Comparison of Clinical Outcomes and Presence of Nephropathy and/or Retinopathy Among Type 2 Diabetes Mellitus Patients with Obesity and Overweight versus those with Normal Body Mass Index: A Cross-Sectional Study

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Abstract

Background: This study aimed to determine the differences in glycemic control, metabolic parameters (blood pressure control, triglycerides, LDL, HDL) and the presence of nephropathy and/or retinopathy between obese and overweight versus normal body mass index (BMI) type 2 diabetes mellitus patients (T2DM).

Methodology: This is an analytic cross-sectional study of T2DM patients from outpatient clinics at St. Luke's Medical Center, Quezon City. Available medical records and laboratory tests were reviewed. Data were analyzed and compared between those overweight and obese versus those with normal BMI based on Asia Pacific Guidelines.

Results: A total of 248 patients with T2DM were included in the study. More patients who are obese and overweight have uncontrolled diabetes (p = 0.011), low HDL (p = 0.037) and nephropathy (p = 0.027) compared to those with normal BMI. There were no significant difference between overweight and obese patients versus those with normal BMI with regards to BP control, high LDL, high triglycerides and retinopathy.

Conclusion: T2DM patients who are obese and overweight have a significantly higher prevalence of uncontrolled diabetes, low HDL and nephropathy compared to those with normal BMI.

Keywords: Diabetes Mellitus, Obese, Overweight, Nephropathy, Retinopathy

Introduction

Type 2 diabetes mellitus (T2DM) is a known health problem. It is one of the leading causes of morbidity and mortality globally due to its numerous complications if left uncontrolled. There are 382 million people living with T2DM and 46% remain undiagnosed. Its global prevalence has doubled from 4.7% in 1980 to 8.5% in 2014.[1] At present, it has been shown that there is a higher number of patients with T2DM, about 75 million, in South East Asia accounting for 8.3% of the adult population.[2] Asians have a strong predisposition to develop diabetes mellitus and it has been estimated that 60% of patients with diabetes will be from this group.[3] Given the burden of the disease, identification of patient at risk for early screening has been utilized by different countries. There is a continuous effort in making strategies for the prevention and management of this disease.

Obesity as defined by the World Health Organization is an abnormal or excessive fat accumulation that presents a risk to health.[4] The basic measurement of obesity is the body mass index (BMI) computed based on a person's weight (in kilograms) divided by the square of his or her height (in meters). Obesity is also an emerging health problem not just in high income countries but also in low- and middle-income countries. It is a major risk factor to several chronic diseases such as T2DM, cardiovascular disease and cancer.[4] However, BMI has its limitations in the assessment of body fat composition. It lacks the sensitivity for assessing the risk for chronic disease for patients with normal BMI.[5] This is particularly true for Asians of different ethnicities (Chinese, Indians, Indonesians, Malays and Japanese) wherein there is a difference in the relationship of fat mass and BMI as compared to Caucasians. There is an increased risk for

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T2DM and cardiovascular diseases at lower BMI probably due to difference in body build.[5]

In the study done by Hubert et al, they reexamined 5209 men and women of the original Framingham cohort. They investigated the 26-year follow-up of the patients that were included in the study. It was shown that obesity is an independent risk factor for cardiovascular disease, such as coronary disease, stroke, congestive failure, and coronary and CVD death, especially women. Weight gain seen in the participants through the years showed increased risk for cardiovascular disease that could not be attributed either to initial weight or the levels of the risk factors leading to the weight gain.[12] Based on the results of this study, it has been shown that obesity is an independent risk factor for cardiovascular disease.

Visceral fat, which is more associated with diabetes mellitus, is metabolically active and secretes hormones and cytokines that predisposes a person to develop T2DM.[6] Waist circumference is a simple way to assess visceral fat distribution and it is a strong predictor of T2DM as shown in several studies.[7] In a retrospective cohort study done by Feller et al, they have studied the interaction of BMI and waist circumference to the risk of developing T2DM. Their study showed statistically significant interaction between BMI and waist circumference and to the development of diabetes. Patients who have stronger risk for diabetes have higher waist circumference and lower BMI. Based on their results, waist circumference is an important predictor of diabetes particularly for patients with normal BMI.

In a study by Doehner, et al, they assessed in a post-hoc analysis body weight and weight change in relation to outcome in 5,202 patients from the *PROactive* trial population who had T2DM and evidence of pre-existing cardiovascular disease. They were randomized to treatment with pioglitazone or placebo in addition to their concomitant glucose-lowering and cardiovascular medication with a mean follow-up of 34.5 months.

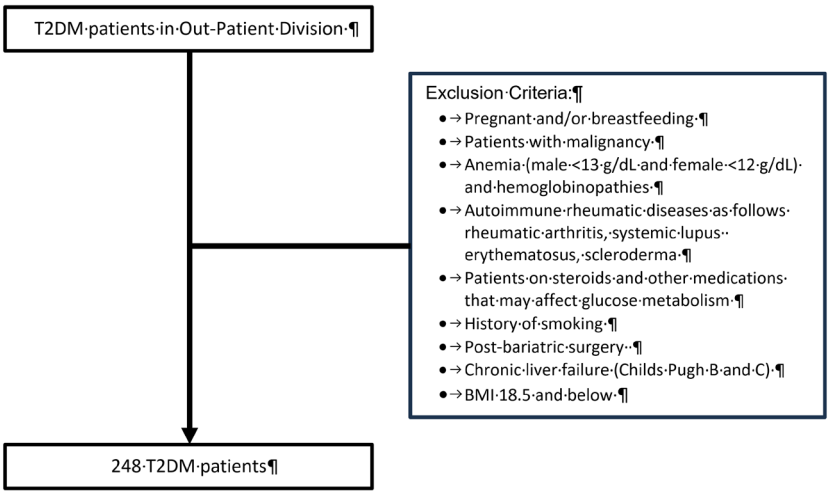

Figure 1. Schematic Diagram of Study Design

Patients who have a BMI between 30-35 kg/m^2 at baseline have the lowest mortality and those with BMI < 22 kg/m^2 had a higher all-cause mortality. It also has been shown in the study that weight loss of ≥ 7.5% body weight was the strongest cut point to predict impaired survival. With these findings, obesity paradox may be seen in patients with T2DM and cardiovascular risk.[7] However, limitation of BMI measurement is that it is a flawed anthropometric biomarker that does not take into account body fat distribution, fat mass/fat-free mass ratio, nutritional status, cardiorespiratory fitness, or other factors affecting health risks and the patient's mortality.[8-9]

Diabetes Mellitus has been associated with increasing trend of morbidity and mortality due to its macrovascular and microvascular complications. Prior to diagnosis of T2DM, years of undiagnosed hyperglycemia has been present hence, there may already be end-organ complications. At the time of first diagnosis, 8% already have cardiovascular disease, 37% have retinopathy, 18% have microalbuminuria and 2.3% have neuropathy.[10] In a study done by Dangi, et al., they looked into the association of BMI and presence of complications of T2DM.[11] Based from their findings which was in contrast to the study by Doehner et al, there was higher prevalence of nephropathy (non-obese 20% vs obese 80%) and retinopathy (non-obese 6.45% versus obese 93.55%) with increase in BMI.

It had also been demonstrated that there can be a significant association of retinopathy with age, BMI, systolic blood pressure, diastolic blood pressure, and blood glucose level (both fasting and postprandial). In a study done by Changnac et al, they looked into 12 non-diabetic obese (BMI > 38) subjects and their renal hemodynamics and compared it with nine healthy control subjects. Based on their findings, there was an increase in the renal plasma flow and glomerular filtration rate in obese subjects compared to control that suggested afferent arteriole vasodilation. They have also shown increase in albumin excretion rate of 89% and fractional albumin clearance of 78% when compared to control. Insulin resistance in obese patients correlated positively to increased GFR ($p < 0.001$) and with increased RPF ($p < 0.001$).

It has been established that obesity is an independent risk factor for the development of cardiovascular disease even for non-diabetic patients. The risk is higher for diabetic patients who have increased BMI to develop these complications as compared to those in non-diabetics who are overweight/obese.

In this study, we aimed to determine the difference of clinical outcomes between obese and non-obese T2DM patients in Filipinos and the presence

of microvascular complications of the disease.

Objectives. To determine the association between BMI and clinical outcomes among patients with T2DM.

Specific Objectives: 1) To determine the difference in glycemic control between obese and overweight versus normal BMI T2DM patients, 2) To determine the difference in metabolic parameters between obese and overweight versus normal BMI T2DM patients, as follows: a) Blood pressure control and b) Levels of Triglycerides, LDL, HDL, and 3) To compare the presence of nephropathy and/or retinopathy between obese and overweight versus normal BMI T2DM patients

Methodology

Study Design. This is an analytic cross-sectional study wherein chart review of patients with T2DM from outpatient clinics were done (*Figure 1*). Purposive sampling was employed.

Study Subjects. Patients diagnosed with T2DM at the outpatient clinics of St. Luke's Medical Center, Quezon City.

Inclusion Criteria: 1) diagnosed case of T2DM, and 2) age > 18 years old

Exclusion Criteria: 1) pregnant and/or breastfeeding, 2) patients with malignancy, 3) anemia (Hb < 13 g/dL (male) Hb < 12 g/dL (female) and hemoglobinopathies, 4) autoimmune rheumatic diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, or scleroderma), 5) patients on steroids and other medications that may affect glucose metabolism, 6) history of smoking, 7) post-bariatric surgery, 8) chronic liver failure (Childs Pugh B and C), and 8) BMI < 18.5 kg/m^2

Study Procedure. In this study, available medical records, and laboratory tests of T2DM from the outpatient clinics of Endocrinology consultants and Social Service census from 2016-2017 were reviewed. The data were extracted by an Endocrinology fellow using a data collection form. If with no record of the specified complications in the chart, it was considered as absent. Once it has been collected, it was collated using the Microsoft Excel™ program.

This study used the Asia Pacific Guidelines for obesity classification wherein BMI = 18.5-22.9 kg/m^2 is normal, BMI = 23-24.9 kg/m^2 is overweight and BMI > 25 kg/m^2 is obese. The data gathered were the following: duration of diabetes, type and dose of insulin, intake of statins, antiplatelet, and/or oral hypoglycemic agents, BMI, HbA1c, triglycerides, LDL, HDL, creatinine, albumin, and history of retinopathy. The gathered data were documented using Microsoft Excel and were utilized for statistical analysis.

Sample Size Determination. Based on the study done by Dangi and Gaur, the prevalence of nephropathy for T2DM patients with normal BMI is 28% and for obese patients the prevalence is 65.2%. Based on the alpha error 0.05, 95% power, one tailed hypothesis, and controlling for four more variables in the analysis (duration of disease, treatment, age and sex) with additional 20% for each of control variable, the final sample size is 248 patients.

Description of Outcome Measure. The primary outcome of this study is the association between excess BMI and presence of nephropathy and/or retinopathy. The secondary outcomes are glycemic control and metabolic parameters of patients.

Operational Definition of Terms.

1. *Retinopathy* – documented by presence of retinopathy as examined by an Ophthalmologist or history of retinal laser surgery
2. *Chronic Kidney Disease* – decreased eGFR of < 60 mL/min/1.73 m2 for more than or equal to 3 months
3. *Albuminuria* – presence of proteinuria of > 300 mg/g (>30 mg/mmol) in the absence of bacteriuria and pyuria or any active infection at the time of examination
4. *Glycemic Control* – determined by the level of glycohemoglobin within 3 months
5. *Blood Pressure Controlled* – usual daily blood pressure of <140/90 mmHg

Statistical Analysis. Descriptive statistics using frequency and percentage was done for qualitative data and mean and standard deviation for quantitative data.

Determination of the association between BMI with qualitative clinical outcomes was analyzed using *chi square test*. *Odds Ratio* with the 95% confidence interval was also calculated. Association of the BMI with quantitative outcomes was analyzed using an *independent t-test*. A $p < 0.05$ was considered statistically significant. Statistical analysis was performed using SPSS® software. Missing data, if not specified, were considered absent.

Ethical Considerations. The Clinical Protocol and all relevant documents were reviewed and approved by the SLMC Institutional Ethics Review Committee. Patient confidentiality was respected by ensuring anonymity of patient records by securing these records in a private room and patient number instead of name was used as identifier. All study data were recorded and investigators were responsible for the integrity of the data i.e., accuracy, completeness, legibility, etc. The manner of disseminating and communicating the study results guaranteed the protection of the confidentiality of patient's data. The data collected will be kept for five years and will be kept in a private room. Afterwards, it will be disposed using paper shredder.

Results

A total of 248 patients with T2DM were included in the study. The baseline demographic and anthropometrics of these patients are presented in *Table I*. The mean age was 58.8 ± 11.75 years, of which 75% were females. The mean height was 155.9 ± 7.78 cm while the mean weight was 66.3 kg ± 12.74 kg. The mean BMI was 27.3 ± 4.95 kg/m^2. Majority (67.7%) were obese, 14.1% were overweight, and 18.1% had normal BMI.

Table I. Baseline Demographic and Anthropometrics of T2DM Patients

Demographic and Anthropometrics,	n=248, n (%)
Age (Mean ± SD)	62 (25.0)
Sex	
Male	186 (75.0)
Female	155.9 ± 7.78
Height (cm) (Mean ± SD)	66.3 ± 12.74
Weight (kg) (Mean ± SD)	27.3 ± 4.95
BMI (3 categories) (Mean ± SD)	168 (67.7)
Obese	35 (14.1)
Overweight	45 (18.1)
Normal	27.3 ± 4.95
BMI (2 categories) (Mean ± SD)	203 (81.9)
Obese/Overweight	45 (18.1)
Normal	58.8 ± 11.75

Table II. Clinical and Laboratory Profile of Type 2 Diabetes Mellitus Patients

Clinical and Laboratory Profile	n=248; n (%)
Duration of Diabetes (Mean ± SD)	10.1 ± 8.10
HbA1c levels within the past 3 months (Mean ± SD)	8.3 ± 1.92
Glycemic Control	
Uncontrolled	175 (71.1)
Controlled	71 (28.9)
Hypertension	161 (64.9)
BP Control	
Uncontrolled	29 (11.7)
Controlled	219 (88.3)
HDL (mg/dl) (Mean ± SD)	46.7 ± 11.08
LDL (mg/dl) (Mean ± SD)	118.6 ± 39.67
Triglycerides (mg/dl) (Mean ± SD)	169.6 ± 89.38
Creatinine (mg/dl) (Mean ± SD)	1.1 ± 0.87
Estimated eGFR (ml/min) (Mean ± SD)	71.3 ± 24.93
Nephropathy	136 (54.8)
Retinopathy	97 (39.1)

Table III. Medications of T2DM Patients

Medications, n=248	n (%)
On Insulin Therapy	131 (52.8)
Type of Insulin	
Basal	52 (39.7)
Basal + Short Acting	8 (6.1)
Biphasic	70 (53.4)
NPH	1 (0.8)
Total units per day (Mean ± SD)	48.6 ± 32.69
Units/kg/day (Mean ± SD)	0.4 ± 0.53
On Oral Hypoglycemic Agent Therapy	240 (96.8)
Metformin	191 (77.0)
Sulfonylurea	62 (25.0)
Thiazolidinediones	21 (8.5)
DPP4 Inhibitors	144 (58.1)
SGLT2 Inhibitors	36 (14.5)
Alpha Glucosidase Inhibitors	3 (1.2)
GLP-1 Agonists	1 (0.4)
On Statin Therapy	210 (84.7)
On Antiplatelet Therapy	55 (22.2)

Table II describes the clinical and laboratory profiles of the T2DM patients. Of the 248 patients included, the mean duration of diabetes was 10.1 ± 8.10 years. The mean HbA1c level was 8.3 ± 1.92, with 71.1% having uncontrolled blood sugar levels. Sixty four percent also have hypertension as comorbidity, with 11.7% having uncontrolled BP levels. The mean HDL level of the patients was 46.7 ± 11.08 mg/dl, the mean LDL level was 118.6 ± 39.67 mg/dl and the mean triglyceride level was 169.6 ± 89.38 mg/dl. Furthermore, 54.8% had albuminuria while 39.1% had retinopathy.

Table III describes the medications taken by the T2DM patients at the time of this study. More than half (52.8%) were on insulin therapy and almost all (96.8%) were on oral hypoglycemic agent therapy. Most were also on statin therapy (84.7%) and antiplatelet therapy (54.8%).

Table IV shows the demographic, clinical and laboratory profile of patients with T2DM with obesity, overweight and normal BMI with insignificant values.

Table V shows the clinical outcomes of T2DM patients with obesity and overweight versus normal BMI. More patients who are obese/overweight have uncontrolled diabetes ($p = 0.011$), low HDL ($p = 0.037$) and albuminuria ($p = 0.027$) compared to those with normal BMI. There was no significant difference between obesity/overweight versus normal BMI with regards to uncontrolled blood pressure, high LDL, high triglycerides, and retinopathy.

Discussion

This study wanted to determine the difference in clinical outcomes, in terms of glycemic control, metabolic parameters, and microvascular complications such as nephropathy and retinopathy, between T2DM patients who are obese/overweight versus those with normal BMI.

T2DM patients who are obese and overweight are 2.35 times more likely to have uncontrolled diabetes than those with normal BMI. In congruence to the study of Bautista, et al they showed that the mean fasting blood sugar and HbA1c levels were significantly higher in the obese/overweight diabetic patients compared to lean diabetic patients.[14] In addition, previous studies described that obesity was associated with chronic systemic inflammation since adipose tissues release pro-inflammatory substances and non-esterified fatty acids. These factors play a role in the development of insulin resistance and beta cell dysfunction, resulting to poor glycemic control.[15-17]

In this study, there was no significant difference in BP control between those obese and overweight T2DM patients versus those with normal BMI. In contrast to previous studies abdominal adiposity is linked to arterial stiffening through insulin resistance.[14,18-19] The reciprocal relationship between insulin resistance and endothelial dysfunction is considered part of the initiating step in the atherosclerotic cascade.[18] The relationship of BP control to BMI could not be generalized in this study due to the sampling method used.

Table IV. Demographic, Clinical and Laboratory Profile among patients with Type 2 Diabetes Mellitus with Obesity, Overweight and Normal BMI

Outcomes	BMI Obese Mean ± SD	Overweight Mean ± SD	Normal Mean ± SD	p-value
Age	58.48 ± 11.79	58.47 ± 11.57	60.27 ± 11.87	0.936
Duration of Diabetes	9.862 ± 8.10	10.21 ± 8.43	10.69 ± 80.01	0.987
Total units per day	51.85 ± 31.82	40.77 ± 34.43	39.50 ± 34.29	0.957
Units/kg/day	0.42 ± 0.51	0.46 ± 0.62	0.23 ± 0.51	0.242
HbA1c	8.29 ± 1.82	9.00 ± 2.26	7.91 ± 1.92	0.921
Creatinine (mg/dl)	1.15 ± 1.03	0.99 ± 0.35	0.94 ± 0.36	0.410
Estimated eGFR (ml/min)	69.81 ± 25.64	72.47 ± 24.68	76.08 ± 22.15	0.102

Table V. Clinical Outcomes of Type 2 Diabetes Mellitus Patients with Obesity and Overweight versus Normal BMI

Outcomes	BMI Obese/Overweight n (%)	Normal n (%)	OR (95% CI)	p-value
Uncontrolled DM	150 (74.6)	25 (55.6)	2.35 (1.21-4.59)	0.011
Uncontrolled BP	25 (12.3)	4 (8.9)	1.44 (0.48-4.36)	0.518
Low HDL	57 (28.1)	12 (26.7)	1.07 (0.52-2.22)	0.037
High LDL	30 (14.7)	5 (11.1)	1.39 (0.51-3.80)	0.409
High Triglycerides	53 (26.1)	5 (11.1)	2.83 (1.06-7.54)	4.624
Nephropathy	118 (58.1)	18 (40.0)	2.08 (1.08-4.02)	0.027
Retinopathy	82 (40.4)	15 (33.3)	1.36 (0.69-2.68)	0.380

With regards to lipid profile, obese and overweight T2DM patients are 1.07 times more likely to have low HDL than those with normal BMI. There was no significant difference in having high LDL and high triglyceride levels between the two groups. This is consistent with the findings of Hussain which had a significant negative correlation between BMI and HDL and no significant correlation between BMI and LDL, triglycerides, and cholesterol.[20] Meanwhile, the studies of Bansal and Augusthy showed significant positive correlation between BMI, and LDL and triglycerides, respectively.[21,22] HDL also had a significant negative correlation with BMI in these two studies. The impact of BMI on LDL and triglycerides may be variable, but there was consistency in the findings of HDL. One possible reason is the difference in the genetic make-up of the patients in these studies. Further studies may be done to establish the association of BMI and lipid profile.

Obese and overweight T2DM patients are 2.08 times more likely to have nephropathy than those with normal BMI. This is in agreement with the study of Ou, et al who revealed that BMI was significantly associated with albuminuria and diabetic nephropathy.[23] In addition, increased incidence of microalbuminuria was seen with increasing BMI, and that this association was even more significant in patients with higher BMI.[24] This is because obesity may directly affect the kidneys through oxidative stress, inflammation, activation of the renin-angiotensin-aldosterone system, abnormal lipid metabolism, and insulin resistance.[23]

Findings from our study also showed no significant difference in the risk of retinopathy between those obese and overweight T2DM patients versus those with normal BMI. It conforms with the meta-analysis of Zhou, et al that neither being obese nor overweight is associated with an increased risk of diabetic retinopathy.[25] On the other hand, the meta-analysis of Zhu, et al concluded that obesity is a risk factor of non-proliferative diabetic retinopathy.[26] Obesity may probably have both protective and adverse effects on the risks of diabetic retinopathy. Increased C-peptide levels found in obese and overweight T2DM patients could reduce the risk of diabetic retinopathy.[27-28] Moreover, these patients are at increased risk for comorbidities, thereby early and aggressive treatments may have been given to reduce the development of diabetic retinopathy.[25]

At the same time, obese and overweight T2DM patients have increased risk of hypertension and dyslipidemia, both being risk factors for diabetic retinopathy.[29] Furthermore, increased leptin levels in these patients increased not only the blood pressure, but also oxidative stress, which may be responsible for the development of diabetic retinopathy.[30] One possible reason for the lack of relationship noted between increased BMI and the risk of diabetic retinopathy in our study is that some patients who were included might not have complied with an ophthalmological consult even if they were already symptomatic or have been advised referral. This possible lack of compliance could have led to an incomplete documentation of findings.

With these results, the need for an individualized management of T2DM patients cannot be overemphasized.

Limitations of the Study. This study has limitations. It is a cross-sectional study, thereby precluding

establishment of causal relations between T2DM and its clinical outcomes. In addition, the presence of specific complications was only based on chart review, so that if no complication was recorded, it was considered absent. The subjectivity of this data gathering may be biased from the patient's reporting and/or the record keeping.

Conclusion and Recommendations

T2DM patients who are obese and overweight have a significantly higher prevalence of uncontrolled diabetes, low HDL and nephropathy compared to those with normal BMI.

We recommend future studies using cohort to better establish the causal relationship of T2DM and clinical outcomes. We recommend to note whether a Nephrology or Ophthalmology referral was done for better documentation of these complications.

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