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COMPLICATIONS AND CARDIOVASCULAR RISK FACTORS AMONG NEWLY-DIAGNOSED TYPE 2 DIABETICS IN MANILA

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ABSTRACT

***Objective*: To determine the prevalence of complications and cardiovascular risk factors among newly-diagnosed type 2 diabetic patients in Manila.**

***Research Design and Methods*: This was a cross-sectional survey of type 2 diabetic patients, diagnosed within 3 months or less from time of screening. Each patient was interviewed and screened for angina, hypertension, peripheral vascular disease, and peripheral neuropathy using questionnaires, electrocardiographic studies, ankle-brachial index and 10 g monofilament testing. Physical and dilated funduscopic examinations were also done. Laboratory tests included glycosylated hemoglobin, lipid profile and urine microalbumin. Data analysis was done using means and standard deviations.**

***Results*: A total of 172 patients were screened. At the time of the study, 20% (n=34) already had peripheral neuropathy. Proteinuria was seen in 42% (n=72), while 12% (n=20) of patients had diabetic retinopathy. The ankle-brachial index was abnormal in 76% of patients. Electrocardiographic findings showed that 2% already had myocardial infarcts, 3% had ischemic changes, 6% had left ventricular hypertrophy. Mean body mass index was 25.42 kg/m2 and the mean waist circumference at 86.87cm. The prevalence of hypertension was 42% with the mean blood pressure at 144/88. Mean total cholesterol was 231.12 mg/dL. Mean LDL was 149.27 mg/dL. Mean Triglyceride was 139.37 mg/dL. Mean HDL was 54.47 mg/dL.**

***Conclusion:* Screening of newly-diagnosed diabetic patients in Manila demonstrated a high prevalence of diabetic complications and cardiovascular risk factors. Because of the high social and economic cost of caring for these patients, it is recommended that a screening program to detect diabetes and even pre-diabetes must be instituted.**

***Keywords:* Diabetes mellitus, Complications, Neuropathy, Hypertension, Insulin resistant**

INTRODUCTION

Diabetes is a worldwide public health problem. The World Health Organization (WHO) estimated the prevalence of diabetes mellitus for all age-groups worldwide to be at 2.8% (171 million) in year 2000. This figure was projected to escalate to 4.4% (366 million) by year 2030.[1] Being a chronic condition that results in multiple complications, previously reported statistics may have underestimated mortality resulting from diabetes. Individuals with this disease mostly die of cardiovascular or renal disease, and not from diabetic emergencies such as ketoacidosis, hyperosmolar state or hypoglycemia.

In the United States, diabetes accounts for almost 14 percent of the health care expenditures in this country, at least half of which is related to managing complications such as myocardial infarctions, strokes, end-stage renal disease, retinopathy, and foot amputations.[2] In 2002, an estimated 132 billion US dollars was spent for direct medical and indirect expenditures for diabetic patients.[3] Outside the United States, where health care is a luxury than basic right and where 3 billion people have to survive on less that 2 dollars a day, diabetes is more than an economic burden that low and medium-income countries have to endure.

The risk for developing complications varies among newly diagnosed diabetics. After 10 years, more than 20% of such persons will have had a major cardiovascular event, about 5% will have developed blindness and less than 2% will have developed endstage renal disease or had a lower extremity amputation.[4]

In the United Kingdom Prospective Diabetes Study (UKPDS), of the 5,102 newly diagnosed Type

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2 diabetics, nearly 50% of the patients already had diabetes-related tissue damage upon recruitment. Eight percent already had signs indicating cardiovascular disease, 37% had microaneurysm or more severe retinopathy in one eye, 18% had retinopathy in both eyes, and 18% had microalbuminuria.[5]

The course leading to complications related to diabetes starts with lingering dysglycemia. A complication could give a hint as to how long the patient has had poor glucose control. In a local study done among diabetic subjects at the University of the Philippines-Philippine General Hospital (UP-PGH), macroalbuminuria was detected among those with diabetes for more than 11 years.[6] At present, there is no available local data on the prevalence of retinopathy among type 2 diabetics.

In 2004, the American Diabetes Association issued standards of medical care that included screening asymptomatic adults with risk factors for diabetes. Filipinos are considered members of a high-risk ethnic population.[7]

The prevalence of diabetes in the Philippines, as estimated by the WHO in year 2000 was at 2.77 M. By year 2030, this is expected to rise to 7.8 M, putting the Philippines in the top 10 countries highest in prevalence for diabetes. In a local study, the prevalence of diabetes was found to be at 3.4% last 2003.[8] This survey was based on a single fasting blood glucose of >125 mg/dL. Hypertension, on the other hand, was estimated to be 17.4%, while the prevalence of hypercholesterolemia was 8.5%. The proportion of diabetics among the surveyed subjects with hypertension and hypercholesterolemia was not mentioned.

With the introduction of the National Cholesterol Education Program Adult Treatment Panel II (NCEP ATP II) in 1993, a study was conducted to investigate the lipid profile of 270 diabetic patients seen at the UP-PGH from 1994-1995.[9] This revealed that 51% had poor LDL-cholesterol (>160 mg%), 38% had poor HDL-cholesterol (<35 mg%), while 8% had poor triglyceride levels (>250mg%). The NCEP guidelines have been updated;[10] newer cholesterol-lowering agents have been introduced, while mass media tries to update the public on diet, fats and cholesterol. With these developments, it is still not known whether the lipid profile of diabetics has improved.

Currently, there is no data as to the prevalence of complications and of the cardiovascular risk factors among newly diagnosed Filipino diabetics despite the known fact that Asians in general are at high risk for developing the disease. Timely information regarding the overall status of a Filipino diabetic patient will help our physicians as to how aggressive one should be in approaching complications related to this endemic disease.

Objectives

A. General Objective

To determine the prevalence of end-organ damage among newly-diagnosed diabetics

B. Specific Objectives

1. To determine the prevalence of the following microvascular complications:
   a. Nephropathy
   b. Retinopathy
   c. Peripheral Neuropathy

2. To determine the prevalence of the following macrovascular complications:
   a. Coronary artery disease
   b. Peripheral arterial disease

MATERIALS AND METHODS

A total of 172 adult patients aged 18 years old and above, newly-diagnosed with type 2 diabetes mellitus for less than 3 months based on the American Diabetes Association criteria were included. Patients who have been diagnosed with diabetes for more than 1 year, gestational diabetics, and steroid-induced diabetics or those with co-morbid conditions that require prolonged steroid therapy were excluded.

Physicians from the local health centers located within Manila, including the UPPGH were contacted and informed of the study. Primary care physicians were contacted for supporting documentation regarding the diagnosis of diabetes was done as necessary. Referrals were received when the study started in April, 2005 to December, 2006.

The patients were contacted and interviewed individually. To screen for hypertension, the patients were asked to answer the hypertension questionnaire[11] that was validated locally to be sensitive at 100% and specific at 87.9%. The patients were also asked the University of Texas Subjective Peripheral Neuropathy (UTSPN) verbal questionnaire.[12] The UTSPN questionnaire was validated by Armstrong, *et al.* in a study among 115 age-matched diabetics, and locally among type 2 Diabetics at the UP-PGH by Isip-Tan.[13] The latter study concluded that the UTSPN questionnaire had a sensitivity of 92.9% and specificity of 15.4%. When combined with the 10-g

monofilament test, its sensitivity increased to 96.4% and specificity to 23.1%.

A third questionnaire was used for screening coronary artery disease. This was the Angina Questionnaire validated in 1998 to be sensitive at 78% and specific at 91%.[8]

Physical examination involved measurement of the body mass index, blood pressure recording, dilated funduscopic examination and 10-g monofilament testing. Other procedures involved the documentation of the ankle-brachial index (ABI), and taking an electrocardiographic (ECG) study.

The ankle-brachial index (ABI) was known to be sensitive at 97% and specific at 100% in detecting peripheral arterial disease, correlating well with angiographically diseased limbs.[14] This, however, was not validated for diabetic limbs. In the PhilPAD Study that used ABI, diabetes combined with at least 1 atherosclerotic risk factor (hypertension, hypercholesterolemia and smoking history) increased the risk for peripheral arterio-occlusive disease.[15] With diabetes, the incidence of PAD increased from 31.67% to 39.25%.

The sensitivity of resting ECG in detecting coronary artery disease was 23%, while its specificity was 87% based on a study of 566 patients in Poland, all of whom underwent coronary angiography.[16]

Other biochemical data taken after a 10 to 12 hour fast were: HbA1c (%), serum insulin (uIU/mL), triglyceride (mmol/dL), total cholesterol (mmol/dL), LDL-cholesterol (mmol/dL), HDL-cholesterol (mmol/dL).

Urinalysis and urine micral testing to detect proteinuria were done. The patients were instructed to collect midstream urine samples in the morning. A second urine sample was collected on a different day for those who were able to follow up. Although the gold standard to diagnose nephropathy is through the urinary albumin excretion rate, this test is not practical for epidemiological studies or clinical settings. Urine micral testing to detect microalbuminuria in type 2 diabetes was found to be sensitive at 95.2% and specific at 84.7% using an immunological semiquantitative test (Micral-test; Roche Diagnostics, Mannheim, Germany), compared with the standard, Urinary Albumin Excretion Rate.[17]

Data Analysis

Quantitative variables were described as mean ± 1SD unless otherwise indicated. Qualitative variables were described by percentages and compared using Chi-square test using STATA Version 6.0. Univariate analysis was also done for nephropathy to determine predictors of this diabetic complication. Odds ratios and 95% CI's were used to describe the predictive value of each variable.

RESULTS

Results and Analysis

A total of 172 patients were screened. The number of participants made 76% of the originally intended study size of 226, as based on the prevalence of microalbuminuria among type 2 diabetics in the UKPDS at 18%.

The demographics are shown in Table I. Patients seen were mostly females and were nonsmokers. More than half the total number of patients had diabetes in a first degree relative (55%). Another finding was that 33% of the parous females had macrosomic babies.

Table I. Demographic Data of Patients with Newly-diagnosed Type 2 Diabetes (n=172)

Age, Mean in years (SD)	50.75 (12.44)
Males, n (%)	51 (30)
Smokers, n (%)	28 (16)
Family History of type 2 Diabetes Mellitus, n (%)	94 (55)
Parous females, n	107
History of Macrosomic babies, n/parous females (%)	35/107 (33)
History of Hypertension, n (%)	73 (42)
History of Angina, n (%)	57 (33)
Intake of oral antihyperglycemic agents upon diagnosis, n (%)	56 (32)
Sulfonylureas, n	38
Biguanides, n	32
Alpha-glucosidase inhibitors, n	2
Thiazolidinediones, n	1
Intake of Hormonal Replacement Agents/ Oral Contraception, n (%)	1 (0.9)
Intake of Anti-hyperlipidemic agents/ HMGCoA Reductase Inhibitors, n (%)	11 (6)
Intake of Aspirin, n (%)	26 (15)
Fasting Plasma Glucose, Mean in mg/dL (SD)	172.32 (82.74)
Glycosylated Hemoglobin, Mean in % (SD)	8.55 (2.69)

The prevalence of microvascular complications are shown in Table II. The prevalence of peripheral neuropathy was 20%. This was based on an affirmative response on any of the questions in the UTSPN Questionnaire and a negative response on monofilament testing. Prevalence of nephropathy was 42% manifesting as proteinuria alone with normal creatinine. Prevalence of diabetic retinopathy was 12%.

Table II. Microvascular Complications Among Newly-Diagnosed Type 2 Diabetic Patients

Peripheral Neuropathy, n (%)	34 (20)
Nephropathy, n (%)	
Normal	99 (58)
Proteinuria	73 (42)
Creatinine, Mean in umol/L (SD)*	85.92 (17.4)
Diabetic Retinopathy, n (%)	20 (12)

* Normal Value 53 - 115 umol/L

For the macrovascular complications, laboratory data using the electrocardiographic tracing to screen for coronary artery disease and ankle-brachial index to screen for peripheral arterial disease were used. Results are shown in Tables III and IV. Although the angina questionnaire indicated a prevalence of 33% for possible coronary artery disease, the electrocardiographic tracings showed that only 2% of patients had infarcts and 3% with ischemic changes. Prevalence of peripheral arterial disease was 24%.

Table III. Summary of Electrocardiographic Findings, n (%)

Normal tracing	88 (51)
Ischemia	6 (3)
Infarct	4 (2)
Left ventricular hypertrophy	11 (6)
Disturbance in rhythm (Blocks)	9 (5)

Table IV. Summary of Data for Ankle-Brachial Index, n (%)

Normal	131 (76)
Abnormal ($\geq$ 1.3, $\leq$ 0.8)	41 (24)

Screening for metabolic syndrome and atherosclerosis-related diseases was also done. Results are shown in Tables V to VII. The prevalence of dyslipidemia in this study was not far off from the findings of the National Nutritional Health Survey,[8] which included non-diabetics. For dyslipidemia, 66% of patients had total cholesterol of >200 mg/dL and 80% had LDL-Cholesterol of >100 mg/dL. HDL-Cholesterol was <40 mg/dL in only 19% of patients, while 38% had triglyceride levels of >150 mg/dL. More than half of the patients seen (53%) had systolic hypertension. The prevalence of obesity (defined as BMI $\geq$ 25) was 46%, while waist circumference for both sexes was beyond the target in 74% of cases. Based on the homeostasis model assessment for measuring insulin resistance (HOMA-IR), the prevalence of insulin resistance in type 2 diabetics was 58%.

Table V. Summary of Lipid Profile Results, mg/dL

	Mean (SD)
Total Cholesterol	231.12 (68.45)
HDL-Cholesterol	54.47 (18.41)
LDL-Cholesterol	149.12 (59.46)
Triglycerides	139.37 (67.69)
	n (%)
Total Cholesterol >200 mg/dL	114 (66)
HDL-Cholesterol <40 mg/dL	32 (19)
LDL-Cholesterol >100 mg/dL	138 (80)
Triglycerides >150 mg/dL	**65 (38)**

Table VI. Summary of Blood Pressure Readings, mm Hg

	Mean (SD)
Systolic blood pressure	144.19 (26.31)
Diastolic blood pressure	87.88 (13.84)
	n (%)
SBP $\geq$ 140	91 (53)
DBP $\geq$ 100	28 (28)

Table VII. Screening for Obesity and Insulin Resistance

	Mean (SD)
Weight, Kg	63.35 (13.56)
Height, m	1.58 (0.08)
Body Mass Index, Kg/m2	25.42 (4.71)
Waist Circumference, cm	86.87 (11.29)
Fasting Serum Insulin,* uIU/mL	23.03 (16.45)
HOMA-IR	9.53 (8.58)
	n (%)
BMI > 25	79 (46)
Waist Circumference†	127 (74)
HOMA-IR > 6‡	100 (58)

* Normal Value 6.4 – 27.2μIU/mL
† males >90cm, females >80cm [29]
‡ **Normal Value: <6 [28]**

Waist circumference correlated well with insulin resistance as well as the body mass index, but not with dyslipidemia (Table VIII).

Table VIII. Relationship Between Waist Circumfercumference and Other Factors

Variable	Odds Ratio	95% CI	P value
LDL – cholesterol	1.01	0.061 – 0.999	0.061
Body Mass Index	1.54	1.318 – 1.805	0.000
HOMA – IR	1.09	1.030 – 1.168	0.004

Of all diabetic complications, nephropathy correlated well with a huge number of other variables, namely, hypertension, glucose control, hypertension and triglyceride levels. (Table IX). Nephropathy also correlated with diabetic retinopathy, with OR 3.67 (p = 0.008, 95% CI 1.339 – 10.103).

Table IX. Factors Predicting Development of Proteinuria

Variable	Odds Ratio	95% CI	P value
Fasting Blood Sugar	1.01	1.005 – 1.014	0.000
Glycosylated Hemoglobin	1.24	1.101 – 1.407	0.000
Triglycerides	1.01	1.002 – 1.012	0.008
Systolic BP $\geq$ 140	2.40	1.284 – 4.484	0.006
Systolic BP	1.02	1.007 – 1.033	0.002
HOMA – IR	1.05	1.015 – 1.097	0.004

Although the percentage of diabetic patients taking aspirin was low (15%), these patients also had significantly better sugar control.

Table X. Relationship Between Intake of Aspirin and Glucose Control

Variable	Odds Ratio	95% CI	P value
Fasting Blood Sugar	0.99	0.982 – 0.998	0.014
Glycosylated Hemoglobin	0.82	0.682 – 0.994	0.043

DISCUSSION

Screening for the prevalence of neuropathy was done with the combined data from a questionnaire and 10 g monofilament testing. The current data revealing 20% prevalence for neuropathy is higher, comparing this with the global prevalence of 10% among newly diagnosed type 2 Diabetics.[18] From the EURODIAB study, it was found that distal polyneuropathy developed over 7.3 years among type 1 diabetics. Our data may imply that the patients seen in this study already had a long duration of dysglycemia.

Locally, trend in the results showed a high prevalence of nephropathy that was higher than foreign data cited in the UKPDS. Although testing for microalbuminuria in this study was done in mostly two visits, which could give false positive results, this high figure may also be due to the fact that most patients seen were off any anti-platelet and antihypertensive agent despite the diagnosis of hypertension on top of diabetes. Again, this may also mean prolonged dysglycemic state since microalbuminuria develops approximately 8 to 10 years from diagnosis of type 2 diabetes mellitus.[19,20]

The presence of microalbuminuria correlated directly with the severity of retinopathy. Although there have been reviews regarding the presence and severity of retinopathy predicting proteinuria, it is currently not known which of the two microvascular complications appears first. The prevalence data in this study is comparable with the prevalence at the clinical diagnosis reported in Iran (13.8%)[21] and the Beaver Dam Eye Study (10.2%),[22] and higher than that reported in AusDiab Study in Australia (6.2%)[23] and in Denmark (5%).[24] This prevalence is quite low compared to the UKPDS (37%). Although one of the limitations of this observational study is the lower number of sample size when compared with the population based studies, this may also be evaluated in connection with patient sampling, i.e. definition of "newly diagnosed" diabetics and number of patients included, and method of eye examination. It is generally recognized that direct slit-lamp fundus examination or indirect ophthalmoscopy has its limits in detecting microaneurysms, cotton wool spots, venous beading and intraretinal abnormalities even to the most experienced ones.[25] In some studies, ophthalmoscopy was not able to detect microaneurysms in approximately 50% of the cases.[26]

While most patients with diabetes are known to be less aware of anginal pain, the angina questionnaire still showed that 33% of patients may have coronary artery disease. Ideally, a better screening tool would have been through exercise stress testing instead of a resting electrocardiographic tracing.

The prevalence of peripheral arterial disease based on the ankle-brachial index is low. There is still no published data that has shown this screening test's sensitivity or specificity in detecting peripheral arterial disease among diabetic subjects. Also, the current figure focuses mainly on the arterial aspect of the foot's vascular supply. Screening for peripheral vascular disease is imperative among diabetics, as this can lead to ulceration and amputation. Risk of ulceration and amputation is increased in people who have had diabetes for more than 10 years.[27]

It is known that more than two-thirds of type 2 diabetics die from cardiovascular disease.[7] The metabolic syndrome makes up established risk factors for cardiovascular disease. Based on these results, majority of the newly-diagnosed type 2 diabetics were dyslipidemic. Although a significant number of patients have achieved HDL-Cholesterol level as recommended by the NCEP ATP III Guidelines, majority of the type 2 diabetics had high LDL-Cholesterol and Triglyceride levels as well. In contrast, the recent NNHeS results revealed a low HD L (<40 mg/dL) prevalence of 54.2% in the country. Obesity and hypertension, likewise, were more than twice the prevalence cited in the same survey. The patients seen were also mostly Insulin resistant.

In general, screening for metabolic syndrome revealed that the newly diagnosed type 2 diabetics were insulin resistant based on HOMA – IR, obese based on the body mass index, had abdominal obesity, were dyslipidemic and hypertensives.

CONCLUSION AND RECOMMENDATION

falls hardest on those who are economically disadvantaged. Once complications have been documented, treating hyperglycemia alone will not suffice. Complications from diabetes can be prevented only up to a certain point, beyond which these will progress.

It is currently not known whether treating patients in the prediabetic states will prevent the occurrence of microvascular and macrovascular diabetic complications, but there is evidence that preventing type 2 diabetes among high risk populations, such as the Filipinos, may offer some benefit.

In the hope of reducing the social and economic costs of the disease & its complications in the future, we recommend that a program to screen for diabetes and prediabetic states should be started. Beyond screening, education of our high risk population regarding diabetic complications must be started also to encourage earlier medical consultation. Medical stakeholders must be encouraged to formulate new guidelines as to how aggressive physicians should be in diagnosing and managing diabetic Filipinos.

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