential confounders. Separate regression models were used for microalbuminuria and macroalbuminuria. P value <0.05 was considered statistically significant.

Ethical Consideration

The study was approved by the NCDEG Ethics committee, the study depended basically on confidentiality, and the data were used only for scientific aspects, moreover, participation was optional and the data were collected after taking the verbal approval from the patients themselves.

Results

Sociodemographic and Anthropometric Characteristics

Of the 880 patients recruited 5(0.6%) were excluded due to the presence of urinary tract infections and 6 (0.7%) for the presence of congestive heart failure, leaving 869 patients for evaluation. There were 487 (56%) men and 382(44%) women .The mean age of the total study population was 57.8 ± 9.1 years and the mean duration of diabetes was 9.5 ± 7.5 years .Of the total sample 15.9% were current smokers while 20.7% were past smokers and 90.4% were obese or over weight .Majority of the patients had their systolic and diastolic blood pressure below the 130/80mmHg target **Table 3** .

Table 3. Sociodemographic and Anthropometric Characteristics of 869 Patients with Diabetes Mellitus Attending National Center for Diabetes Endocrinology and Genetics (NCDEG).

Variable	n	(%)
Gender		
Males	487	(55.0)
Females	382	(44.0)
Age (year)	Mean(SD)=57.8 (9.1)	
<45	79	(9.1)
45-55	266	(30.6)
56-65	362	(41.7)
>65	162	(18.6)
Duration of D.M(year)	Mean(SD)=9.5 (7.5)	
≤5	331	(38.1)
6-10	234	(26.9)
≥11	304	(35.0)
Smoking		
Non	551	(63.4)
Current	138	(15.9)
Past	180	(20.7)
Body Mass Index(Kg/m ²)	Mean(SD)=31.5 (5.5)	
<25	83	(9.6)
25-29.9	275	(31.6)
≥30	511	(58.8)

Variable	n	%
Systolic Blood Pressure(mmHg)	Mean(SD)=128 (14.5)	
<130	541	(62.3)
≥130	328	(37.7)
Diastolic Blood Pressure(mmHg)	Mean(SD)=76.8 (7.5)	
<80	654	(75.3)
≥80	215	(24.7)

Clinical and Biochemical Characteristics of the Study Population

As shown in **Table 4** , the majority of the sample population (67.9%) had hypertension. Dyslipidemia was present in 94.6% of the study patients. Hypertriglyceridaemia, hypercholesterolemia, high LDL cholesterol ,low HDL cholesterol levels among male and low HDL cholesterol levels among female were reported among 40.4% , 13.5%, 46.1%, 46.4%, 58.9% of these patients , respectively .Only 35.3 had HbA1c <7%. About one third of patients had retinopathy.

Table 4 .Clinical and Biochemical Characteristics of the Participants

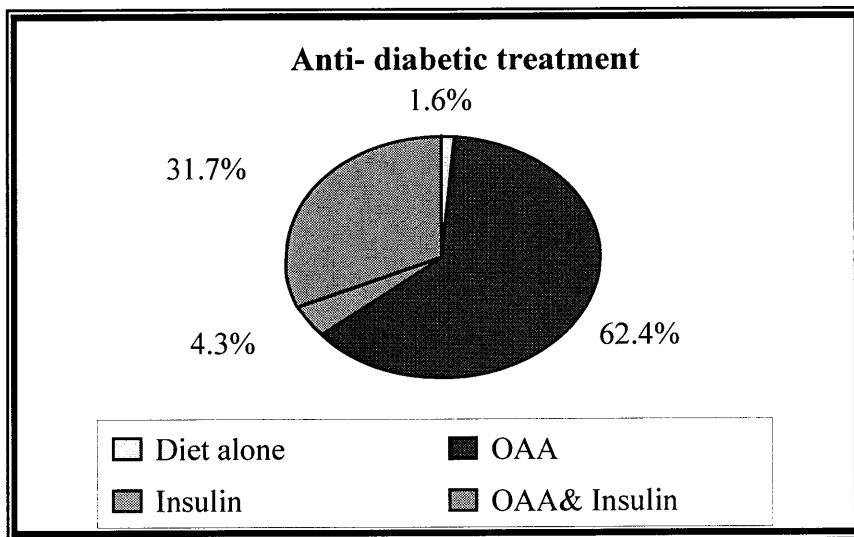
Variable	n	%
Hypertension		
Yes	590	(67.9)
No	279	(32.1)
Dyslipidemia		
Yes	822	(94.6)
No	47	(5.4)
Diabetes retinopathy(DR)		
Yes	268	(30.8)
No	601	(69.2)
Glycated hemoglobin	Mean(SD)=7.716 (1.5)	
<7.0%	307	(35.3)
≥7.0%	562	(64.7)
Cholesterol(mg/dl)	Mean(SD)=162.4 (35.3)	
<200	752	(86.5)
≥200	117	(13.5)
Low density lipoprotein	Mean(SD)=101.5 (32.4)	
<100	468	(53.9)
≥100	401	(46.1)

Variable	n	%
High density lipoprotein male	Mean(SD)= 42.0 (10.3)	
<40	266	(46.4)
≥40	261	(53.6)
High density lipoprotein female	Mean(SD)= 48.2 (13.4)	
<50	225	(58.9)
≥50	157	(41.1)
Triglyceride(mg/dl)	Mean(SD)=153.6 (82.8)	
<150	518	(59.6)
≥150	351	(40.4)

Treatment Modalities for the Diabetic Participants

High proportions of patients (62.4%) were managed by oral antidiabetic agents alone, (4.3%) by insulin alone , (31.7%) of patients were on combination of oral antidiabetic agents and insulin ,while 1.6% of the patients were following only diet regime as part of their diabetes management **Figure 2** .

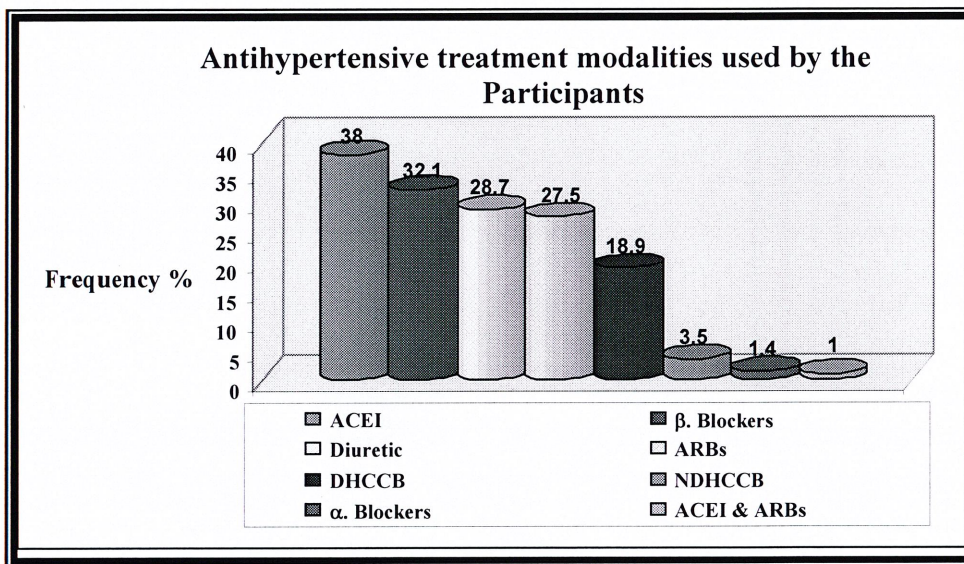
Figure 2. Shows the Anti-diabetic Treatment Modalities of the Participants



OAA: Oral Antidiabetic Agents

Most of the study subjects (74.8%) were on antihypertensive treatment. Drugs used for this purpose were angiotensin-converting enzyme inhibitors(ACE)(38.1%) ,angiotensin receptor blockers(ARBs) (27.5%), combined ACEI and ARBs (1%), beta-blockers(32.1%),alpha-blockers (1.4%) ,dihydropyridine ca-channel blockers(18.9%) ,nondihydropyridine ca-channel blockers (3.5%) and diuretic (28.7%) (**Figure 3**) .Majority of patients (74.5%) were receiving lipid-lowering agent.

Figure 3. Shows Antihypertensive Treatment Modalities Used by the Participant.



The prevalence of Diabetic Microalbuminuria and Macroalbuminuria According to Sociodemographic and Anthropometric Characteristics

Table 5

Overall, 34.6% of patients with diabetes had albuminuria (29.3% had microalbuminuria and 5.3% had macroalbuminuria).No significant differences in gender and smoking were noted among patients with micro- and macroalbuminuria. The microalbuminuric patients were

older compared with normoalbuminuric group ($p=0.001$). There was an increase in frequency of microalbuminuria and macroalbuminuria in patients who had diabetes of more than 11 years duration. Mean SBP were significantly higher with micro- and macroalbuminuria compared with normoalbuminuria ($p<0.0005$). However diastolic blood pressure was higher only in the microalbuminuric patients ($p<0.0005$). Patients with microalbuminuria was predominantly obese and over weight ($p=0.02$).

Table 5. Prevalence of Diabetic Microalbuminuria and Macroalbuminuria Among Jordanian Diabetics According to Sociodemographic and Anthropometric Characteristics.

Variable	Normoalbuminuria n%=568(65.4)	Microalbuminuria n%=255(29.3)	Macroalbuminuria %=46(5.3)
Gender			
Men	316 (64.9)	139 (28.5)	32 (6.6)
Women	252 (66.0)	116 (30.4)	14 (3.7)
P-value	–	0.764	0.067
Age (years)			
<45	59 (74.7)	17 (21.5)	3 (3.8)
45-55	187(70.3)	65 (24.4)	14 (5.3)
56-65	236(65.2)	108 (29.8)	18 (5.0)
>65	86 (53.1)	65 (40.1)	11 (6.8)
P-value	–	0.001	0.416
Body mass index			
<25	65 (78.3)	15 (18.1)	3 (3.6)
25-29.9	188 (68.4)	75 (27.3)	12 (4.4)
≥30	315 (61.6)	165 (32.3)	31 (6.1)
P-value	–	0.020	0.461
Duration of DM (years)			
≤5	241 (72.8)	77 (23.3)	13 (3.9)
6-10	156 (66.7)	70 (29.9)	8 (3.4)
≥11	171 (56.3)	108 (35.5)	25 (8.2)
P-value	–	0.001	0.003
Smoking			
Non	370 (67.2)	153 (27.8)	28 (5.1)
Current	89 (64.5)	42 (30.4)	7 (5.1)
Past	109 (60.6)	60 (33.3)	11 (6.1)
P-value	–	0.229	0.737
SBP(mmHg)			
<130	406 (75.0)	116 (21.4)	19 (3.5)
≥130	162 (49.4)	139 (42.4)	27 (8.2)
P-value	–	<0.0005	<0.0005

Continue table 5			
DBP(mmHg)			
<80	453 (69.3)	168 (25.7)	33 (5.0)
≥80	115 (53.5)	87 (40.5)	13 (6.0)
P-value	–	<0.0005	0.192

The Prevalence of Diabetic Microalbuminuria and Macroalbuminuria According to Clinical and Biochemical Characteristics Table 6

The presence of hypertension, hypertriglyceridaemia and hypercholesterolemia were significantly higher with both micro- and macroalbuminuric groups. HbA1c levels were significantly higher in all groups with abnormal albumin. The prevalence of diabetic retinopathy was significantly higher in micro- and macroalbuminuric patients compared with those with normoalbuminuria ($p<0.0005$).

Table 6 . Prevalence of Diabetic Microalbuminuria and Macroalbuminuria Among Jordanian Diabetics According to Clinical and Biochemical Characteristics

Variable	Normoalbuminuria n (%)=568(65.4)	Microalbuminuria n (%)=255(29.3)	Macroalbuminuria n (%)=46(5.3)
Hypertension			
Yes	349 (59.2)	204 (34.6)	37 (6.3)
No	219 (78.5)	51 (18.3)	9 (3.2)
P-value	–	<0.0005	0.010
Dyslipidemia			
Yes	537 (65.3)	240 (29.2)	45 (5.5)
No	31 (66.0)	15 (31.9)	1 (2.1)
P-value	–	0.806	0.335
Diabetes retinopathy (DR)			
Yes	136 (50.7)	103(38.4)	29 (10.8)
No	432 (71.9)	152(25.3)	17 (2.8)
P-value		<0.0005	<0.0005
Glycatd hemoglobin (HbA1c %)			
<7%	235 (76.5)	63 (20.5)	9 (2.9)
≥7%	333 (59.3)	192 (34.2)	37 (6.6)
P-value	–	<0.0005	0.004

Continue table 6			
Cholesterol (mg/dl)			
<200	505 (67.2)	211(28.1)	36 (4.8)
≥200	63 (53.8)	44 (37.6)	10 (8.5)
P-value	—	0.015	0.032
Low density lipoprotein (LDL)			
<100	311 (66.9)	129 (27.7)	25 (5.4)
≥100	257 (63.6)	126 (31.2)	21 (5.2)
P-value	—	0.268	0.958
High density lipoprotein (HDL) male			
<40	135 (59.7)	74 (32.7)	17 (7.5)
≥40	181 (69.3)	65 (24.9)	15 (5.7)
P-value	—	0.060	0.258
High density lipoprotein (HDL) female			
<50	145 (64.4)	68 (30.2)	12 (5.3)
≥50	107 (68.2)	48 (30.6)	2 (1.3)
P-value	—	0.845	0.073
Triglyceride (mg/dl)			
<150	358 (69.1)	141 (27.2)	19 (3.7)
≥150	210 (59.8)	114 (32.5)	27 (7.7)
P-value	—	0.036	0.004

Multivariate Analysis of Factors Associated with Diabetic

Microalbuminuria After Adjusting for Other Factors Table 7

In the bivariate analysis, microalbuminuria significantly associated with age, BMI, duration of diabetes, diabetes retinopathy, HbA1c, hypercholesterolemia, hypertriglyceridemia, SBP, and DBP. After using stepwise logistic regression analysis, the only variables remained significantly associated with Microalbuminuria were mean HbA1c, mean SBP and the presence of retinopathy. For each 1% increase in HbA1c, the odds of having microalbuminuria increased by 86%. Patients with mean SBP ≥ 130 mmHg were found to be 1.85 times more likely to have microalbuminuria than those with SBP <130mmHg. Patients with mean DBP ≥ 80 mmHg were found to be 1.47 times more likely to have microalbuminuria than those with DBP <80 mmHg. The odds of having microalbuminuria

for those who had diabetic retinopathy are 1.45 times more than those who did not have diabetic retinopathy.

Table 7. Logistic Regression Analysis of Factors Associated with Microalbuminuria

Variables	OR (95% confidence interval)	P-value
Mean HbA1c (Uncontrolled vs. control)	1.86(1.30, 2.64)	0.001
Mean SBP (Uncontrolled vs. control)	1.85(1.57, 3.01)	0.001
Mean DBP (Uncontrolled vs. control)	1.47(1.02, 2.15)	0.043
Diabetes retinopathy (Yes vs. no)	1.61(1.02, 2.28)	0.007

OR: Odds ratio

HbA1c: Glycated hemoglobin

SBP: Systolic Blood Pressure

DBP: Diastolic Blood Pressure

Multivariate Analysis of Factors Associated with Diabetic

Macroalbuminuria After Adjusting for Other Factors Table 8

In the bivariate analysis, macroalbuminuria significantly associated with duration of diabetes, diabetes retinopathy, HbA1c, hypercholesterolemia, hypertriglyceridemia, SBP and DBP. After using stepwise logistic regression analysis, the only variables remained significantly associated with macroalbuminuria were mean SBP, male sex and the presence of diabetic retinopathy. Patients with mean SBP ≥ 130 mmHg were found to be 2.33 times more likely to have macroalbuminuria than those with SBP <130 mmHg. Males were found to be 2.13 times more likely to have macroalbuminuria than females. Patients with diabetic

retinopathy were found to be 4.77 times more likely to have macroalbuminuria than those without diabetic retinopathy.

Table 8. Logistic Regression Analysis of Factors Associated with Macroalbuminuria

Variables	OR (95% confidence interval)	P-value
Mean SBP (Uncontrolled vs. control)	2.33(1.19, 4.53)	0.013
Gender (Male vs. female)	2.13(1.06, 4.29)	0.034
Diabetes retinopathy (Yes vs. no)	4.77(2.47, 9.22)	0.000

OR: Odd ratio

SBP: Systolic blood pressure

DISCUSSION

This study measures the prevalence of the different stages of albuminuria in type 2 diabetes among patients attending the (NCDGE). As a national center receiving patients from all the country either directly or referred from other clinics in Jordan, we believe that patients included in this study are somehow representative of all diabetics in Jordan. Numerous studies carried out to determine the prevalence of albuminuria in patients with type 2 diabetes. These studies yielded different rates between (17% to 58.6) for albuminuria ^(40, 44, 47, 50). Our study showed the prevalence rate of 34.6% which is somewhere in median range. The marked variation in rate might be due to study design, sample selection, method used for collecting of urine, race and the age and sex structure of the population it self ⁽⁴⁰⁾. The prevalence of microalbuminuria and macroalbuminuria in our study was 29.3% and 5.3% respectively. The prevalence of microalbuminuria in this study is comparable to the Hungarian study conducted by Molnar et al ⁽³²⁾. Which showed close prevalence (27.5%), but considerably higher prevalence of macroalbuminuria 38.5% vs. 5.3% in our study. In Finland a study conducted by Wirta et al in a recent onset diabetic patients, showed almost the same prevalence as in our study; microalbuminuria and macroalbuminuria prevalence value of (29%, 4%) vs. (29.3%, 5.3%) among our patients ⁽³⁹⁾. However a study carried out in United Kingdom on NIDDM patients showed a lower prevalence of albuminuria (19%) ⁽³¹⁾. Concerning Arab countries, studies in the Kingdom of Saudi Arabia ⁽⁵¹⁾ and United Arab Emirates ⁽⁵³⁾, showed a relatively higher rate of microalbuminuria (41.3%, 61%) respectively than that observed in our results. On the other hand, a study in Sultanate of Oman ⁽⁵⁰⁾, showed nearly similar rate (27%).

Glycaemic Control

Hyperglycemia is considered to be one of the important risk factors for the development and progression of diabetic retinopathy ^(36,46,57,58,59). Several studies clearly demonstrated the benefits of improving glycaemic control and decreasing HbA1c concentration in decreasing the complication rate ^(20,55,56,57,76). In our study, HbA1c showed a high significance with microalbuminuria. On the other hand macroalbuminuria showed no significant association with HbA1c. This finding is consistent with the results obtained by De pablois et al ⁽³⁴⁾, but results must be considered with caution because of the cross-sectional design of the study.

Blood Pressure

Our study showed a significant association between systolic blood pressure and both micro- and macroalbuminuria. Systolic blood pressure is identified as a risk factor for microalbuminuria ^(23, 40, 47, 76) and macroalbuminuria ^(16, 40, 47) in many studies. On the other hand our data showed that diastolic blood pressure comes out significant with microalbuminuric groups only, which is consistent with the results of (CURES-45) study ⁽⁴⁷⁾.

Diabetes Duration

The association observed between albuminuria and the number of years since diagnosis was not significant in our study. However, this effect is difficult to determine in type 2 diabetes. A plausible explanation for this is the fact that non-insulin dependent diabetes may be silent for many years before clinical recognition, as well as these patients subjected for recall bias. This may explain why previous studies have reported both significant ^(22,33,48,66) and non significant ^(22,32) association between albumin excretion and known duration of the disease.

Smoking

The study data failed to show a positive association with smoking. The hazardous effect of smoking may be blurred by the substantially lower proportion of current smokers 15.9% in our patients sample than that in the United Kingdom study 31% ⁽⁶⁶⁾. A plausible explanation for this association that at the diagnosis of nephropathy; patients tend to quit smoking as part of nephropathy interventional program, of which this is not the case in patients with normal albumin that see no reasons to quit smoking .As well as no information was taken regarding when they quit. This finding justify further research for this phenomenon .Contrary to our results, smoking was significantly associated with albuminuria ^(23, 32, 48, 69, 76). However Gall M et al (1997) and Varghese A et al (2001) did not observe any significant differences ^(22, 46).

Gender

Surprisingly gender which was not statistically different when tested alone against the occurrence of micro-and macroalbuminuria; in the final regression model it shows significant correlation of male gender with macroalbuminuria. Earlier studies have reported an increased association of microalbuminuria ^(23, 48, 76, 79, 82) and macroalbuminuria ⁽⁴⁴⁾ with men compared with women. On the other hand, other study revealed that female sex was positively associated with microalbuminuria ⁽⁴⁶⁾. Because women have a lower creatinine excretion due to less muscle mass than men there is, however, a problem about using the albumin creatinine ratio when comparing prevalence across genders. Thus some authors use a lower threshold for men than women ⁽⁴⁶⁾.It remains to be seen whether the difference in albumin excretion between men and women has significance for long-term risk of chronic disease or merely reflects the greater size of men compared to women.

diabetic kidney disease, as evidenced by several studies, that lipid reduction by antilipidemic agents might decrease proteinuria in diabetic patients ^(29, 71). While there was a number of studies showed a significant association between serum lipid and either microalbuminuria, or macroalbuminuria ^(22, 23, 32, 33). This result remains a debatable issue concerning albuminuria and need to be addressed by future studies, preferably longitudinal studies.

Diabetic Retinopathy

In the present study ,we found that patients with microalbuminuria and macroalbuminuria were statistically significant with the presence of retinopathy .This finding were supported by other studies (^{43,47,49,53}) Besides, our results revealed that the prevalence of DR in microalbuminuria patients was higher than that in macroalbuminuria patients (38.4% vs.10.8%) , so that we agreed that even patients who have microalbuminuria were at high risk of developing retinopathy ^(16, 35 , 48).It was surprisingly , however, that in our 46 patients with macroalbuminuria ,29(63%) of them had DR ,whereas diabetic retinopathy was absent in 17(37%) of the 46 patients with macroalbuminuria. In different study, analysis of type 2 diabetes with proteinuria found that approximately 30% did not have diabetes nephropathy on renal biopsy among those without retinopathy ⁽¹⁷⁾.Type 2 diabetics with marked proteinuria and retinopathy are most likely to have DNP, whereas those without retinopathy may be caused by disease other than diabetic glomerulopathy (hypertension, atherosclerosis, chronic glomerulonephritis, chronic pylonephritis) ⁽³²⁾.

CONCLUSION & RECOMMENDATION

This is a center-based study to explore the prevalence of albuminuria in patients attending the NGDEC in Amman -Jordan, a tertiary center with referrals from all over Jordan .Our study showed:

- The prevalence of albuminuria (microalbuminuria and macroalbuminuria) observed in Jordanian patients diagnosed with type 2 diabetes aged ≥ 30 years in NCDEG reached up to 34.6% (29.3% with microalbuminuria and 5.3% with macroalbuminuria).
- The main risk factors for the development of albuminuria and its related stages in our study are HbA1c, SBP, presence of DR and male sex.
- Microalbuminuria is significantly associated with HbA1c, SBP, and presence of retinopathy.
- Macroalbuminuria is significantly associated with SBP, presence of diabetic retinopathy, and male sex.

In conclusion, given the large numbers of persons with diabetes in Jordan ^(3, 4), the numbers of diabetic patients with microalbuminuria and macroalbuminuria is undoubtedly enormous. The large pool of microalbuminuria suggests that there could be large increases in the macroalbuminuria with time ⁽¹⁴⁾. Most patients with macroalbuminuria eventually reach the stage of end-stage renal disease (ESRD) ⁽¹⁴⁾. Although the cost of haemodialysis in Jordan is relatively low (US \$ 17 385/patient /year), the burden is huge in a country with limited resources like Jordan ⁽¹⁰⁾. This urgently calls for implementing early and universal screening programs for microalbuminuria in type 2 diabetic patients. Through cardiovascular risk reduction, lowering blood pressure, renin-angiotensin system blockade and glycaemic control, such early and targeted intervention could significantly reduce the occurrence of

renal complication. In addition, early referral to nephrologists is mandatory especially for those with macroalbuminuria in the absence of retinopathy for further evaluation of “non-diabetic” glomerulopathies. Since DR is frequent in the presence of diabetic nephropathy, it is particularly important to investigate all patients with albuminuria for DR by an experienced ophthalmologist. According to ADA guidelines which recommended annual measurement of serum creatinine for the estimation of GFR in addition to measurement of urine albumin excretion ⁽⁸⁴⁾ another future study is suggested to consider these guidelines, especially in those patients who manifest with decreased GFR in the absence of increased urine albumin excretion.

DATA SHEET FOR TYPE 2 DM

Sociodemographic Data

File no: _____.Name:

1. Age: ____yrs

2. Sex: 1.Male 2.Female

3. Duration of DM: ____yrs

4. Smoking: 1.non 2.current smoker 3.past smoker

Anthropometric Measurement

5. Height: ____cm

6. Weight: ____kg

7. SBP: ____mmHg

8. DBP: ____mmHg

9. Temperature ____ °c

Current Medical Problems

10. Dyslipedemia	1.YES	2.NO
11. Hypertension	1.YES	2.NO
12. Retinopathy	1.YES	2.NO
13. Congestive heart failure	1.YES	2.NO
14. Hematuria	1.YES	2.NO
15. Pyria	1.YES	2.NO

Current Treatments:

18. Diet/Life style	1.YES	2.NO
19. Oral hypoglycemia drug	1.YES	2.NO
20. Insulin	1.YES	2.NO
21. Antihypertensive drugs	1.YES	2.NO
21,1. ACEI	1.YES	2.NO
21,2. ARB	1.YES	2.NO
21,3. β -Blocker	1.YES	2.NO
21,4. α -Blocker	1.YES	2.NO
21,5. Dihydropyridine Ca-Channel Blockers	1.YES	2.NO
21,6. Non- Dihydropyridine Ca-Channel Blockers	1.YES	2.NO
21,7. Diuretic	1.YES	2.NO
22. Lipid Lowering Drugs	1.YES	2.NO

TEST

23. ACR mg/g

24. HbA1c

25. T.cholesterol

26. HDL

27. LDL

28. TG

29. Did you do excessive exercise in the last 24hrs? 1. YES 2.NO

REFERENCES

1. Shaw JE, Zimmerman P, McCarthy D, De Courten M. Type 2 diabetes world wide according to the new classification and criteria. **Diabetes care** 2000; 23 Suppl 2:5-10
2. The world Health Organization, The Diabetes Program 2004. Available at <http://www.who.int/diabetes/en>. Accessed on May 31, 2005
3. Ajlouni K, Jaddou H, Batieha A. Diabetes and impaired glucose tolerance in Jordan: Prevalence and associated risk factors. **Journal of Internal Medicine** 1998; 44:317-
4. Ajlouni K, Khader Y, Batieha A, Ajlouni H, El-khateeb M. An increased prevalence of diabetes mellitus in Jordan during ten years. Accepted for publication at **journal of diabetes and its complication**.
5. Nathan D.M. Long-term complications of diabetes mellitus. **New Engl J Med** 1993; 328:1676-1685.
6. Fabre J, Balant LP, Dayer PG, Fox HM, Vernet AT. The kidney in maturity onset diabetes mellitus: a clinical study of 510 patients. **Kidney Int** 1982; 21:730-738.
7. Ritz E, Orth SR. Nephropathy in patients with type 2 diabetes. **N Engl J Med** 1999; 341: 1127- 1133
8. Remuzzi G, Schieppati A, Ruggeneni P. Diabetic nephropathy in patients with type2 diabetes mellitus. **N Engl J Med** 2002;346:1145-1151
9. Takruri HR, Hamzeh YS, Sweiss A. Haemodialysis patients in Jordan .A comprehensive survey. **Archives of dialysis and transplantation** 1995; 24(12):678-82.
10. Batieha A, Abdullah S, Maghaireh M, Awad Z, Al-Akash N, Batieneh A, Ajlouni K. Epidemiology and cost of haemodialysis in Jordan. **Eastern Mediterranean Health Journal** 2007; 13:654-662

11. Hafez M, Abdulatif D, Elkhatib M. Prevention of renal disease progression and renal replacement therapy in emerging countries. **Arit organs** 2006; 30:501-509
12. Hall P. Prevention of progression in Diabetic Nephropathy .**Diabetes spectrum** 2006; 19:18-24
13. Mogensen CE. Microalbuminuria predicts clinical proteinuria and early mortality in maturity-onset diabetes. **N Engl J Med** 1984; 310:356-60.
14. American Diabetes Association .Nephropathy in diabetes (position statement). **Diabetes care** 2004; 27 Suppl. 1:S79-S83
15. Gerstein HC, Mann JF, Yi Q, Zinman B, Dinneen SF, Hoogwerf B, et al. Albuminuria and risk of cardiovascular events, death, and heart failure in diabetic and nondiabetic individuals. **JAMA** 2001; 286:421–426.
16. Lu B, Wena J, Song XY, Dong XH, Yang YH, Zhang ZY, et al. High prevalence of albuminuria in population-based patients diagnosed with type 2 diabetes in the Shanghai downtown. **Diabetes Research and Clinical Practice** 2007; 75:184–192
17. Christensen P.K, Larsen S, Horn T, Oslen S, Parving H.H.Causes of albuminuria in patients with type 2 diabetes without diabetic retinopathy.**Kidney Int** 2000; 58:1719-1731.
18. Hovind P, Rossing P, Tornow L, Smidt U, Parving H. Progression of diabetic nephropathy. **Kidney Int** 2001; 59:702-709
19. Ritz E. Nephropathy in type 2 diabetes .**Journal of Internal Medicine** 1999; 245:111-126.
20. United Kingdom Prospective Diabetes Study Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of

complications in patients with type 2 diabetes (UKPDS 33). **Lancet** 1998; 352: 837-853.

21. United Kingdom Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. **BMJ** 1998; 317: 703-713.

22. Gall M, Honngaard P, Borch-Johnsenk, Parving HH. Risk factors for development of incipient and overt diabetic nephropathy in patients with non-insulin dependent diabetes mellitus: prospective, observational study. **BMJ** 1997; 314:783

23. Cederholm J, Eliasson B, Nilsson P.M, Weiss L, Gudbjörnsdóttir S. Microalbuminuria and risk factors in type 1 and type 2 diabetic patients. **Diabetes Research and Clinical Practice** 2005; 67:258-266

24. Mogensen CE, Schmitz O. The diabetic kidney: from hyper filtration and microalbuminuria to end-stage renal failure. **Med Clin North Am** 1988; 72:1465-

92

25. Osterby R, Gundersen HJ, Horlyck A. Diabetic glomerulopathy. Structural characteristics of early and advanced stages. **Diabetes** 1993; 32(Suppl 2):79-82

26. Veldman BAJ, Vervoort G. Pathogenesis of renal microvascular complication in diabetes mellitus. **The Netherlands journal of medicine** 2002; 60:390-396

27. Cooper ME. Pathogenesis, prevention and treatment of diabetic nephropathy. **Lancet** 1998; 352:213-219

28. American Diabetes Association. Nephropathy screening and treatment. **Diabetes care** 2007; 29 Suppl. 1:S21-S23

29. Gross JL, De Azevedo M, Silveiro Sp, et al. Diabetic nephropathy: Diagnosis, Prevention and Treatment. **Diabetes Care** 28:164-176, 2005

30. Klein R, Klein BE, Moss SE. Prevalence of microalbuminuria in older-onset diabetes. **Diabetes Care** 1993; 16:1325-30

31. Neil A, Hawkins M, Potok M, Thorogood M, Cohen D, Mann J. A prospective population based study of Microalbuminuria as a predictor of mortality in NIDDM. **Diabetes Care** 1993; 16:996-1003
32. Monlar M, Wittmann I, Nagy J. Prevalence, course and risk factors of diabetic nephropathy in type 2 diabetes mellitus. **Med Sci Monit** 2000; 6(5):929-936
33. Bruno G, Cavallo-Perin P, Borra M, Calvi V, D'Errico N, Deambrogio P, Pagano G. Prevalence and risk factors for micro- and macroalbuminuria in an Italian population-based cohort of NIDDM subjects. **Diabetes Care** 1996; 19:43-47
34. De Pablos PL, Martinez J, Martinez MP, Doreste JA. Prevalence of macro- and macroalbuminuria in a Canarian population of type 2 diabetic patients. Relationship with blood pressure, lipid profile, obesity and metabolic control. **Diabetes Metab** 1998; 24:337-343
35. Parving HH, Gall MA, Skøtt P, Jørgensen HE, Løkkegaard H, Jørgensen F, et al. Prevalence and causes of albuminuria in non-insulin-dependent diabetic patients. **Kidney Int** 1992; 41:758-62
36. Tapp RJ, Shaw JE, Zimmet PZ, Balkau B, Chadban SJ, Tonkin AM, et al. Albuminuria is evident in the early stages of diabetes onset: results from the Australian Diabetes, obesity, and lifestyle study (Aus Diab). **Am J kidney Dis** 2004; 44:792-798
37. Collins VR, Dowse GK, Plehwe WE, Imo TT, Toelupe PM, Taylor HR et al. High prevalence of diabetic retinopathy and nephropathy in Polynesians of Western Samoa. **Diabetes Care** 1995; 18:1140-9
38. Gall MA, Rossing P, Skøtt P, Damsbo P, Vaag A, Bech K, et al. Prevalence of micro- and macroalbuminuria, arterial hypertension, retinopathy and large vessel disease in European type 2 (non-insulin dependent) diabetic patients. **Diabetologia** 1991; 34:655-661.

39. Wirta OR ,Pasternak AI, Oksa HH, Mustonen JT,Koivula TA, Helin HJ, et al. occurrence of late specific complications in type II (Non-Insulin-Dependent) diabetes mellitus. **Journal of diabetes and its complications** 1995; 9:177-185
40. Lutale J.J, Thordarson H, Abbas ZG, Vetvik K.Microalbuminuria among Type 1 and Type 2 diabetic patients of African origin in Dar Es Salaam, Tanzania. **BMC Nephrology** 2007; 8:1-8
41. Agaba EI, Agaba PA, Puepet FH. Prevalence of microalbuminuria in newly diagnosed type 2 diabetic patients in Jos Nigeria .**Afr J Med Med Sci** 2004; 33:19-22
42. Dasmahapatra A, Bale A, Raghuwanshi MP, Reddi A, Byrne W,Suarez S,et al. Incipient and overt diabetic nephropathy in African American with NIDDM. **Diabetic care** 1994; 17:297-304
43. Sobngwi E, Mbanya JC, Moukouri EN, Ngu KB. Microalbuminuria and retinopathy in diabetic population of Cameroon. **Diabetes Research and Clinical Practice** 1999; 44:191 -196.
44. Wu AY, Kong NC, de Leon FA, Pan CY, Tai TY,Yeung Vt , et al. An alarmingly high prevalence of diabetic Nephropathy in Asian type 2 diabetes patients: the Microalbuminuria Prevalence (MAP) Study. **Diabetologia** 2005; 48:17-26.
45. Tam TK, Cheng LP, Lau DM, Lai TC, Lai WY, Ng KK, et al. The prevalence of microalbuminuria among patients with type II diabetes mellitus in a primary care setting: Cross-sectional study. **Hong Kong Med J** 2004; 10:307-11
46. Varghese A, Deepa R, Rema M, Mohan V .Prevalence of microalbuminuria in type 2 diabetes mellitus at a diabetes centre in southern India. **Postgrad Med J** 2001; 77:399-402
47. Unnikrishnan R, Rema M, Pradeepa R, Deepa M, Shanthirani CS, Deepa R, Mohan V.Prevalence and risk factors of diabetic nephropathy in an Urban South Indian population :The Chennai Urban Rural Epidemiology Study (CURES 45). **Diabetes Care** 2007; 30:2019-2024

48. Ahmedani MY, Hydrie MZ, Iqbal A, Gul A, Mirza WB, Basit A. Prevalence of microalbuminuria in type 2 diabetic patients in Karachi: Pakistan: a multicenter study. **Pak Med Assoc J** 2005; 55:382-386
49. Manaviat MR, Afkhami M, Shoja MR. Retinopathy and microalbuminuria in type II diabetic patient's .**BMC ophthalmology** 2004; 4:1-4
50. Al-Futaisi A, Al-Zakwani I, Almahrezi A, Al-Hajri R, Al-Hashmi L, Al-Muniri A. Prevalence and predictors of microalbuminuria in patients with type 2 diabetes mellitus: A cross-sectional observational study in Oman. **Diabetes Research and Clinical Practice** 2006; 72: 212–215
51. Alzaid A, Sobki, De Silva V. Prevalence of microalbuminuria in Saudi Arabians with non-insulin dependent diabetes mellitus: a clinic based study .**Diabetes Research and Clinical Practice** 1994; 26:115-120
52. Al-Shaikh A. Prevalence of microalbuminuria in type 2 diabetes mellitus at diabetic clinic in King Abdulaziz University Hospital. **Pak J Med Sci** 2007; 23:223-226.
53. Al-Maskari F, El-Sadig M, Obineche E. Prevalence and determinants of microalbuminuria among diabetic patients in the United Arab Emirates. **BMC Nephrology** 2008; 9:1-25
54. Herman WH, Aubert RE, Engelgau MM, Thompson TJ, Ali MA, Sous ES, et al. Diabetes mellitus in Egypt :glycemic control and microvascular and neuropathic complications. **Diabet Med** 1998; 15:1045-1051
55. Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of Diabetes on the development and progression of long-term complications in Insulin-dependent diabetes mellitus. **N Engl J Med** 1993; 329:977-86.
56. United Kingdom Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). **Lancet** 1998; 352: 854-65.

57. Ohkubo Y, Kishikawa H, Araki E, Miyata T, Isami S, Motoyoshi S, et al. **Diabetes Research and Clinical Practice** 1995; 28:103-117
58. Gilbert RT, Tsalamandris C, Bach LA, et al. Long-term glycemic control and the rate of progression of early diabetic renal disease. **Kidney Int** 1993; 44:855.
59. Estacio RO, Jeffers BW, Gifford N, Schrier RW. Effect of blood pressure control on diabetic microvascular complications in patients with hypertension and type 2 diabetes. **Diabetes Care** 2000; 23 (Suppl. 2):54-64
60. Mogensen. Microalbuminuria and hypertension with focus on type 1 and type 2 diabetes. **Intern Med J** 2003; 254:45-66
61. United Kingdom Prospective Diabetes Study Group. Efficacy of atenolol and captopril in reducing risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 39. **BMJ** 1998; 317:713-720.
62. Ruggenenti P, Fassi A, Ilieva AP, Bruno S, Iliev IP, Brusegan V, et al. Bergamo Nephrologic Diabetes Complications Trial (BENEDICT) Investigators. Preventing microalbuminuria in type 2 diabetes. **N Engl J Med** 2004; 351:1941-1951.
63. Schrier RW, Estacio RO, Esler A, Mehler P. Effects of aggressive blood pressure control in normotensive type 2 diabetic patients on albuminuria, retinopathy and strokes. **Kidney Int** 2002; 61:1086.
64. Heart Outcomes Prevention Evaluation Study Investigators. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. **Lancet** 2000; 355:253-259.
65. Parving HH, Lehnert H, Brochner-Mortensen J, Gomis R, Andersen S, Arner P. The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. **N Engl J Med**. 2001; 345:870-878.

66. Adler AI, Stevens RJ, Manley SE, Bilous RW, Cull CA, Holman RR. Development and progression of nephropathy in type 2 diabetes: The United Kingdom Prospective Diabetes Study (UKPDS 64). **Kidney Int** 2003; 63:225-232.
67. Harris MI, Klein R, Welborn TA, Knudman MW. Onset of NIDDM occurs at least 4-7 years before clinical diagnosis. **Diabetes Care** 1992; 15:815-819
68. Niskanen LK, Penttilä I, Parviainen M, Uusitupa MI. Evolution, risk factors and prognostic implications of albuminuria in NIDDM. **Diabetes Care** 1996; 19:486-93
69. Olivarius N, Andreassen AH, Keiding N, Mogensen CE. Epidemiology of renal involvement in newly diagnosis middle aged and elderly diabetic patients. Cross-sectional data from the population-based study „Diabetes Care in General Practice“, Denmark. **Diabetologia** 1993; 10:1007-1016.
70. Nelson R, Knowler WC, Pettitt DJ, et al. Diabetic kidney disease in Pima Indians. **Diabetes Care** 1993; 16:335-341.
71. Ansquer JC, Foucher C, Rattier S, et al. Fenofibrate reduces progression to microalbuminuria over 3 years in a placebo- controlled study in type 2 diabetes: results from the Diabetes Atherosclerosis Intervention study (DAIS). **Am J Kidney Dis** 2005; 45:485
72. Diehl AM, Non-alcoholic steatosis and steatohepatitis IV. Nonalcoholic fatty liver disease abnormalities in macrophage function and cytokines. **Amj physiol .Gastrointest Liver physiol** 2000; 282:G1-G5
73. Morales E, Valero MA, Leon M, Hernandez, praga M. Beneficial effect of weight loss in over weight patients with chronic proteinuric nephropathies. **AM J Kidney Dis** 2003; 41:319

74. Ramirez SP, McClellan W, Port FK, Hsu SI. Risk factors for proteinuria in a large, multiracial, Southeast Asian population. **J Am Soc Nephrol** 2002; 13:1907-1917.

75. Chase HP, Garg SK, Marshall G, et al. Cigarette smoking increases the risk of albuminuria among subjects with type 1 diabetes. **JAMA** 1991; 265:614

76. Rossi MCE, Nicolucci A, Pellegrini F, Commaschi Ceriello A, Cucinotta D, et al. Identifying patients with type 2 diabetes at higher risk of microalbuminuria: Result of DEMAND (Developing Education on Microalbuminuria for Awareness of renal and cardiovascular risk in Diabetes) study. **Nephrol Dial Transplant** 2007; 0:1-7

77. Nelson RG, Kunzelman CL, Pettitt DJ, Saad MF, Bannett PH, Knowler WC. Albuminuria in type 2 (non-insulin-dependent) diabetes mellitus and impaired glucose tolerance in Pima Indians. **Diabetologia** 1989; 32:870-6

78. Yeung VTF, Lee KF, Chan SH, Ho LF, Leung SK, Wong HY, et al. Microalbuminuria Prevalence Study (MAPS) in hypertensive type 2 diabetic patients in Hong Kong. **Hong Kong Med J** 2006; 12:185-189

79. Anderson AR, Chistian JS, Andersen JK, Kreiner S, Deckert T. Diabetic nephropathy in Type 1(insulin-dependent)diabetes :an epidemiological study .**Diabetologia** 1983; 25:496-501

80. Boelter MC, Gross JL, Canani LH, Costa LA, Lisbosa HR, Tres GS et al. Proliferative diabetic retinopathy is associated with microalbuminuria in patients with type 2 diabetes. **Braz Med Biol Res** 2006; 39(8):1033-1039

81. American Diabetes Association: Clinical Practice Recommendations 2002. **Diabetes Care** 2002; 25 (Suppl1):5-24.

82. World Health Organization. Physical status: The use and interpretation of anthropometry: report of a WHO Expert Committee. **Technical report series 854**. Geneva: **World Health Organization**, 1995

83. Guidelines for controlling and monitoring: the tobacco epidemic
Geneva: **World Health organization** 1998.

84. American Diabetes Association. Standards of medical care in diabetes .**Diabetes Care** 2007; 30 Suppl.1:S4-S41

85. National High Blood Pressure Education Program: The Seventh report of the Joint National and Treatment Committee on Prevention, Detection, Evaluation of High Blood Pressure .**JNC Express**. Pp1-52, 2003.

86. American Academy of Ophthalmology International Clinical Classification of Diabetic Retinopathy Severity of Diabetic Macular Edema. Available at: <http://www.icoph.org/pdf/Macular-Edema-Detail.pdf> .Accessed January 11, 2006.

87. International Council of Ophthalmology ICO international clinical guidelines: diabetic retinopathy (initial and follow up evaluation).ICO of ophthalmology ICO Accessed [http://www. Icoph org/guide/guidedi.htm](http://www.Icoph.org/guide/guidedi.htm)website Available at: March 15, 2006.

88. American Diabetes Association .Dyslipidemia management in adult with diabetes. **Diabetes Care** 2004; Suppl 1:68-71.

معدل انتشار نسبة بيلة الألبومين المجهرية والصريحة وعوامل الخطورة عند مرضى السكري من النمط الثاني عند المراجعين لدى المركز الوطني للسكري والغدد الصم والوراثة

إعداد
زينب عباس الحسن

المشرف:
الدكتور نبيل العكش

ملخص

تهدف هذه الدراسة إلى استقصاء مدى انتشار نسبة بيلة الألبومين المجهرية والصريحة وعوامل الخطورة عند مرضى السكري من النمط الثاني بين عينة عشوائية تتكون من 869 مريض من مرضى الداء السكري المراجعين للمركز الوطني للسكري والغدد الصماء والوراثة، كما تهدف الدراسة إلى تحديد مدى وجود ارتباط بين بيلة الألبومين المجهرية والصريحة وعدد من المتغيرات المستقلة والتي تتضمن ارتفاع الخضاب الغليكوزي في الدم وارتفاع التوتر الشرياني و مدة الداء السكري وشحوم الدم ومشعر كتلة الجسم والتدخين والعمر والجنس ووجود اعتلال الشبكية السكري .

تم إجراء الدراسة في المركز الوطني للسكري والغدد الصم والوراثة (عمان-الأردن).تضمنت عينة الدراسة (869) مريضاً والتي تتراوح أعمارهم من 30 سنة فما فوق من الذين يعانون من الداء السكري النمط الثاني والذين يراجعون المركز الوطني للسكري والغدد الصم والوراثة.

لقد بدأت الدراسة بتاريخ 1 أيلول 2007 وامتدت إلى 10 كانون ثاني 2008. و قد تم تشخيص بيلة الألبومين المجهرية والصريحة عندما يكون هناك إيجابية في نسبة الألبومين على الكريتينين في عينة الصباح العشوائية ، على الأقل في عينتين من ثلاث عينات متوالية خلال فترة الجمع التي امتدت من شهر إلى ثلاثة شهور على حسب تعريف جمعية السكري الأمريكية. و قد تم الحصول على النتائج المخبرية والفحوص السريرية من ملفات المرضى الطبية.

- بلغت نسبة الذكور (56.0%) ونسبة الإناث (44.0%) من بين جميع المرضى المفحوصين .
- بلغ كل من متوسط العمر ومدة السكري 57.8 و 9.5 سنة على التوالي.
- تبين أن 62.4% من المرضى كانوا يعالجون بخافضات السكر الفموية ، و 4.3% كانوا يعالجون بالإنسولين، و 31.7% كانوا يعالجون بخافضات السكر الفموية و الإنسولين معاً، بينما 1.6% كانوا يعتمدون على الحمية وحدها.
- بلغ متوسط قيمة الخضاب الغليكوزي 7.71 %.

- بلغت نسبة بيلة الألبومين الكلية بين المشاركين 34.6% ، و ذلك على النحو التالي
 1. بيلة الألبومين المجهرية وجدت في 29.3% من المشاركين.
 2. بيلة الألبومين الصريحة وجدت في 5.3% من المشاركين.

باستخدام تحليل الانحدار الخطي المتعدد تبين أن بيلة الألبومين المجهرية تتأثر بمعدل الخضاب الغليكوزي وبمعدل ضغط الدم الانقباضي و الانبساطي واعتلال الشبكية السكري، بينما تتأثر بيلة الألبومين الصريحة بمعدل ضغط الدم الانقباضي وعامل الجنس واعتلال الشبكية السكري.

تبين من نتائج الدراسة أن بيلة الألبومين الكلية هو مرض شائع بشكل كبير بين المرضى الأردنيين. وكذلك يتضح أن المسح المبكر لبيلة الألبومين والجهود الحثيثة لتحسين السيطرة على السكري ، وتخفيض الضغط الشرياني، مع أهمية التدخل العلاجي بمثبطات الخميرة القابلة للأنجيوتنسين الذي ينبغي أن تؤخذ بعين الاعتبار لمقاومة هذا الداء وإمراضيته بشكل جدي حيث أنها تساهم في الحد من انتشاره.