Clinical, Metabolic, and Autoimmune Characteristics of Newly Diagnosed Young Filipino Adults with Diabetes Mellitus

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ABSTRACT

Background and Objective. In Asia, younger individuals (below age 45) are diagnosed to have type 2 diabetes with increased rates of obesity defined by lower BMI yet with greater visceral adiposity (waist circumference and waist-hip ratios). The prevalence data on type 1 diabetes is not well established, considered to be low, but is seen to be increasing as well. This changing phenotype therefore, presents a clinical dilemma in terms of correctly classifying diabetes and deciding on the consequent appropriate treatment. Distinguishing type 1 from type 2 diabetes has become more difficult with type 2 diabetes dramatically increasing in young adults and children. This study aims to define the characteristics of diabetes among young adults in the Philippines to provide a basis for appropriate management amidst changes in diabetes phenotypes seen globally.

Methods. In this cross-sectional analytic study, we characterized the demographic, metabolic, and autoimmune features of diabetes among young adult Filipinos aged 18 to 45 years old consulting at a tertiary referral center in Manila, Philippines. Baseline serum A1c, FBS, 75-g oral glucose tolerance test, insulin, serum C-peptide, insulin autoantibodies, leptin, adiponectin, lipid profile, and thyroid function tests were obtained from the participants and analyzed. The homeostasis model assessment (HOMA) was used to estimate the insulin sensitivity.

Results. A total of 348 patients with diabetes were included, with females comprising two-thirds of the participants. The mean age at diagnosis of diabetes was 35.9±7.22 years. The mean BMI was 28.12 kg/m^2, with median waist to hip ratio (WHR) of 0·93. Metabolic syndrome was found in 60% of participants and 67.82% were obese by body mass index. The mean A1c was 9.07±2.52%. Good glucose control (A1c less than 7.0%) was seen in 23% of participants while nearly half (48%) had HbA1c which was >9.0%. The median levels of fasting insulin and C-peptide were 12.62 (range 1.33–90.42) mIU/L and 0.78 ng/mL (range 0–16.2), respectively.

Included participants were diagnosed with diabetes within a year and as such, majority did not have any micro- or macrovascular complications. The most common diabetes complication was sensory neuropathy detected by monofilament testing, which was found in 28% of participants, followed by non-proliferative diabetic

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retinopathy in 13%. A history of previous diabetic ketoacidosis was found in 10 patients (2.87%). Glutamic acid decarboxylase (GAD) and insulin auto-antibodies were found in 3.2% and 19.3% of participants, respectively. Approximately half (51.73%) of the participants were insulin resistant by HOMA-IR.

Conclusion. In contrast with Caucasians and other Asians, diabetes among young Filipino adults is associated with lower BMI but with a similarly high visceral adiposity as shown by an elevated WHR. Metabolic syndrome with insulin resistance as defined by a variety of indices is predominant. Type 1 diabetes with autoantibodies occur in only a small fraction of this population. Data derived from this work can provide a framework for cluster analysis towards personalized management specific to this population.

Keywords: type 2 diabetes, type 1 diabetes, metabolic syndrome, HOMA-IR

INTRODUCTION

Diabetes mellitus is a major health concern in Asia, owing to its increasing prevalence in younger age groups, providing longer lifetime disease exposure and risks for complications causing morbidity and mortality.[1,2] Younger individuals (below age 45) are diagnosed to have type 2 diabetes with increased rates of obesity defined by lower BMI yet with greater visceral adiposity (waist circumference and waist-hip ratios).[3,4] The prevalence data on type 1 diabetes is not well established, considered to be low, but is seen to be increasing as well.[5]

Epidemiologic data based on the 2019 Philippine National and Nutrition Survey show increasing rates of diabetes and the components of the metabolic syndrome.[6] Diabetes mellitus (FBS of >7 mmol/L) rates have increased dramatically, to 8.2% from 4.8% in 2008. Obesity rates (WHO BMI >30) account for 37% of Filipino adults. Visceral adiposity measured by waist circumference (>88 cm in females) is seen in 23% and WHR (>0.85 in females), 63%: rates that are significantly higher than males. The prevalence of metabolic syndrome is astoundingly high at 80%, for both individuals with young-onset (age 37.6 years) and late-onset (age 59.9 years) diabetes. Obesity (Obese II, or those with BMI ≥30 kg/m^2), current alcoholic drinking, and smoking are identified risk factors for diabetes in the younger group. With every unit increase in age and fat intake, the odds of having metabolic syndrome have been shown to increase by 5.4% and 1.6%, in young- and late-onset diabetics, respectively.[7]

The changing phenotype therefore, presents a clinical dilemma in terms of correctly classifying diabetes and deciding on the consequent appropriate treatment. Distinguishing type 1 from type 2 diabetes has become more difficult with type 2 diabetes dramatically increasing in young adults and children. As the general pediatric population becomes more obese, reliance on phenotypic characteristics for distinguishing between these types of diabetes is becoming increasingly untenable. Some of these younger patients with type 2 diabetes present with diabetic ketoacidosis, and as the general population increases in weight, many people with type 1 diabetes are also obese.[2,7] Data are lacking on understanding the pathophysiological mechanisms of diabetes among patients in the Philippines. It is not known as to whether there is a predominance of insulin resistance over insulin deficiency. The actual prevalence of islet cell autoimmunity is likewise not described.

Type 2 diabetes accounts for over 90–95% of diabetes worldwide. This type of diabetes is heterogenous, with variation in clinical phenotypes and underlying defects, due to changes in body weight, adiposity, and beta cell function. Genetic susceptibility and environmental factors are specific to populations.[8,9] Hence, studies from various investigators in Caucasian populations incorporated these features as a framework for subgrouping adult-onset diabetes.

Re-classifying diabetes is essential in various populations, with differing phenotypes, physiologic and metabolic features, as well as genetic, pharmacogenetic, epigenetic, and environmental factors. This cross-sectional analytical study aimed to describe the demographic, metabolic, and autoimmune features of adult Filipinos 45 years old and below who are newly diagnosed with diabetes mellitus. Data derived from this work can provide a framework for cluster analysis towards personalized management specific to this population.

MATERIALS AND METHODS

We carried out this cross-sectional analytical study at the University of the Philippines-Philippine General Hospital (UP-PGH), a tertiary referral center in Manila, Philippines. The study was conducted in compliance with the ethical principles set forth in the Declaration of Helsinki and the (Philippine) National Ethical Guidelines for Health and Health-related Research of 2017. The study protocol and subsequent amendments underwent review and approval by the University of the Philippines Manila Research Ethics Board (UPM-REB) prior to study initiation. Informed consent was obtained from all the included subjects. The study funder is independent with the collection, analysis, interpretation, and writing of this report.

Inclusion and Exclusion Criteria

Individuals of Filipino nationality between ages 18–45 years with diabetes mellitus diagnosed according to the American Diabetes Association criteria were included in this cohort.[10] Patients were excluded if they had use of medications or had any secondary conditions that promote hyperglycemia. The period of recruitment was five years and approximately 1000 patients were screened.

Data Collection

Baseline serum A1c, FBS, 75-gram oral glucose tolerance test (OGTT), and lipid profile were measured using the COBAS Integra 400 Plus Chemistry Analyzer. Blood insulin levels, free thyroxine (FT4, Beckman Coulter), and thyroid stimulating hormone (TSH IRMA, IZOTOP) levels were measured using radioimmunoassay. Determination of serum C-peptide levels at fasting and 1 hour and 2 hours after a 75-gram oral glucose tolerance test utilized immunoradiometric assay (IZOTOP).

Various methods were used to measure insulin sensitibity such as HOMA-IR, Matsuda index, QUICKI and eGFR. In this study, a comparison of the different calculations was made. The homeostasis model assessment (HOMA) was used to estimate the insulin sensitivity, as deemed suitable for epidemiologic studies. In each subject, the degree of insulin resistance was estimated at the baseline by HOMA according to the method described by Matthews et al.[11] An insulin resistance score (HOMA-IR) was computed with the formula: IR = (fasting plasma glucose mmol/L × fasting serum insulin mU/L) / 22.5. Low HOMA-IR values indicated high insulin sensitivity, whereas high HOMA-IR values indicated low insulin sensitivity (insulin resistance). Filipino epidemiologic studies have demonstrated that a HOMA-IR value of greater than or equal to 2 is indicative of the presence of insulin resistance.[12] This model will also be referred to as the HOMA1 or the original HOMA model.

The HOMA2 or the HOMA2-IR is the updated or correctly solved computer model. This updated (1996) version of the HOMA model accounts for variations in hepatic and peripheral glucose resistance [i.e., the reduction in the suppression of hepatic glucose output (by hyperglycemia) and the reduction of peripheral glucose-stimulated glucose uptake].[13] This was computed to allow for comparisons with the other indices of insulin resistance. The calculator was downloaded from the website of the University of Oxford, Radcliffe Department of Medicine.[11]

For participants determined to have low endogenous insulin values precluding the use of HOMA-IR, insulin sensitivity was measured using the estimated glucose disposal rate method, which was computed as follows: 24.31–12.22 (WHR) – 3.29(HTN) – 0.57(HbA1); where, WHR was waist-to-hip ratio, HTN was history of hypertension either ≥ 140/90 mmHg or antihypertensive medications (0 = No, 1 = Yes), and A1c level expressed in percent. Another simple surrogate index for insulin sensitivity was the Quantitative Insulin Sensitivity Check Index (QUICKI) which was computed as follows: 1 / [log (fasting insulin) + log (fasting glucose)]. Matsuda index was also used to estimate insulin sensitivity with the following formula: 10,000 / [(fasting glucose × fasting insulin) × (mean glucose × mean insulin)], where fasting glucose and insulin data were taken from time 0 of the OGTT and mean data represent the average glucose (mmol/L) and insulin (uIU/mL) values obtained during the entire OGTT.[14]

Finally, as several patients were either on insulin or sulfonylureas (insulin secretagogues) as part of their treatment and thus, the fasting insulin levels may be elevated during sampling and could cause false results for the HOMA-IR and the HOMA2-IR, we also computed for the HOMA using the fasting C-peptide (HOMA-CP) using the same calculator that was downloaded from the University of Oxford, Radcliffe Department of Medicine for the computation of HOMA2-IR.[11]

Blood extraction for insulin autoantibodies (IAAs), glutamic acid decarboxylase autoantibodies (GADAs), IA-2 autoantibodies (IA-2As), and zinc transporter 8 autoantibodies, which have emerged as the four most useful autoimmune markers in identifying type 1 from type 2 diabetes were determined using an enzyme linked immunoassay (ELISA).

Concentrations of human leptin and adiponectin in subjects' serum were assayed using the Mediagnost ELISA for Leptin E07 (IBL-America) and the Mediagnost ELISA for Adiponectin E09 (IBL-America).

Statistical Analyses

Descriptive statistics were used to summarize the general and clinical characteristics of the participants. Frequency and proportion were used for categorical variables. Shapiro-Wilk test was used to determine the normality distribution of continuous variables. Continuous quantitative data that met the normality assumption were summarized using mean and standard deviation (SD), while those that do not were described using median and range. All valid data were included in the analysis. Missing variables were neither replaced nor estimated. Null hypothesis was rejected at 0·05 α-level of significance. STATA 15.0 (StataCorp SE, College Station, TX, USA) was used for data analysis.

RESULTS

In this cross-sectional study, we characterized the demographic, metabolic, and autoimmune features of diabetes among young adult Filipinos aged 18-45 years old. A total of 342 participants were included with 229 (67%) females comprising the cohort. The mean age at enrolment is 36, 7.2 SD years and age at diagnosis was similar at 36, 7.22 SD years. Among the women, only 23/210 or 11% had a prior diagnosis of gestational diabetes (GDM). Table 1 summarizes the demographic characteristics, and risk factors and co-morbidities for diabetes and cardiovascular diseases.

Only 39 participants (11.54%) were current smokers, while 47 (13.91%) had previous smoking history. Among 338 participants, 127 (37.57%) were taking alcohol with males comprising 62.5% of total alcoholic beverage drinkers. A history of thyroid dysfunction was noted in 11 (3.22%) of the participants; however, it was not specified what type of thyroid disorder they were diagnosed with.

Mean systolic and diastolic blood pressures were 123.58, 16.0 SD mmHg, and 81.25, 11.0 SD mmHg, respectively.

Table 1. Distribution of Participants According to Demographic Characteristics, Risk Factors, and Comorbidities, and Pertinent Physical Examination Findings (N=342)

	Overall (n=342)	Male (n=113)	Female (n=229)
General Profile			
Mean age in years (range) ± SD	36 (18 - 45) ± 7.2	36 (20 - 45) ± 6.33	36 (18 - 45) ± 7.63
Mean Age at diagnosis in years ± SD	35.9 ± 7.22	35.8 ± 6.33	35.9 ± 7.65
Risk Factors			
Family history of diabetes	280 (82.0%)	77 (68.1%)	203 (88.6%)
Smoking history [n=338]			
Never	252 (74·6%)	60/112 (53.6%)	192/226 (85.0%)
Yes, current	39 (11.5%)	25/112 (22.3%)	14/226 (6.2%)
Yes, previous	47 (13.9%)	27/112 (24.1%)	20/226 (8.8%)
Alcohol use [n=338]	127 (37.6%)	70/112 (62.5%)	57/226 (25.2%)
Comorbidities			
Thyroid dysfunction	11 (3.2%)	4/113 (3.5%)	7/229 (3.1%)
Hypertension	100 (29.2%)	34/113 (30.1%)	66/229 (28.8%)
Dyslipidemia	103 (30.1%)	38/113 (33.6%)	65/229 (28.4%)
Metabolic syndrome	205 (59.9%)	61/113 (54.0%)	144/229 (63.0%)

Table 2. Distribution of Participants According to the Presence of Vascular Complications (N=342)

Type of Vascular Complication	n (%)
Microvascular complications	
Retinopathy on History	2 (0.6)
Retinopathy on Fundoscopy	
Non-proliferative Retinopathy	29 (12.9)
Proliferative Retinopathy	3 (1.3)
Neuropathy on History	
Motor	3 (0.9)
Sensory	55 (16.2)
Neuropathy on Monofilament Testing	95 (28.2)
Nephropathy	2 (0.6)
Macrovascular complications	
Coronary Heart Disease	3 (0.9)
Cerebrovascular Disease	4 (1.2)
Peripheral Arterial Occlusive Disease	7 (2.1)

Table 3. Distribution of Participants according to the Criteria of Metabolic Syndrome which have been Fulfilled (N=348)

Syndrome Diagnosis	MetS Criteria Fulfilled, n (%)
None [Participant does not have MetS]	138 (39.6)
WC BP T2DM	44 (12.6)
WC HDL T2DM	37 (10.6)
WC Triglyceride HDL T2DM	29 (8.3)
WC Triglyceride T2DM	27 (7.7)
WC Triglyceride HDL BP T2DM	19 (5.5)
Triglyceride HDL T2DM	16 (4.6)
WC HDL BP T2DM	12 (3.5)
WC Triglyceride BP T2DM	11 (3.2)
Tri BP T2	4 (1.2)
Triglyceride HDL BP T2DM	4 (1.2)
WC Triglyceride HDL	2 (0.6)
HDL BP T2DM	2 (0.6)
WC Triglyceride BP	2 (0.6)
WC Triglyceride HDL BP	1 (0.3)
Total	**348**

Despite the participants being relatively young, hypertension and dyslipidemia were found equally as prevalent at almost a third of the participants, at 29.24% and 30.12%, respectively.

Included participants were diagnosed within a year and as such, majority did not have any micro- or macrovascular complications. The most common diabetes complication was sensory neuropathy detected by monofilament testing, which was found in 28% of participants, followed by non-proliferative diabetic retinopathy in 13% (Table 2). Macrovascular complications obtained from history-taking were uncommon, with peripheral arterial occlusive disease being noted in only seven participants (2%).

Metabolic Syndrome and Measures of Obesity

Acanthosis nigricans, which is a physical examination finding that is associated with insulin resistance was found in 58/337 (17.21%) of participants. Metabolic syndrome (MetS) was found in 205 (60%) of participants, with 54% and 63% prevalence among men and women, respectively. This group are then presumptive of having type 2 diabetes mellitus (T2DM). The most common combination of the MetS criteria is elevated waist circumference, elevated blood pressure and diabetes/elevated plasma glucose at 44/205 (21.46%), followed by elevated WC, low HDL and diabetes at 37/205 (10.6%). The third most common combination is equally between high WC, high triglyceride, low HDL and high BS at 29%, and elevated WC, high TG and high BS at 27% (Table 3).

Mean body weight for the participants was 69.3, 16 SD kg with extremes of weight ranging from 34 to 138 kilograms

Table 4. Distribution of Participants according to Anthropometric Measures and Measures of Obesity and Adiposity (N=342)

Anthropometric Measures	Total (n=342)	Male (n=113)	Female (n= 229)
Mean weight in kg (range) ± SD	69.3 (34 -138) ± 16.0	75.2 (38.5 - 138.0) ± 17.9	66.3 (34.0 - 131.0) ± 14.1
Mean height in cm (range) ± SD	156 (104 - 181)	165.39 (104 - 181) ± 9.0	153 (104 - 176) ± 8.51
Mean BMI (range) ± SD	28.2 (14.9 - 63.8) ± 6.5	27.6 (15.8 - 63.8) ± 6.7	28.5 (14.9 - 57.3) ± 6.4
Underweight, BMI <18.5 (%)	11 (3.2%)	7 (6.2%)	4 (1.7%)
Normal, BMI 18.5 to <23 (%)	48 (14.0%)	17 (15.0%)	31 (13.5%)
Overweight, BMI 23 to 24.9 (%)	51 (14.9%)	21 (18.6%)	30 (13.1%)
Obese Class I, BMI 25 to <30 (%)	129 (37.7%)	33 (29.2%)	96 (41.9%)
Obese Class II, BMI ≥30 kg/m² (%)	103 (30.1%)	36 (31.9%)	67 (29.3%)
Mean waist circumference in cm (range) ± SD	91.1 (27.5 - 140.3) ± 13.225	91.8 (27.5 - 140.3) ± 16.1	90.75 (62 - 128) ± 11.51
Waist circumference above IDF cut-off (N, %)	253 (74.0%)	60 (53.1%)	193 (84.3%)
Mean hip circumference in cm (range) ± SD	97.54 (36 - 151) ± 12.29	97.06 (36 - 151) ± 13.7	97.77 (61 - 143) ± 11.56
Mean waist-hip ratio (range) ± SD	0.93 (0.76 - 1.23) ± 0.06	0.94 (0.76 - 1.22), ± 0.07	0.93 (0.80 - 1.16) ± 0.06
Waist-hip ratio above WHO cut-off (N, %)	291 (85.1%)	85 (75.2%)	206 (89.9%)

(kg). For males, the mean body weight was 75.2, 17.9 SD kg (range 38.5 to 138 kg) while for women it was 66.31, 14.07 SD kg (range 34 to 131 kg) (Table 4).

The mean BMI was 28.2, 6.52 SD kg/m^2 with again extremes of values ranging from 14.91 to 63.79 kg/m^2. Among males, the mean BMI was 27.57, 6.73 SD kg/m^2 (range 15.81 to 63.79) while among females, the mean BMI was 28.5, 6.41 SD kg/m^2 (range 14.91 to 57.32). Around 15% of the participants was overweight (BMI 23 to 24.9) by BMI while 232/342 (68%) were obese. The total proportion of overweight and obese were 83% (283/342).

Regarding the measures of adiposity, the mean waist circumference was 91, 13.225 cm (range 27.5 to 140.3). For males, mean WC was 91.8, 16 cm (range of 27.5 to 140.3) while for females, mean WC was 90.75, 11.51 cm (range 62 to 128). Finally, the mean WHR is 0.93, 0.06 SD (range 0.76 to 1.23) with these values for males and females respectively: 0.94, 0.07 SD (range 0.76 to 1.22) and 0.93, 0.06 SD (0.80 to 1.16) which were likely above the average Filipino adult WHR.

In terms of visceral adiposity, 73.98% of the study participants (53.10% of men, 84.28% of women) met the International Diabetes Federation cut-off for waist circumference, and as much as 85.09% (75.22%, 89.96% of men and women, respectively) reached the WHO cut-off for visceral adiposity by WHR.

From these results, it can be seen that in this cohort of relatively younger adults with new onset diabetes, majority were overweight and obese by BMI, and that majority had visceral adiposity both by WC and WHR.

Metabolic Profile

The mean HbA1c was elevated at 9, 2.5 SD % with a range of 4.7 to 17.6%. Good glucose control (A1c less than 7.0%) was seen in only 79/348 (23%) while nearly half or 167/348 (48%) had HbA1c which was ≥9.0% (Table 5). Despite these results, only half or 174/348 (50%) were on any medications with 24 (7%) on insulin, 19 (5.56%) on insulin

Table 5. Summary of Biochemical Characteristics of Study Participants (N=342)

Biochemical Characteristics	Mean ± SD (range) or N (%)
HbA1c in %	9.0 ± 2.5 (4.7 - 17.6)
HbA1c <7.0%	79 (23%)
Creatinine (mg/dl)	0.6 (0.3 - 191.5)
ALT (U/L)	24.7 (0.9 - 201.4)
OGTT	
Fasting (mmol/L)	8.7 (0.4 - 113.99)
1h Plasma glucose [n=341] (mmol/L)	18.3 (6.3 - 35.1)
2h Plasma glucose (mmol/L)	18 (3.42 - 37.72)
Lipid Profile	
Total Cholesterol (mg/dl)	195.2 (2.4 - 398.1)
Triglycerides (mg/dl)	131.9 (0.8 - 884.9)
HDL (mg/dl)	42.0 (0.9 - 116.6)
LDL (mg/dl)	124.4 (0.8 - 299.6)
Thyroid Function	
FT4 (pmol/L)	18.2 (11.2 – 100.0)
TSH (uIU/mL)	1.6 (0.01 - 22.9)
Adipokines	
Leptin [n=310] (ng/mL)	13.0 (0.7 - 106.1)
Adiponectin [n=340] (ng/mL)	2.7 (0.5 - 54.6)
Insulin Levels	
Insulin (fasting) (mIU/mL)	12.6 (1.3 to 90.4)
Insulin (1h) [n=341] (mIU/mL)	32.9 (0.6 to 336.1)
Insulin (2h) (mIU/mL)	35.2 (1.9 to 445)
C-peptide (fasting) (ng/mL)	0.78 (0.0 - 16.2)
Type of Treatment Initiated	
Insulin	24 (7.0%)
Insulin + oral meds	19 (5.5%)
Oral meds	131 (38.3%)
No medications	168 (49.1%)

Table 6. Distribution of Participants According to the Indices of Insulin Resistance (N=348)

Insulin Resistance Indices	Mean (Range)	No. with Insulin Resistance (%)
Matsuda	0.3 (0 - 12.55)	337/348 (97)
HOMA-IR	0.0 (0 - 63.5)	148/348 (42.53)
HOMA 2-IR	2.0 (0.2 - 13.0)	257/348 (74)
HOMA 2-CP	1.7 (0 - 13.5)	156/348 (45)
QUICKI	0.71 (0.6 - 3.9)	348/348 (100)
eGDR	6.9 (-0.9 - 11.1)	208/348 (60)

plus oral antidiabetic (OAD) agents, while 131 (38%) were taking OADs, within a year of diagnosis.

Measures of Insulin Resistance

The median levels of fasting insulin and C-peptide were 12.62 (range 1.33–90.42) mIU/L and 0.78 ng/mL (range 0–16.2), respectively (Table 5). At 1 and 2 hours after glucose challenge, the median concentrations of insulin in the blood were 32.9 (0.6–336.1) mIU/L and 35.22 (range 1.97–445) mIU/L, respectively (Figure 1).

The fasting blood sugar, fasting insulin, and the C-peptide were used for the calculation of the indices of insulin resistance including HOMA-IR, HOMA2-IR, HOMA-CP, QUICKI, Matsuda Index, and eGDR. Since several of the participants were maintained on insulin and sulfonylureas (insulin secretagogues), the plasma insulin level may be falsely elevated. Hence, the HOMA-CP was also calculated substituting the fasting C-peptide in nmol/L for the fasting insulin level (Table 6).

Using a cut-off of >2 for the original HOMA-IR, almost half (42.53%) were determined to be insulin resistant. The updated HOMA-2 IR with >1.0 as cut-off estimated that 74% had insulin resistance. The estimates from the HOMA-CP were similar to the original HOMA-IR at 45%, while the Matsuda Index, QUICKI, and eGDR had much higher estimates at 97%, 100%, and 60%, respectively.

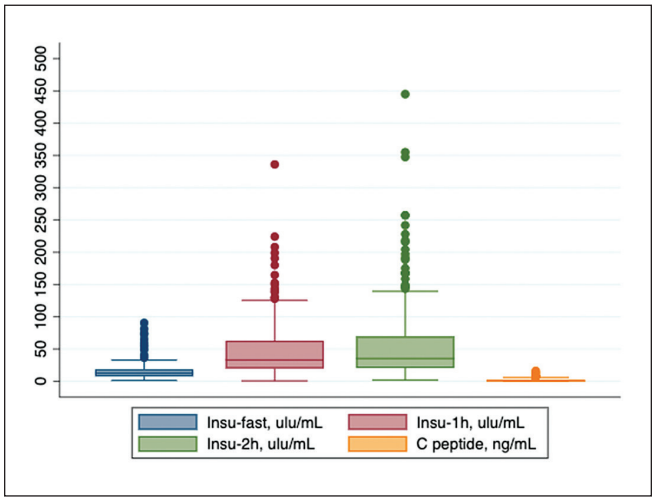

Figure 1. Fasting insulin and C-peptide, and insulin levels 1-hr and 2-hrs after 75-gram glucose load.

The Matsuda Index and QUICKI probably overestimate the prevalence of insulin resistance given that a significant proportion of the participants had low C-peptide levels indicating insulin deficiency.

Leptin and Adiponectin

Median leptin values were 13.03 ng/mL (range 0.69 to 106.09) and adiponectin was 2.69 µg/mL (range 0.52 to 54.58).

Leptin levels ≥17.9 ng/mL (the cut-off which represents the 75th percentile in non-obese females) were more common among the overweight and obese patients combined (83%) than in underweight to pre-overweight groups combined (64%) (p=0.001).[15] Adiponectin levels <3.8 µg/mL, which corresponds to the lower limit of plasma adiponectin concentration, were also more common among the overweight and obese patients combined (75.5%) than in underweight to pre-overweight groups combined (50%) (p<0.001).[16]

Serum concentrations of leptin and adiponectin showed steady increasing and decreasing trends, respectively, with higher BMI ranges (Figures 2A and 2B).

Leptin levels among females were generally of higher levels than that of males, increasing with BMI, except for the underweight group. Adiponectin levels were higher in males than in females, regardless of BMI. Adiponectin decreases as BMI increases in both groups.

Insulin Deficiency

There were 12 participants out of 337 (3.56%) who had a history of diabetic ketoacidosis (DKA) which is a hallmark of type 1 diabetes mellitus (T1DM). There was no data for five participants hence, the number (337) is less than the total number of participants (342). Of the 12 with a history of DKA, nine were male and three were females. Regarding the medications which these patients are using, two are not taking any medicines, another two are using insulin and oral anti-diabetic (OAD) agents, one is on OADs alone while the remaining seven are on insulin. Eleven participants had a fasting connecting or C-peptide (fCP) that was less than 0.2 nmol/L and likely have T1DM, but only seven out of 11 had any one of the antibodies for T1DM positive. Their BMI range was from 16-26 kg/m^2 with three in the underweight category, six with normal BMI, and two participants in the obese category (Appendix).

In insulin-treated individuals, fCP less than 0.2 nmol/l and glucose stimulated C-peptide value less than 0.32 nmol/l have been found to correlate significantly with T1DM, with greater sensitivity and specificity than urinary testing.[16] Glucagon stimulated C-peptide determination was not done in this study, and the greater majority of patients were also not on insulin treatment but almost half of participants had

fasting C-peptide less than 0.2 nmol/L at 165/348 (47.41%). This group is presumptive of having insulin deficiency but only around one-third of the participants had auto-antibodies which could indicate immune-mediated diabetes. Insulin autoantibodies showed higher positivity rates compared to anti-GAD levels (Table 7).

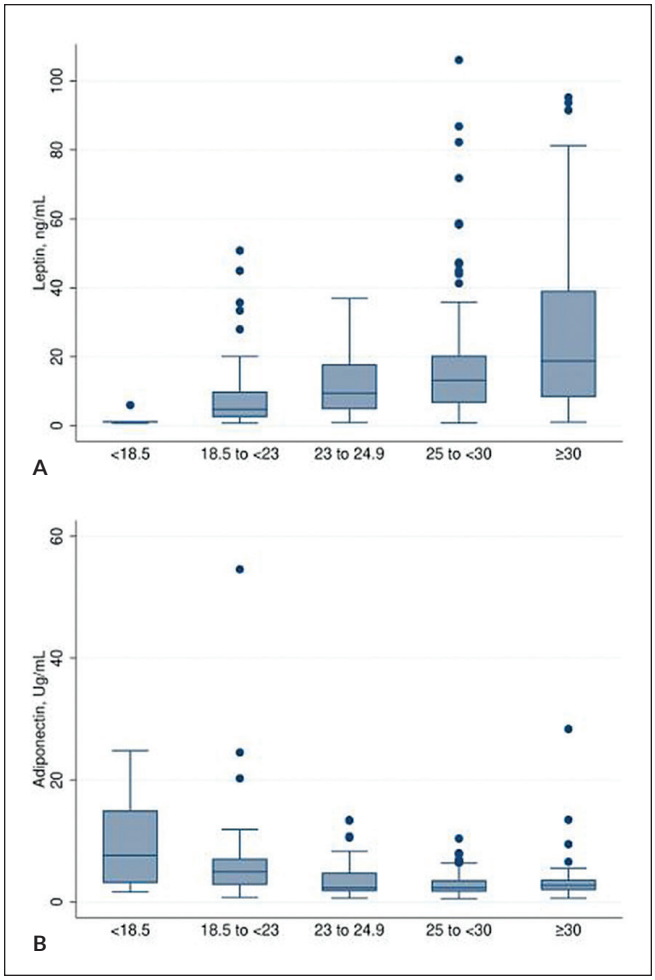

Figure 2. Levels of leptin **(A)** and adiponectin **(B)** across BMI groupings.

Table 7. Auto-antibodies Detected in this Cohort

Antibody Positivity Rate	N (%)
Anti-GAD (U/ml)	11 (3.2)
IAA positive (IU/ml)	66 (19.3)
IA2 (U/ml)	4 (1.2)
Zinc transporter (RU/ml)	10 (2.9)
Any antibody positive	83 (33.5)
Anti-TG (IU/ml)	41 (11.78)
Anti-TPO (IU/ml)	29 (8.33)
Both anti-TG and anti-TPO positive	19 (5.5)

DISCUSSION

This study characterized in depth the demographic, metabolic, and autoimmune characteristics of newly diagnosed Filipino young adults with diabetes. This cohort is distinct from our Caucasian counterparts with increased visceral adiposity at a lower BMI, a phenotype that has been shown in Asian populations.[17] However, compared even to the general adult population in the Philippines, this cohort is more overweight and obese, and have greater visceral adiposity. The mean BMI in this study for both sexes was 28.2, 6.52 SD kg/m^2, and 27.57, 6.73 SD kg/m^2 and 28.5, 6.41 SD kg/m^2 for men and women, respectively. For both sexes, the mean BMI is above the values seen for the general population in the 2018 National Nutrition Survey which was 24.0 kg/m^2 with mean BMI of 23.5 kg/m^2 and 24.4 kg/m^2 for males and females, respectively.[6] For the measures of adiposity, the mean waist circumference was 91, 13.225 SD cm and 91.8, 16 SD cm and 90.75, 11.51 cm for males and females, respectively. Again for both males and females in this study, the mean waist circumference was higher than the average adult Filipino WC found in the 2018 NNS. The values for the general adult population in the 2018 NNS was a mean WC of 80 cm, with 80.4 and 79.6 for males and females, respectively.[6] Finally, the mean WHR is 0.93, 0.06 SD with these values for males and females respectively: 0.94, 0.07 (range 0.76 to 1.22) and 0.93, 0.06 (0.80 to 1.16). These again are much higher compared to the general population where mean WHR was 0.89, with 0.90 and 0.88 for males and females, respectively.[6]

Metabolic syndrome rates are high, and islet cell autoimmunity rates are low. The high rates of metabolic syndrome found in this cohort are consistent with the findings in previous researches showing that metabolic syndrome is more prevalent among Filipino-Americans, compared to Caucasians and even other Asian ethnic groups.[18-20] Data on underlying diabetes mechanisms are scarce. This study shows a robust response of insulin levels after 75 g glucose load indicating appropriate insulin secretion in early diabetes. Measurement of insulin resistance indices revealed that this young group of Filipino patients were predominantly insulin resistant. Likewise, the proportion of participants with auto-antibodies related to T1DM is very low. This again is consistent with the "Asian" phenotype of high rates of central obesity and metabolic syndrome but with low rates of autoimmune type 1 diabetes.[17] Given the variability of the results in a population where the cut-offs have not been validated, we can only conclude that the estimates of insulin resistance range from around 45% to 75% of the participants.

Leptin and adiponectin concentrations both showed consistently increasing and decreasing trends with higher BMI, respectively. Leptin levels were generally higher and adiponectin levels lower in females than in males. These findings are consistent with studies that showed lower adiponectin concentrations among Filipinos.[21,22] Very little

though is known about leptin among Filipino populations. In a study done by Conroy et al., which included 11 Filipinos, mean leptin levels were found to be significantly elevated in overweight and obese women compared to those with normal BMI (18.0 and 34.8 vs. 8.8 ng/mL, respectively).[23] Such an observation is reinforced by a study done on 596 lean Filipino adolescents wherein females were found to have higher leptin levels than males and BMI was a significantly positive predictor of increased leptin levels in females.[24]

While this is the largest cohort of young Filipino adults newly diagnosed with diabetes mellitus which has been extensively characterized, the sampling design (convenience) preludes representation of the diverse populations of Filipinos with diabetes across the various islands and provinces of the country. Participants were recruited from Metro Manila, an urban center with access to diabetes care at the Philippine General Hospital. However, the results of the study parallel a recent publication on younger adults aged 20-44 years which was based on the 8th FNRI DOST National Nutrition Survey.[6] In this survey, the mean age of those with diabetes is similar to the current report at 37, 6 SD years, with high mean BMI at 26.24, 5.05 SD kg/m^2, a combined prevalence of overweight plus obesity of 70.41 % and metabolic syndrome prevalence of 81.13%. Thus, the results of the current study could be generalizable to the greater population of younger adult Filipinos with diabetes.

CONCLUSION

We described in depth the clinical, metabolic, and autoimmune characteristics of diabetes among newly diagnosed young adult Filipinos. In contrast with Caucasians and other Asians, diabetes among younger adult Filipinos is associated with lower BMI and greater visceral adiposity. Metabolic syndrome as defined by clinical criteria was reported in more than half of the patients. Type 1 diabetes, with autoantibodies, was seen in only a very small fraction of this population.

As a low resource country, the Philippines needs to establish more effective guidelines for prevention, early detection, and cost-effective management of diabetes, based on a clearer understanding of the demographic, metabolic, and autoimmune characteristics and risks. Incorporating these various features with genomic and related data will provide a risk score for prediction of the development of diabetes and its complications. Data derived from this work can provide a framework for cluster analysis towards personalized management specific to this population.

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Statement of Authorship

All authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure

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APPENDIX

Table 1. Participants with Low C-Peptide Levels Presumptive of T1DM

Pt. No.	C-peptide (nmol/L)	BMI (kg/m^2)	Treatment	HbA1c (%)	GAD +	IA2+	IAA+	Zinc+
84	0.04	21	Long-Acting Glargine + Metformin	6	0	0	0	0
121	0.00	18	Long-Acting Glargine + Rapid Acting Glulisine	8	Yes	0	0	0
139	0.02	26	No Treatment	14	0	0	0	0
170	0.00	17	Long-Acting Glargine + Metformin	15	0	0	Yes	0
174	0.02	37	Biphasic insulin aspart/protamine aspart	10	0	0	0	0
177	0.16	24	Long acting Glargine + Regular Insulin	10	Yes	Yes	Yes	Yes
233	0.00	20	Long Acting Glargine + Rapid Acting Glulisine	9	0	0	Yes	0
252	3.62	29	Metformin alone	9.0%	0	0	0	0
276	0.00	16	Long-Acting Glargine + Regular Insulin	7	0	0	Yes	0
285	0.14	20	No treatment	11	0	0	0	0
319	0.17	24	Biphasic human insulin 70/30	6	0	0	Yes	0
324	0.02	23	Long-Acting Glargine	7	0	0	Yes	0