

# Adiponectin as a Biomarker of Type 2 Diabetes Mellitus

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**Abstract-** Adiponectin is an adipocyte-derived peptide that acts as a hormone with anti-inflammatory and insulin-sensitizing properties. Lower serum levels of adiponectin have been consistently associated with increased risk of type 2 diabetes in numerous prospective studies of diverse nationalities. However, few studies among Filipinos were documented. The objective of this study is to identify if adiponectin could serve as a biomarker of type 2 diabetes mellitus among Filipino respondents by determining the association of its levels with the presence of impaired fasting blood glucose, type 2 diabetes mellitus, insulin resistance and other anthropometric parameters. This study, conducted in University of Santo Tomas Hospital-Out Patient Department, compared the levels of adiponectin in normal, pre-diabetic and diabetic groups, with each having 28 randomly selected samples and equivalent gender ratio. Blood samples were analyzed for fasting blood glucose (FBS), insulin and adiponectin. Homeostatic model assessment of insulin resistance (HOMA-IR) was also computed. Adiponectin and insulin levels were determined using enzyme-linked immunosorbent assay (ELISA). Adiponectin was significantly decreased ( $p < 0.001$ ) in diabetic ( $23.6 \pm 10.5$  ug/ml) and pre-diabetic ( $67.6 \pm 10.6$  ug/ml) groups compared to the normal group ( $143.9 \pm 11.6$  ug/ml). It was also found to have a significant inverse correlation with FBS ( $r_{xy.z} = -.370$ ,  $p = 0.001$ ), and HOMA-IR ( $r_{xy.z} = -.326$ ,  $p = 0.003$ ) in all of the subjects. Serum adiponectin was also significantly decreased in insulin-resistant (HOMA-IR  $> 3$ ) compared to insulin-sensitive (HOMA-IR  $< 3$ ) subjects ( $57.1 \pm 11.2$  ug/ml vs.  $95.1 \pm 9.9$  ug/ml;  $p = 0.014$ ). The researchers conclude that lower adiponectin level is associated with insulin resistance and development of type 2 diabetes mellitus.

**Keywords:** adiponectin, HOMA-IR, insulin resistance, type 2 diabetes mellitus

## I. INTRODUCTION

The burden of diabetes mellitus is dramatically increasing worldwide affecting approximately 382 million people, 80% of whom live in low- and middle-income countries where four out of five people are said to have diabetes. Cases of all the types of diabetes are increasing. Of note are Type 2 diabetes mellitus cases wherein the number of people affected is expected to increase by 55% by the year 2035 [1]. This type of diabetes is characterized by a combination of impaired insulin secretion from pancreatic beta cells and insulin resistance of the peripheral target tissues and is most often associated with older age, obesity, family history of diabetes, previous history of gestational diabetes, physical inactivity, and certain ethnicities [2]. Identifying individuals with high risk of Type 2 diabetes at an

early reversible stage is critical for controlling its epidemic trend [3].

Adiponectin, an adipocyte-derived peptide that is exclusively and abundantly expressed in adipose tissue, acts as a hormone with anti-inflammatory and insulin-sensitizing properties [4]. Higher adiponectin levels are consistently associated with lower risk of Type 2 diabetes in prospective studies of diverse populations. Future studies that evaluate whether adiponectin is a useful predictor of Type 2 diabetes in addition to established risk factors using statistical techniques appropriate for prognostic analysis are encouraged [5]. Several cross-sectional studies have already been conducted, most of which documented that lower plasma levels of adiponectin in human subjects can be related with obesity [6], insulin resistance [7], and Type 2 diabetes [8].

In addition, several epidemiological researches in African-Americans, Pima-Indians [9], Asian Indians [10], Japanese-Americans [11], Japanese [12], Chinese [3] and Korean [13] population support the protective role of adiponectin against diabetes but few studies are documented in Filipino subjects. The first population-based investigation on Filipinos in determining the association of adiponectin levels with the presence of diabetes mellitus and impaired fasting glucose conducted by Paz-Pacheco et al. (2009) [14] recommends further studies to be performed, including investigations of the correlation of adiponectin with the degree of insulin resistance, on Filipino subjects.

This study evaluated whether adiponectin could serve as a biomarker of Type 2 diabetes mellitus among Filipino respondents. Furthermore, this study: (1) compared serum adiponectin levels of normal subjects with serum adiponectin levels of pre-diabetic and diagnosed Type 2 diabetic individuals, (2) identified if lower serum adiponectin levels is associated with the presence of Type 2 diabetes mellitus, and (3) determined the association of adiponectin with fasting blood glucose, insulin resistance, and other anthropometric parameters.

## II. METHODS

A cross-sectional study design was used to compare the levels of serum adiponectin in normal, pre-diabetic, and Type 2 diabetic individuals. Its association with insulin resistance and other anthropometric parameters was also identified.

### 2.1 Research Setting

The study was conducted at the University of Santo Tomas Hospital Out-Patient Department (OPD) Diabetic Clinic supervised by Dr. Bien J. Matawaran and Dr. Erick Mendoza where the diabetic and pre-diabetic patients were screened.

### 2.2 Population and Sample

Subjects that were included were normal, pre-diabetic, and Type 2 diabetic Filipino males and non-pregnant females ages 30 years old and above who are willing to participate and give their consent. Subjects excluded were individuals with diseases or conditions, including Type 1 diabetes mellitus, congestive heart failure, established renal disease requiring hemodialysis, history of endocrine disorders such as thyroid diseases, severe psychological disorders, physical disabilities, cancer, cardiovascular disease, Alzheimer’s disease, tuberculosis, AIDS, and other communicable diseases [14]. The presence or absence of the aforementioned conditions for disqualification was identified through the patient’s history interview and questionnaire, and was verified through the supervising physicians in the USTH-OPD Diabetic Clinic.

All respondents who passed the inclusion criteria were included in the study. Subjects were categorized according to American Diabetes Association (ADA) classification of diabetes [15] into 3 groups: normal, pre-diabetic and Type 2 diabetic groups. Individuals having fasting blood glucose level of < 100mg/dl (< 5.6 mM) were grouped to the normal/control group. Subjects having fasting blood glucose level of 100 to 125 mg/dL (5.6 mM to 6.9 mM) and/or having a history of impaired fasting glucose/ glucose tolerance for the past three months were grouped into pre-diabetic group. Individuals with a clinical diagnosis of Type 2 diabetes and/or having  $\geq 126$  mg/dL ( $>7.0$  mmol/L) were grouped into Type 2 diabetic group. All individuals were randomly selected.

Twenty-eight patients were used in each group to achieve 84.8% power of the statistical test at two-sided 5% level of significance. This calculation is based on the report of Snehalatha et al. (2003) [10] that the mean serum adiponectin of non-diabetic Indian patients and Type 2 diabetic patients are 16.7 (SD = 7.6) and 11.3  $\mu\text{g/mL}$ , respectively. OpenEpi was used in the computation of this sample size. A population of 28 per group (total n=84) from the total screened pool was obtained through random numbers to increase the power of the test (28 normal, 28 pre-diabetic and 28 diabetic subjects).

### 2.3. Ethical Considerations

Permission was requested from the ethics committee of the University of Santo Tomas Hospital Institutional Review Board and authorized physicians to conduct a study among normal, prediabetic and type 2 diabetic patients. The study was supervised by Dr. Bien J. Matawaran, FPSCP, DPSEM and Dr. Erick Mendoza. Diabetic and pre-diabetic patients were screened in the USTH Out-Patient Department Clinic. The participants were informed of the detailed objectives of the study and were reassured of the confidentiality of data upon signing the informed consent.

### 2.4. Data and Specimen Collection

Subjects were recruited and screened through a questionnaire which covered the demographic, anthropometric, and clinical parameters, including family and personal medical history.

Blood sample (5.0 ml) of each subject was drawn by venipuncture after an 8- to 10-hour fast. Serum was separated from whole blood within 30 minutes and the samples were tested for fasting blood glucose, adiponectin levels, and insulin levels. Fasting blood sugar was measured using Hitachi 902 Chemistry

Analyzer. Serum adiponectin and fasting insulin were measured using Enzyme-Linked Immunosorbent Assay (ELISA) kits from Abcam U.K. product code ab99968 and Monobind Inc. Lake Forest, CA 92630, USA product code: 2425-300, respectively. HumaReader HS Human (Biocare ELISA reader) was used to obtain the absorbance of each sample.

### 2.5 Statistical Analysis

The clinical characteristics and demographic data of the respondents such as age, body mass index (BMI), systolic and diastolic blood pressure, waist-hip ratio, fasting blood sugar (FBS), adiponectin, insulin, and homeostatic model assessment for insulin resistance (HOMA-IR) were summarized using mean  $\pm$  standard error of mean (SEM).

Analysis of variance (ANOVA) was used to compare the means of the summarized clinical characteristics and demographic data of the three groups (normal, pre-diabetic and diabetic). Analysis of covariance (ANCOVA) adjusted for age and body mass index (BMI) was used to compare the means of insulin, HOMA-IR, and adiponectin. Partial correlation adjusted for age and BMI was calculated to determine the correlation between adiponectin and other variables. HOMA-IR was calculated using the equation: [fasting serum insulin (uIU/ml) x fasting plasma glucose (mmol/L)]/22.5 [16]. P-values of less than 0.05 were considered significant. All statistical tests were performed using SPSS 17.0.

## III. RESULTS AND DISCUSSION

The table below shows the summarized demographic and clinical characteristics of the recruited normal, pre-diabetic, and diabetic groups.

**Table 1.** Demographic and Clinical Characteristics of Study Groups

Parameters	Normal	Pre-diabetic	Diabetic	p-value	Post-hoc
Age (years)	47.7 $\pm$ 2.5	59.1 $\pm$ 2.0	57.9 $\pm$ 1.9	<0.001	N<(D=P)
BMI	22.0 $\pm$ 0.5	24.6 $\pm$ 0.6	24.8 $\pm$ 0.8	0.004	N<(D=P)
W/R	0.86 $\pm$ 0.01	0.89 $\pm$ 0.01	0.89 $\pm$ 0.01	0.085	-
Systolic (mmHg)	124.3 $\pm$ 2.2	124.8 $\pm$ 1.3	125.7 $\pm$ 2.4	0.899	-
Diastolic (mmHg)	80.5 $\pm$ 1.8	83.0 $\pm$ 1.1	83.2 $\pm$ 1.4	0.343	-
FBS (mmol/L)	4.4 $\pm$ 0.1	5.8 $\pm$ 0.1	10.5 $\pm$ 0.9	<0.001	(N=P)<D

Legend: BMI, Body Mass Index; W/R, Waist-Hip Ratio; FBS, Fasting Blood Sugar; N, Normal; D, Diabetic; P, Pre-diabetic

Each group was composed of 28 respondents with equal gender ratio (14 males and 14 females). The age of pre-diabetic [(Mean  $\pm$  SEM) 59.1  $\pm$  2.0] and diabetic (57.9  $\pm$  1.9) respondents were significantly higher ( $p<0.001$ ) than the normal group (47.7  $\pm$  2.5) based on the *Post-hoc* analysis [(P=D)>N], however, there is no significant difference between the age of pre-diabetic and diabetic groups. The BMI of the pre-diabetic (24.6  $\pm$  0.6) and diabetic (24.8  $\pm$  0.8) groups were significantly higher ( $p=0.004$ )

compared to the normal group ( $22.0 \pm 0.5$ ) based on the *Post-hoc* analysis [(P=D)>N], however, there is no significant difference between the BMI of pre-diabetic and diabetic groups. The FBS of the diabetic group ( $10.5 \pm 0.9$  mmol/L) was significantly higher ( $p < 0.001$ ) compared to the normal ( $4.4 \pm 0.1$  mmol/L) and pre-diabetic ( $5.8 \pm 0.1$  mmol/L) groups based on the *Post hoc* analysis [D>(N=P)], however, there is no significant difference between the FBS of normal and pre-diabetic groups. The systolic and diastolic blood pressure, and waist-hip-ratio did not significantly differ statistically among the subject groups.

**Table 2.** Analysis of Covariance (Age and BMI Adjusted) of Insulin, HOMA-IR and Adiponectin Among the Study Groups

Parameters	Normal	Pre-diabetic	Diabetic	p-value	Post Hoc
Insulin (mIU/L)	$6.9 \pm 1.1$	$12.3 \pm 1.0$	$11.4 \pm 1.0$	0.003	N<(D=P)
HOMA-IR	$1.3 \pm 0.4$	$3.2 \pm 0.4$	$5.2 \pm 0.4$	<0.001	N<P<D
Adiponectin (ug/ml)	$143.9 \pm 11.6$	$67.6 \pm 10.6$	$23.6 \pm 10.5$	<0.001	D<P<N

Legend: HOMA-IR, Homeostatic Model Assessment of Insulin Resistance; N, Normal; D, Diabetic; P, Pre-diabetic

In Table 2, the comparison of the adjusted means of insulin, homeostatic model for insulin resistance (HOMA-IR) and adiponectin among the three study groups is shown. The means were adjusted for age and BMI to avoid bias since both significantly differed among the study groups. Insulin was significantly decreased ( $p=0.001$ ) in normal subjects [(Mean  $\pm$  SEM)  $6.9 \pm 1.1$  mIU/L] compared to the pre-diabetic ( $12.3 \pm 1.0$  mIU/L) and diabetic groups ( $11.4 \pm 1.0$  mIU/L). *Post-hoc* analysis revealed that there is no significant difference between the insulin of diabetic and pre-diabetic groups [N<(D=P)]. HOMA-IR was significantly lower ( $p < 0.001$ ) in the normal group ( $1.3 \pm 0.4$ ) compared to the pre-diabetic ( $3.2 \pm 0.4$ ) and diabetic groups ( $5.2 \pm 0.4$ ), and *post-hoc* analysis also showed that the HOMA-IR of the pre-diabetic group was also significantly lower than the diabetic group (N<P<D). Adiponectin was found to be significantly lower ( $p < 0.001$ ) in the diabetic group ( $23.6 \pm 10.5$  ug/ml) compared to the pre-diabetic ( $67.6 \pm 10.6$ ) and normal groups ( $143.9 \pm 11.6$  ug/ml), also, the *post-hoc* analysis revealed that adiponectin levels of the pre-diabetic group was significantly lower than the normal group (D<P<N).

**Table 3.** Age and BMI Adjusted Means of Adiponectin Between Insulin-Sensitive and Insulin-Resistant Groups

Parameter	HOMA-IR < 3	HOMA-IR > 3	p-value
Adiponectin (ug/ml)	$95.1 \pm 9.9$	$57.1 \pm 11.2$	0.014

Legend: HOMA-IR, Homeostatic Model Assessment of Insulin Resistance

To assess adiponectin levels and influence of insulin resistance, the subjects were further divided based on homeostatic model assessment of insulin resistance (HOMA-IR) into insulin sensitive (HOMA-IR < 3) and insulin-resistant (HOMA-IR > 3) groups, similar to the previous study of Urbanavičiu *et al.* (2008) [17] (Table 3). Adiponectin was found to be significantly lower ( $p=0.014$ ) in insulin-resistant group

[(Mean  $\pm$  SEM)  $57.1 \pm 11.2$  ug/ml] compared to the insulin-sensitive subjects ( $95.1 \pm 9.9$  ug/ml).

HOMA-IR, the index regulated by FBS and fasting insulin level, is a method used to evaluate the insulin resistance where insulin secretion capacity is sustained to some extent, and is widely used as a research tool in epidemiological studies [18]. Decreased serum adiponectin levels in insulin resistant compared to insulin sensitive group may be due to its association with insulin sensitization. The findings of this study show that adiponectin secretion is closely related to insulin resistance and insulin sensitivity appear to be a major determinant of adiponectin levels, consistent with previous studies [7, 17].

**Table 4.** Partial Correlation Adjusted for Age and BMI of Adiponectin Among Other Variables in All Subjects Combined

Parameters	$r_{xy.z}$	p-value
Waist-Hip Ratio	-0.019	0.866
Systolic (mmHg)	0.155	0.165
Diastolic (mmHg)	0.109	0.330
Fasting Blood Glucose (mmol/L)	-0.370	0.001
Insulin (uU/ml)	-0.131	0.239
HOMA-IR	-0.326	0.003

Legend: HOMA-IR, Homeostatic Model Assessment of Insulin Resistance

In Table 4, the partial correlation of adiponectin among other variables in all of the subjects is shown. Adiponectin levels have a significant inverse correlation with fasting blood glucose ( $r_{xy.z} = -0.370$ ,  $p = 0.001$ ) and HOMA-IR ( $r_{xy.z} = -0.326$ ,  $p = 0.003$ ). This indicates that higher adiponectin level correlates with better insulin sensitivity and glucose metabolism, and lower adiponectin level correlates with higher insulin resistance and abnormal glucose metabolism, consistent with previous studies [7, 17, 18]. Adiponectin also has a negative correlation with insulin but this was not statistically significant. The correlation of adiponectin with waist-hip ratio, and systolic and diastolic blood pressure, likewise, did not significantly differ.

The results of this study showed the ability of adiponectin in differentiating diabetic from pre-diabetic and normoglycemic individuals. Based on the findings, adiponectin secretion is already altered in pre-diabetic conditions leading to much lower adiponectin levels in the diabetic state. This is supported by the findings of the study of Ahsan *et al.*, (2012) [18] wherein it was mentioned that adiponectin indicates the energy abundance in the body and its secretion is neither regulated nor influenced by the glycemic status of the individuals, rendering this hormone a suitable candidate for assessment of pre-diabetes. Thus, lower serum adiponectin levels leading to abnormal glucose metabolism is associated with the development of Type 2 diabetes mellitus. The mechanism is not very clear, however; it was mentioned in the study of Durrani *et al.*, (2013) [8] that the diabetes susceptibility locus which is seen on chromosome 3q27 has been found to contain adiponectin gene and multiple polymorphisms of the adiponectin gene have also been observed in Type 2 diabetes mellitus.

#### IV. CONCLUSION AND RECOMMENDATIONS

Based on the findings of the study, the researchers hereby make the following conclusions: (1) Subjects with Type 2 diabetes mellitus and pre-diabetes exhibit lower levels of serum

adiponectin compared to normal individuals ( $23.6 \pm 10.5$  ug/ml &  $67.6 \pm 10.6$  ug/ml vs.  $143.9 \pm 11.6$  ug/ml;  $p < 0.001$ ). (2) Lower serum adiponectin level is associated with the presence of type 2 diabetes mellitus. (3) Adiponectin is inversely associated with FBS ( $r_{xy,z} = -0.370$ ,  $p = 0.001$ ) and HOMA-IR ( $r_{xy,z} = -0.326$ ,  $p = 0.003$ ). This indicates that higher adiponectin levels correlates with better insulin sensitivity and glucose metabolism, and lower adiponectin levels correlates with higher insulin-resistance and abnormal glucose metabolism. The researchers conclude that lower adiponectin level is associated with insulin resistance and development of type 2 diabetes mellitus.

The researchers recommend for further investigations that will warrant a longitudinal large-scale study to be conducted due to the limitation of this cross sectional study. Other risk parameters including oral glucose tolerance (OGTT), lipid profile, glycosylated hemoglobin, metabolic syndrome and obesity are also recommended to be included. A more homogenous age group among Filipino population is also suggested.

The researchers also recommend for future studies to elaborate the role of adiponectin in insulin sensitivity including its mechanism and other factors that could affect its level in relation to the development of Type 2 diabetes mellitus.

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