The Correlation of Body Mass Index With Fasting C-peptide Levels of Newly Diagnosed Type 2 Diabetes Mellitus Filipino Patients

Patrick Y. Siy, M.D.*; Oliver Allan C. Dampil, M.D.*; Joselynna A. Quimpo, M.D.*

Abstract

Introduction: Type 2 diabetes mellitus (DM) is one of the leading non-communicable causes of death in the Philippines with a prevalence of 5.4% and its pathogenesis includes insulin resistance correlated with excess weight and BMI. Asian-based studies have shown that serum C-peptide is strongly associated with newly diagnosed diabetes and has a linear increasing trend with BMI, hence, this study aimed to determine the correlation of body mass index (BMI) with fasting C-peptide levels in Filipino patients with newly diagnosed type 2 DM. Also, to determine the correlation of fasting C-peptide, markers of insulin secretion and sensitivity (Homeostasis Model Assessment of beta cell function and insulin resistance: HOMA-IR, HOMA-B) with other metabolic parameters in newly diagnosed diabetics: waist circumference, HbA1C, fasting blood sugar (FBS), lipid profile.

Methods: This cross-sectional study included 35 treatment naïve, newly diagnosed type 2 DM Filipino patients evaluated with anthropometric measurements, fasting C-peptide, and other metabolic parameters. The correlations among fasting C-peptide, BMI, waist circumference, FBS, HbA1c, lipid profile, HOMA-IR, and HOMA-B were determined using Pearson correlation.

Results: A significant positive relationship were observed between BMI and HOMA-IR(r=0.335); C-peptide and waist circumference (r=0.363); C-peptide and HOMA-B(r=0.357); HOMA-IR and C-peptide (r=0.892); HOMA-IR and waist circumference (r=0.438); HOMA-IR and triglycerides (r=0.543). HOMA-B was negatively correlated with FBS and HbA1C (r=-0.771, and r=-0.641, respectively). No correlation was seen between BMI and C-peptide (*p*=0.61).

Conclusion: Body mass index (BMI) is not correlated with fasting C-peptide levels in newly diagnosed type 2 DM Filipino patients. The positive relationship between C-peptide, waist circumference, and HOMA-IR merits further evaluation with larger studies.

Keywords: c-peptide, type 2 diabetes mellitus, body mass index, insulin resistance

Introduction

Type 2 diabetes mellitus (DM) is one of the leading non-communicable causes of death in the Philippines and the number of people being diagnosed with type 2 DM is growing with a prevalence of 5.4%.[1,2] Complex mechanisms are involved in the pathogenesis of type 2 DM. This involves an interplay of genetic and environmental risk factors which contribute strongly to the development of insulin resistance, as well as β-cell failure.[3] Uncontrolled diabetes mellitus can lead to microvascular and macrovascular complications like diabetic retinopathy, nephropathy, neuropathy, myocardial infarction, hypertension and peripheral arterial disease.[4]

Insulin resistance has been considered to have an important role in the pathogenesis of type 2 DM and an increase in body fat is generally associated with an increase in risk of metabolic diseases.[5,6] An established risk factor for developing type 2 DM is excess weight and most patients with type 2 DM are obese.[7] Also, the risk of developing type 2 DM for individuals who were overweight or obese was about 1.5 to five times higher than for individuals with normal body mass index (BMI).[8] It must be noted that BMI is a powerful and modifiable risk factor for diabetes.[9]

Since insulin resistance is involved in DM, the quantification of insulin secretion and insulin sensitivity are important in the assessment of beta-cell function in diabetes. The gold-standard methods for evaluation are the hyperglycemic and euglycemic-hyperinsulinemic clamp, but these tests are time consuming, expensive and require trained personnel. Other methods used to evaluate insulin secretion and sensitivity include surrogate markers derived from basal measurements (such as homeostasis model assessment (HOMA) indexes), fasting insulin and C-peptide; and oral stimulation tests (with glucose or mixed meals), intravenous stimulation tests (with glucose, glucagon or arginine).[10]

*Section of Endocrinology, Diabetes and Metabolism, St. Luke's Medical Center

Corresponding author: Patrick Y. Siy, M.D., St. Luke's Medical Center, Quezon City, Philippines
Email:siy_patrick@yahoo.com

C-peptide can be used to compute for the HOMA indices. It is a pancreatic peptide of about 31 residues and is the middle segment of proinsulin. Equimolar insulin and C-peptide are released on proteolytic cleavage of proinsulin. C-peptide immunoassay has been used to assess pancreatic beta cell function in diabetic patients with circulating insulin antibodies or exogenous insulin. The half-life of C-peptide is 30 minutes, almost eight times that of insulin which makes it a more stable parameter in assessing insulin secretion and sensitivity.[11] Recent studies have suggested that C-peptide is not only a marker of beta cell function but is also biologically active. C-peptide increases glucose utilization when studied on type 1 diabetic patients.[12]

In a study done in Thailand, it showed that fasting serum insulin and C-peptide levels progressively increased from normal subjects to the diabetic subjects. Serum C-peptide was also more strongly associated with newly diagnosed diabetes than insulin, and was an independent factor associated with newly diagnosed diabetic subjects.[13] While in China, they found that fasting C-peptide showed linear increasing trend while HbA1C showed decreasing trend with BMI. They also saw that underweight patients had the lowest C-peptide and highest HbA1C while overweight patients had the highest C-peptide, blood pressure, triglyceride but lowest HbA1C levels.[14] Interestingly, a study done in Denmark showed that C-peptide concentrations below 0.4 nmol/L would predict insulin dependence on patients who are already on oral hypoglycemic agents.[15]

The correlation of BMI and C-peptide has been mentioned in previous studies in other countries but there are no local studies yet. This study aims to answer if BMI is correlated with fasting C-peptide levels in Filipinos, newly diagnosed with type 2 DM. Taking into consideration that the pathophysiology of type 2 DM involves BMI, insulin sensitivity and insulin resistance, this study would help improve the knowledge on BMI, beta-cell function, insulin resistance and severity of diabetes in newly diagnosed Filipino patients and help in the decision on the treatment of these patients. We would also want to determine if BMI could be a surrogate marker for insulin resistance in place of the more expensive C-peptide test. This study could also be used as a reference for future research on correlating C-peptide levels with initiation of insulin treatment and development of complications on this subset of patients.

The general objective of this study is to determine the correlation of BMI with fasting C-peptide levels in patients with newly diagnosed type 2 DM. Specifically, this study aimed:

1. To determine the correlation of fasting C-peptide with other metabolic parameters in newly diagnosed diabetics: waist circumference, HbA1C, FBS, lipid profile, HOMA-IR, HOMA-B.
2. To determine the correlation of insulin secretion and sensitivity (HOMA-B, HOMA-IR) with waist circumference, HbA1C, FBS, lipid profile.

Methods

Study design and subjects

This was a cross-sectional study approved by the Institutional Review Board and Institutional Ethics Review Committee of St. Luke's Medical Center (SLMC), Quezon City that included 35 treatment-naïve, newly diagnosed type 2 DM Filipino patients seen at both the private clinics and social service out-patient department of SLMC, Quezon City, Philippines from August 2016-January 2017. Endocrinologists, fellows-in-training and medical residents informed the researchers on potential participants then they were screened during out-patient visit, and asked to participate in the study based on the inclusion and exclusion criteria. Patients were included if they are adults (age more than 18 years old) and newly diagnosed patients who matched the American Diabetes Association (ADA) criteria[16] for the diagnosis of type 2 DM within three months who are also medication-naïve. They were excluded if the patients were on anti-diabetic medications for other indications; on steroid therapy; pregnant; with active infection; with chronic kidney disease stage three, four and five (eGFR <60), since there was higher levels of C-peptide compared to those with stage one and two disease[17]; and with history of liver disease since liver disease can cause alteration in levels of C-peptide particularly in cirrhotic patients.[18] The subjects were recruited by consecutive sampling.

All participants signed the informed consent voluntarily after thorough explanation on the nature of the research; objectives, risks, and expected benefits to participation. Participants were interviewed by the researcher. Demographic information was collected, as well as medical history and other related diseases, they then underwent a physical examination. Height, weight, waist circumference, and blood pressure were measured by the researcher using the weighing scale, tape measure and sphygmomanometer of the diabetes, thyroid and endocrine center at SLMC, Quezon City.

Laboratory analysis

Blood samples were collected and processed by the pathology department at SLMC, Quezon City. Complete blood count was measured by electrical impedance using the Sysmex XN-3000. Fasting blood sugar was measured by hexokinase method using Dimension RXL Max with versacell. Creatinine, lipid profile and SGPT were measured using the same machine. C-peptide was measured by chemiluminescence using Architect 1000ISR. HbA1C was measured by HPLC using Biorad Variant II Turbo. HOMA-B

Table I. The anthropometric and metabolic characteristics of participants

Characteristics	Overall (n=35)	Males (10)	Females (25)
Age (years ± SD)	50 ± 9	50 ± 7	50 ± 10
Height (cm ± SD)	156.4 ± 9.8	164.8 ± 5.9	153 ± 9
Weight (kg ± SD)	70.1 ± 12.5	76.6 ± 11.3	67.5 ± 12
Body Mass Index (kg/m2 ± SD)	28.6 ± 4.1	28.3 ± 3.9	28.8 ± 4.1
Waist circumference (cm ± SD)	96.6 ± 7.8	97.2 ± 7.2	96.4 ± 8
Family History of Diabetes (with family history %)	60%	50%	64%
Systolic BP (mmHg ± SD)	128 ± 14	134 ± 17	126 ± 12
Diastolic BP (mmHg ± SD)	80 ± 7	83 ± 8	78 ± 5
Creatinine (mg/dL ± SD)	0.76 ± 0.19	0.95 ± 0.17	0.68 ± 0.14
SGPT (U/L ± SD)	49.8 ± 33	47 ± 25.8	50.9 ± 35.6
FBS (mg/dL ± SD)[a]	174 ± 63	208 ± 66	160 ± 56
HbA1C (% ± SD)	8.8 ± 2.3	10.1 ± 2.9	8.3 ± 1.9
Total Cholesterol (mg/dL ± SD)	220 ± 43	221 ± 53	220 ± 38
Triglycerides (mg/dL ± SD)	170 ± 114	227 ± 152	148 ± 85
HDL (mg/dL ± SD)[b]	46 ± 13	39 ± 8	49 ± 13
LDL (mg/dL ± SD)[c]	140 ± 34	134 ± 40	142 ± 30
C-peptide (ng/mL ± SD)	2.79 ± 1.03	2.76 ± 1	2.8 ± 1
HOMA-IR (IR ± SD)[d]	2.56 ± 0.97	2.78 ± 1	2.47 ± 0.95
HOMA-B (% ± SD)[e]	65.14 ± 40.39	51.49 ± 28.93	70.6 ± 42.95

[a]Fasting blood sugar, [b]High Density Lipoprotein, [c]Low Density Lipoprotein, [d]Homeostasis Model Assessment of Insulin Resistance, [e]Homeostasis Model Assessment of beta cell function

and HOMA-IR were computed using an online calculator downloaded from the University of Oxford website: https://www.dtu.ox.ac.uk/homacalculator/.

No further follow-up was required after all data collection and laboratory extraction. Patients proceeded with their regular check-up or follow-up with their respective physicians.

Sample size calculation

Sample size was computed using piface program for linear regression. Given a correlation of 0.488, and assuming SD of one and error SD of one, 35 subjects were needed to achieve 80% power at 0.05 alpha.

Statistical analysis

Descriptive statistics was used to characterize the study population. Data were expressed as percentage and mean±SD. These included the age, gender, family history of diabetes, blood pressure, height, weight, BMI and waist circumference. Statistical analyses were performed using the SPSS software package. Pearson's correlation analyses were used for correlating BMI with fasting C-peptide levels, and were also used for correlating C-peptide levels with waist circumference, HbA1C, Lipid Profile, FBS, HOMA-IR and HOMA-B. Pearson's correlation analyses were used for correlating HOMA-IR and HOMA-B with waist circumference HbA1C, Lipid Profile, and FBS. A *p*-value of <0.05 was considered statistically significant.

Results

Mean age was 50 years in this set of newly diagnosed type 2 DM patients. (Table I). The youngest subject included in this study was 26 years of age. Almost a third of the subjects were male. 80% (n=28) were obese, 17% (n=6) were overweight, and three percent (n=1) with normal BMI, based on the Asia-Pacific guidelines on obesity, with a mean of 28.6 kg/m^2. Mean FBS was 174 with an HbA1C of 8.8 with males having a higher HbA1C compared to females. More than half of the participants had a first degree relative with type 2 DM. The mean cholesterol, triglyceride, low-density lipoprotein (LDL) were elevated and the mean high-density lipoprotein (HDL) were below normal based on gender.

No correlation was seen between BMI and C-peptide with a *p*-value of 0.61 but positive correlations with moderate association were noted with BMI and HOMA-IR(*r*=0.335). C-peptide showed a linear positive correlation with waist circumference (*r*=0.363). HOMA-IR was positively correlated with C-peptide with a strong association (*r*=0.892), and with waist circumference with moderate association (*r*=0.438).

Table II. Pearson's correlations (95% CI) of C-peptide with BMI and other metabolic parameters

	C-peptide (r) p-value (95% CI)	HOMA-IR[d] (r) p-value (95% CI)	HOMA-B[e] (r) p-value (95% CI)
BMI	0.320 0.61 (0.39-5.68)	0.335 0.049 (0.055-0.569)	0.025 0.886 (0.141-0.572)
C-peptide	-	0.892 <0.001 (0.742-0.964)	0.357 0.035 (-0.138-0.570)
Waist circumference	0.363 0.032 (0.136-0.583)	0.438 0.009 (0.238-0.634)	0.061 0.728 (-0.222-0.343)
FBS[a]	-0.118 0.5 (-0.32-0.12)	0.312 0.068 (0.36-5.91)	-0.771 <0.001 (-0.880-0.653
HbA1C	-0.187 0.281 (-0.427-0.82)	0.165 0.343 (-0.149-0.495)	-0.641 <0.001 (-0.792-0.505)
Total Cholesterol	0.043 0.806 (-2.33-0.385)	0.096 0.584 (-0.234-.422)	0.029 0.869 (-0.333-0.337)
Triglycerides	0.173 0.119 (-0.05-0.452)	0.543 0.001 (0.252-0.75)	-0.156 0.372 (-0.354-0.29)
HDL[b]	0.173 0.321 (-0.05-0.452)	0.069 0.692 (-0.176-0.326)	0.069 0.692 (-0.176-0.326)
LDL[c]	-0.178 0.306 (-0.43-0.078)	-0.334 0.05 (-0.565-0.063)	0.282 0.101 (-0.086-0.569)

[a] Fasting blood sugar, [b] High Density Lipoprotein, [c] Low Density Lipoprotein, [d] Homeostasis Model Assessment of Insulin Resistance, [e] Homeostasis Model Assessment of beta cell function

HOMA-IR was also positively correlated with triglycerides with strong association (r=0.543). HOMA-B was positively correlated with C-peptide (r=0.357), and negatively correlated with FBS and HbA1C (r=-0.771, and r=-0.641, respectively). (Table II).

Discussion

Unlike in the study done in China and Thailand[13,14], this cross-sectional studies showed no association between the BMI and C-peptide. This non-association may be due to differences in body composition of a person, a higher BMI does not necessarily correlate to disturbed glucose tolerance or increase in body fat percentage which could affect C-peptide levels.[19] Also, although of the same race, there might be ethnic differences which could have contributed to the difference in the results of the studies. Another factor to consider with the non-correlation of BMI and C-peptide is the patient's physical activity. It has been shown that habitual physical activities are associated with lower C-peptide levels.[20, 21] Some of these individuals may have these activities hence altering the results. None of the patients had a C-peptide level of <1.2 ng/mL (<4 nmol/L) indicating that these patients can still be treated with oral hypoglycemic agents and there is a lower possibility for future insulin requirement.[15]

Insulin resistance calculated with HOMA-IR is correlated positively with increasing BMI, more so with increasing waist circumference. Studies showed different results regarding waist circumference and BMI as predictors of insulin resistance. Some studies suggest that waist circumference could be a better predictor of insulin resistance and cardiovascular risk while others showed no difference.[22,23,24] In this study, both BMI and waist circumference were associated with HOMA-IR but waist circumference showed a stronger statistical significance. This may provide us with another parameter to consider on how to treat our patients with greater waist circumference seeing that it is correlated with insulin resistance. Triglycerides were also associated with insulin resistance probably due to the physiology and interaction of triglycerides and insulin.

Increasing HOMA-B in relation to a decreasing FBS and HbA1C is the physiologic response of the body to decrease glucose levels. This trend is seen during the early stages of type 2 DM where the pancreas still has enough beta cell activity to compensate but cannot totally normalize the fasting blood glucose.

Based on this study, BMI may not be a good surrogate marker in place of C-peptide in determining insulin resistance in Filipinos with newly diagnosed type 2 DM.

Conclusion

Body mass index (BMI) is not correlated with fasting C-peptide levels in newly diagnosed type 2 DM Filipino patients. The researchers recommend further investigation on waist circumference since this may be used as a less expensive way of determining insulin resistance and aid in a more appropriate management of DM.

Acknowledgement
This study was funded by the research, and biotechnology department of SLMC, Quezon City, Philippines.

References

1. **Department of Health**, Republic of the Philippines. Twenty years of non-communicable disease (NCD) prevention and control in the Philippines (1986-2006). 2009.
2. **Paz-Pacheco E, Jimeno C.** Diabetes Care in the Philippines. Journal of the ASEAN Federation of Endocrine Societies, 2015;30(2):118-23
3. **D'Adamo E, Caprio S.** Type 2 diabetes in youth: epidemiology and pathophysiology. Diabetes Care. 2011;34 Suppl 2:S161–5.
4. **Sosale A, Prasanna Kumar KM, Sadikot SM, Nigam A, Sarita**

B, Zargar AH, et. al. Chronic complications in newly diagnosed patients with type 2 diabetes mellitus in India. Indian Journal of Endocrinology and Metabolism, 2014:18(3):355–360.

5. **Mahler RJ, Adler ML.** Type 2 Diabetes Mellitus: Update On Diagnosis, Pathophysiology, And Treatment. Clinical Review 102. J Clin Endocrinol Metab 1999, 84(4):1165-1171.
6. **Bays HE, Chapman RH, Grandy S.** The relationship of body mass index to diabetes mellitus, hypertension and dyslipidaemia: comparison of data from two national surveys. International Journal of Clinical Practice, 2007:61(5):737-747.
7. **Eckel RH, Kahn SE, Ferrannini E, Goldfine AB, Nathan DM, Schwartz MW, et. al.** Obesity and type 2 diabetes: what can be unified and what needs to be individualized? J Clin Endocrinol Metab 2011;96:1654–1663.
8. **Schienkiewitz A, Schulze MB, Hoffmann K, Kroke A, Boeing H.** Body mass index history and risk of type 2 diabetes: results from the European Prospective Investigation into Cancer and Nutrition (EPIC)-Potsdam Study. The American Journal of Clinical Nutrition, 2006:84(2):427–433.
9. **Narayan KMV, Boyle JP, Thompson TJ, Gregg EW, Williamson DF.** Effect of BMI on lifetime risk for diabetes in the U.S. Diabetes Care, 2007:30(6):1562–1566.
10. **Cernea S, Dobreanu M.** Diabetes and beta cell function: from mechanisms to evaluation and clinical implications. Biochem Med (Zagreb). 2013;23:266-280.
11. **National Center for Biotechnology Information.** PubChem Compound Database; CID=16132309,https://pubchem.ncbi.nlm.nih.gov/ compound/16132309 (accessed Feb. 2, 2016)
12. **Wilhelm B, Kann P, Pfützner A.** Influence of C-peptide on glucose utilisation. Experimental Diabetes Research. 2008;2008:3
13. **Chailurkit LO, Jongjaroenprasert W, Chanprasertyothin S, Ongphiphadhanakul B.** Insulin and C-peptide levels, pancreatic beta cell function, and insulin resistance across glucose tolerance status in Thais. J Clin Lab Anal. 2007;21:85–90.
14. **Chan WB, Tong PC, Chow CC, So WY, Ng MC, Ma RC, et al.** The associations of body mass index, C-peptide and metabolic status in Chinese Type 2 diabetic patients. Diabet Med. 2004;21:349–353.
15. **Nielsen NV, Tronier B.** C-peptide and insulin secretion in diabetes mellitus treated with oral hypoglycaemic agents or diet alone. A 3 years epidemiological cohort study on the Island of Falster, Denmark. Diabetes Res. 1987 Mar;4(3):135-9.
16. **American Diabetes Association.** Standards of medical care in diabetes 2015. Diabetes Care. 2015;38(Suppl 1):S8-S13.
17. **Chen J, Muntner P, Lee H, Fonseca V, Batuman V, Whelton PK, et. al.** Insulin Resistance and Risk of Chronic Kidney Disease in Nondiabetic US Adults. J. Am. Soc. Nephrol. 2003;14:469-477.
18. **Gragnoli G, Signorini AM, Tanganelli I.** Plasma levels of insulin, C-peptide and glucagon in liver cirrhosis. J Endocrinol Invest. 1981Jan-Mar;4(1):1-5.
19. **Gomez-Ambrosi J, Silva C, Galofre JC, Escalada J, Santos S, Gil MJ, et al.** Body adiposity and type 2 diabetes: increased risk with a high body fat percentage even having a normal BMI. Obesity (Silver Spring) 2011;19: 1439–1444.
20. **Huus K, Åkerman L, Raustorp A, Ludvigsson J.** Physical Activity, Blood Glucose and C-Peptide in Healthy School-Children, a Longitudinal Study. PLoS ONE. 2016; 11(6):e0156401.
21. **Larsen J, Dela F, Madsbad S, Galbo H.** The effect of intense exercise on postprandial glucose homeostasis in Type II diabetic patients. Diabetologia (1999) 42: 1282-1292.
22. **Huang LH, Liao YL, Hsu CH.** Waist circumference is a better predictor than body mass index of insulin resistance in type 2 diabetes. Obesity Research & Clinical Practice. 2012;6(4):e314-e320.
23. **Farin HM, Abbasi F, Reaven GM.** Body mass index and waist circumference both contribute to differences in insulin-mediated glucose disposal in nondiabetic adults. Am J Clin Nutr. January 2006;83(1):47-51.
24. **Elbassuoni E.** Better association of waist circumference with insulin resistance and some cardiovascular risk factors than body mass index. Endocr Regul. 2013 Jan;47(1):3-14.