HIDDEN RISKS: RELATIONSHIP AMONG VAT, IL-18, AND ADIPONECTIN IN THE DEVELOPMENT OF TYPE 2 DIABETES IN FILIPINO AMERICANS

by

Julian L. Gallegos

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As members of the Dissertation Committee, we certify that we have read the dissertation prepared by Julian Gallegos, titled Hidden Risks: Relationship among VAT, IL-18, and Adiponectin in the Development of Type 2 Diabetes in Filipino Americans and recommend that it be accepted as fulfilling the dissertation requirement for the Degree of Doctor of Philosophy.

Leslie Ritter, PhD, RN, FAAN, FAHA — Date: 4/13/2018

Ruth Taylor-Piliae, PhD, RN, FAHA — Date: 4/13/2018

Matthew Gallek, PhD, RN, CNRN — Date: 4/13/2018

Thaddeus Pace, PhD — Date: 4/13/2018

Final approval and acceptance of this dissertation is contingent upon the candidate's submission of the final copies of the dissertation to the Graduate College.

I hereby certify that I have read this dissertation prepared under my direction and recommend that it be accepted as fulfilling the dissertation requirement.

Dissertation Director: Leslie Ritter, PhD, RN, FAAN, FAHA — Date: 4/13/2018

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SIGNED: Julian L. Gallegos

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ABSTRACT

Background and Aims: Filipino Americans (FAs) are at high risk for developing type 2 diabetes however little research exists as to why this occurs. There is some evidence that pro-inflammatory Interleukin-18 (IL-18) and anti-inflammatory (adiponectin) markers associated with visceral adipose tissue (VAT) may explain this risk but have not been examined in FAs without diabetes, with pre-diabetes and with type 2 diabetes. In these groups the aims were to 1) Quantify VAT, IL-18, and adiponectin and describe the values in relation to known reference ranges (RR) 2) Determine the relationships of VAT, IL-18, and adiponectin within the three groups 3) Determine if VAT, IL-18, and adiponectin were significantly different among the three groups.

Methods: FAs were recruited from healthcare and community centers in Solano County, California. VAT was measured using the InBody 570 © body impedance analyzer. Blood was obtained for HgA1c and plasma was used to quantify IL-18 and adiponectin with ELISA. Correlation coefficients were conducted to determine the association among VAT, IL-18 and adiponectin in the three groups. One-way ANOVAs were conducted for each variable to assess if there was significance among groups.

Results: Seventy-five participants were recruited (N=25 per group); 68% were female; mean age of 42 years. 57% of women but only 27 % of men had VAT values above the RR. The percentage of participants with an IL-18 above the RR used for this study was greater in the pre-diabetes (68%) and diabetes groups (64%) vs. the non-diabetes group (40%). Interestingly, 90-100% of the adiponectin values in both men and women were well above the RR. There was no correlation among the biomarkers within any group. VAT and IL-18 were not significantly

different among groups; however, adiponectin was significantly lower in the diabetes group vs. the non-diabetes group ($p<0.05$).

Significance: This is the first time VAT, IL-18 and adiponectin have been examined in FAs without diabetes, with pre-diabetes and with diabetes. While a young, active and mostly female sample may have confounded the biomarker findings, the results point toward the need for further study of the mechanisms of diabetes development and progression in FAs.

CHAPTER 1: INTRODUCTION

Type 2 diabetes affects 30.3 million people in the United States (US) or 9.4% of the population, with an estimated, economic cost of $174 billion annually (National Institute of Diabetes and Digestive and Kidney Diseases, 2018). Type 2 diabetes accounts for about 95% of diagnosed diabetes in adults and is a major cause of heart disease and stroke (CDC, 2014). The prevalence of type 2 diabetes has grown especially in native and migrant Asian populations in the United States (Cuasay, Lee, Orlander, Steffen-Batey, & Hanis, 2001). Asian populations are multiracial and have complex and varied mechanisms contributing to the development of type 2 diabetes (Ramachandran, Ching Wan Ma, & Snehalatha, 2010). According to Palaniappan et al. (2010) the first Filipinos immigrated to the United States (U.S.) in the 1760s with most settling in Louisiana, by the late 1800s more Filipinos came to the U.S. and settled in California as agricultural workers, then after World War II a dramatic increase of Filipino immigrants arriving in the USA occurred, with most settling in California.

The total population of Filipino Americans (FAs) living in the U.S. reported in 2010 was 2.7 million (Dalusung-Angosta & Gutierrez, 2013). Karter, Schillinger, Adams, Moffet, Liu, Adler, and Kanaya (2012) report that Pacific Islanders, South Asians, and Filipinos had the highest incidence and prevalence of diabetes in the U.S. compared to all other ethnicities. The U.S. Census (2010) reported the largest Asian population in California was comprised of Filipinos (64%). According to the California Diabetes Program [CDP] (2012), 1 in 7 adult Californians has diabetes and has the greatest number of new cases annually compared to other U.S. states. In California, 1 in 11 Asian Americans in 2010 was diagnosed with type 2 diabetes (CDP, 2012).

In the U.S., Filipino Americans (FAs) are the second largest Asian subgroup and according to several published studies have a higher risk for developing type 2 diabetes compared to other Asian subgroups (Cuasay et al., 2001). FAs have a higher rate of type 2 diabetes compared to Caucasians (Cuasay et al., 2001). There is scant research that explains the pathophysiological and physical factors of type 2 diabetes, specifically among FAs. This lack of research is due to studies universally combining individuals of Asian ancestry into a single group, which may result in masking any unique characteristics of FAs with type 2 diabetes (Palaniappan, Araneta, Assimes, Barrett-Connor, Carnethon, Criqui, Fung, Narayan, Patel, Taylor-Piliae, Wilson, & Wong, 2010).

In most populations, the development of type 2 diabetes has been thought to be associated with increased body weight, obesity, sedentary lifestyle, inflammation, and insulin resistance (CDC, 2014). Obesity is a major determinant of type 2 diabetes and is associated with several metabolic disturbances that impair many pathophysiological processes in the body that affect insulin sensitivity (Ramachandran, Ching Wan Ma, & Snehalatha, 2010). In the general population, Visceral Adipose Tissue (VAT) accounts for 20% of total fat in men and 5-8% in women (Freedland, 2004). Adipose tissue, which includes subcutaneous adipose tissue (SAT) and VAT is a major source of inflammatory cytokines. It is well documented that excess adipose tissue, is associated with a chronic inflammatory state (Spoto, Di Betta, Mattace-Raso, Sijbrands, Vilardi, Parlongo, Pizzini, Pisano, Vermi, Testa, Cutrupi, D'Arrigo, Lonardi, Tripepi, Cancarini, & Zoccali, 2014).

The location of adipose tissue such as SAT versus VAT is also considered relevant for the risk of developing type 2 diabetes (Spoto et al., 2014). It is suggested that in all ethnicities,

obesity contributes to the development of type 2 diabetes through the release of proinflammatory cytokines such as interleukin-18 (IL-18) and a decrease in proteins such as adiponectin (Paz-Pacheco, Lim-Abrahan, Sy, Jasul, Sison, & Laurel, 2009). Obesity impairs the action of insulin by changing secretion of cytokines, specifically of leptin and adiponectin, contributing to the presence of pro-inflammatory conditions (Ramachandran, Ching Wan Ma, & Snehalatha, 2010).

IL-18, a pro-inflammatory cytokine from the interleukin 1 family is present at a higher percentage in VAT compared to SAT (Spoto et al., 2014). Normal levels of IL-18 in the body produce a standard curve range between 78-5000 pg/mL (Thermofisher Scientific, 2017). IL-18 primarily originates from nonfat cells in adipose tissue and displays chemo attractant properties inducing mononuclear cell recruitment that cause inflammation (Bruun, Stallknecht, Helge, & Richelson, 2007). Because of an increased presence of IL-18 in the body, insulin sensitivity is altered by the lineal effects on insulin signaling thus affecting glucose homeostasis (Syed Ikmal, Zaman Huri, Vethakkan, & Wan Ahmad, 2013).

Conversely, adiponectin, a protein of adipose, is decreased as the levels of VAT increase (Shehzad, Waqas, Shehzad, & Lee, 2012). Normal values of adiponectin in the human body are dependent on sex and BMI and range from 4mcg-37mcg (Quest Diagnostics, 2018). As an insulin-sensitizing hormone, adiponectin is elevated in Type 1 diabetes but reduced in obese and insulin resistant models (Shehzad et al., 2012). Low levels of adiponectin contribute to a decrease in its ability to reduce circulating free fatty acids through oxidation and prevention of insulin resistance (Shehzad et al., 2012). The expression of low levels of adiponectin is a consequence of suppression by high levels of IL-18 in 3T3-Li adipocytes, a cell line derived from mouse 3T3 cells used in biological research on adipose tissue, via a signal transduction

pathway (Shehzad et al., 2012). This reduction of adiponectin is believed to contribute to the presence of type 2 diabetes.

Interestingly, and of primary interest to this dissertation study, is the fact that the relationships between adiposity and BMI inflammation and diabetes in FAs do not mirror those in Caucasian or other Asian populations (Cuasay, Lee, Orlander, Steffen-Batey, & Hanis, 2001). In stark contrast to other ethnicities, the relationships between obesity, adiposity, inflammation and type 2 diabetes are not straightforward in FAs. It has been documented that FAs have a higher prevalence of type 2 diabetes despite similar body size compared to other Asians and Caucasians (Araneta & Barrett-Connor, 2005). FAs tend to have a lower Body Mass Index compared to Caucasians, yet have higher rates of type 2 diabetes. In addition, it has been reported that when compared to other Asian individuals, FAs tend to have higher rates of metabolic syndrome which suggests that the triad of hypertension, hyperglycemia, and increase fat contribute to the eventual progression to type 2 diabetes (Palaniappan et al., 2010).

Additional studies demonstrate that while Asian populations have a lower body mass index (BMI) compared to other races, they have higher levels of leptin and lower levels of adiponectin, independent of obesity or intrabdominal fat distribution (Ramachandran, Ching Wan Ma, & Snehalatha, 2010). Further, a handful of studies suggest that in FAs, the amount of VAT and existing lower levels of adiponectin may contribute to the presence of type 2 diabetes (Straczkowski, Kowalska, Nikolajuk, Otziomek, Adamska, Karolczuk-Zarachowicz, & Gorska, 2007). It has been suggested that excess VAT may result in changes in the production of several pro-inflammatory markers, for example, IL-18 (Negi, Pankow, Fernstrom, Hoogeveen, Zhu, Couper, Schmidt, Duncan, & Ballantyne, 2012) and decrease in protective proteins such as

adiponectin (Araneta & Barrett-Connor, 2005). To date, little if any information is known about the nature of VAT, IL-18 and adiponectin as type 2 diabetes develops in FAs.

In summary, it is known that FAs are at high risk for developing type 2 diabetes (Cuasay, Lee, Orlander, Steffen-Batey, & Hanis, 2001). While some studies indicate that in fact, physiologic and physical factors that contribute to type 2 diabetes in FAs may be different than in other ethnicities, more research is needed to address the gap in knowledge related to mechanisms of type 2 diabetes in Filipino Americans. The results of this research may provide the needed information for the development of population-specific type 2 diabetes prevention and management programs in this US population.

Aims and Purpose

The overall purpose of this study was to examine VAT, IL-18, and adiponectin in Filipino Americans (FAs) with type 2 diabetes, FAs with pre-diabetes and FAs without diabetes. The specific aims were:

- Aim 1: Quantify VAT, IL-18, and adiponectin and describe the values in relation to known reference ranges.
- Aim 2: Determine the relationship of VAT, IL-18, and adiponectin within each of the three groups of FAs:
    - Hypothesis 1: VAT and Il-18 will be significantly increased and adiponectin will be significantly decreased in FAs with type 2 diabetes.

      ↑↑VAT + IL↑↑18 + adipo↓↓nectin = Type 2 Diabetes
    - Hypothesis 2: VAT will be significantly increased and IL-18 and adiponectin will be within normal range in FAs with pre-diabetes.

      ↑VAT + IL→18 + adipo→nectin = Pre-diabetes

- Hypothesis 3: VAT, IL-18, and adiponectin will be within normal range in FAs without diabetes.

  ↑VAT + IL-18 + adiponectin = No Diabetes

- Aim 3: Determine if VAT, IL-18, and adiponectin were significantly different among participants classified into non-diabetes, pre-diabetes, and diabetes groups:
  - Hypothesis 1: VAT will be significantly greater in type 2 diabetes than in pre-diabetes and no diabetes groups
  - Hypothesis 2: IL-18 will be significantly greater in type 2 diabetes than in pre-diabetes and no diabetes groups
  - Hypothesis 3: Adiponectin will be significantly lower in type 2 diabetes than in pre-diabetes and no diabetes groups

Theoretical Framework

The Theory of Unpleasant Symptoms (TOUS) was designed to integrate existing knowledge about a variety of symptoms, based on the premise that there are commonalities across different symptoms, which are not limited to one symptom (Lenz & Pugh, 2008; Lenz, Pugh, Milligan, & Gift 1997). This theory was developed inductively from the specific to the general and from concrete observations to theoretical ideas (Lenz & Pugh, 2008). The TOUS has three major components: the symptoms the individual is experiencing, the influencing factors that give rise to or affect the nature of the symptom experience, and the consequences of the symptom experience (Lenz et al., 1997).

Although symptoms are thought to be subjective in nature within the model, Kim, McGuire, Tulman, & Barsevick (2005) argue that the term symptom and by extension can include both self-reported symptoms and objective, observed signs. These observable signs are those that that patient cannot subjectively articulate but may understand has an overall impact on

their health and performance. The model asserts that symptoms can occur alone or in isolation but that more often, multiple symptoms are experienced simultaneously (Lenz et al., 1997). Two or more symptoms occurring at the same time are likely to catalyze each other (Lenz et al., 1997). In the TOUS, symptoms are conceptualized as manifesting multiple variable and measurable dimensions, varying in intensity or severity, the degree of associated distress, and timing and quality (Lenz & Pugh, 2008).

The TOUS has a great advantage in addressing the many factors that impact symptoms associated with type 2 diabetes; however, it is necessary to re-conceptualize the definitions of the model to fit the description of symptoms and performance that are proposed in this study. Through re-conceptualization of the model definitions, symptoms are no longer seen as subjective in nature, rather they become measurable through the presence of identifiable biomarkers such as levels of IL-18 and adiponectin within the individual's circulating blood. Furthermore, the definition of performance is no longer addressed at the macro level of individual functioning, rather at the microvascular level in relation to the functioning of the vessel's endothelium and presence of type 2 diabetes. All other definitions of antecedents such as physiological factors, psychological factors, situational factors, and descriptors such as intensity, timing, quality, and distress remain the same. By redefining the concepts of symptoms and performance, the hope is for a better understanding of how objective symptoms fit within the model and can explain the effects of performance in the micro level as it relates to functioning and performance (Figure 1).

Figure 1 (below) depicts the re-conceptualization of the TOUS framework as it relates to type 2 diabetes in FAs. The three boxes on the left indicate that physiologic, environmental, and

psychological factors are important to the FA with type 2 diabetes. Collectively these factors directly influence the physiologic elements specific to this study, indicated by the round discs, to include VAT level, adiponectin level, and IL-18 level. These physiologic factors, commonly known as symptoms in the TOUS, may not be obvious but often occur unsuspectingly within the body predisposing the individual for the clinical disease.

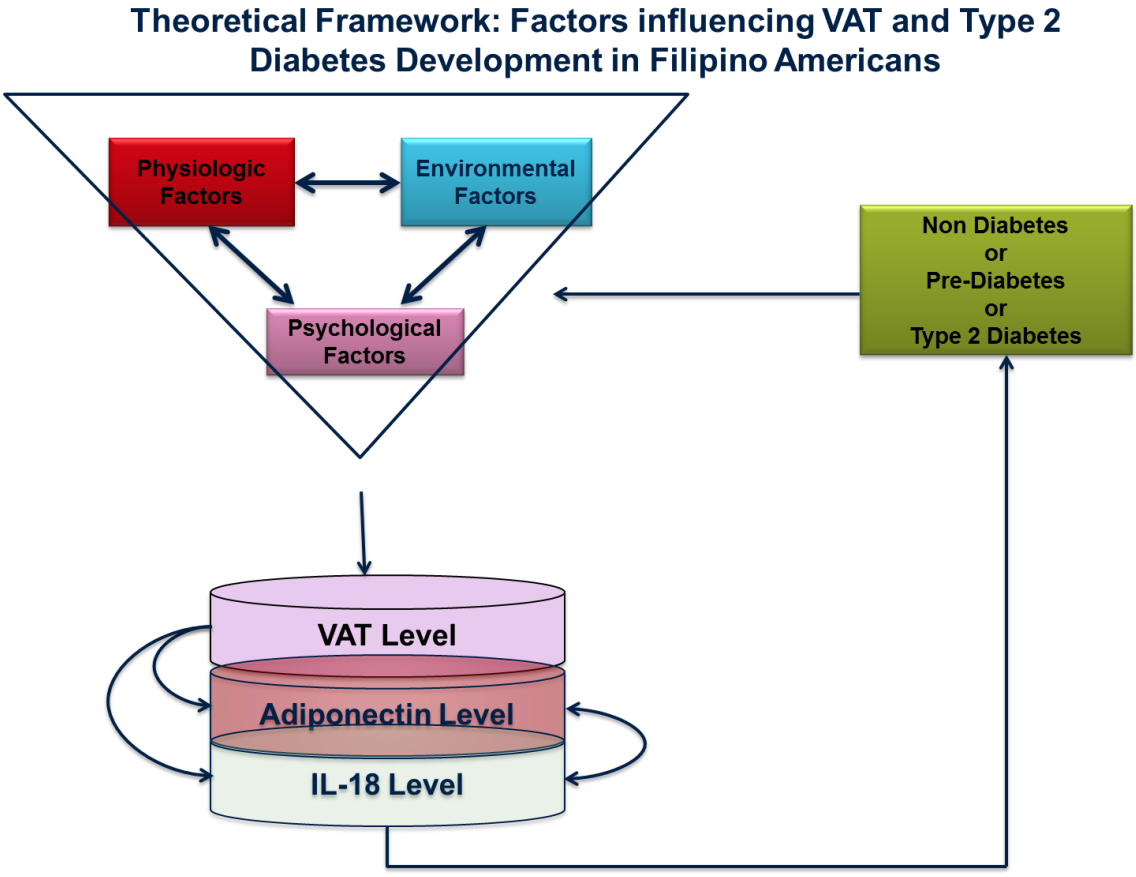

FIGURE 1. Modified from Theory of Unpleasant Symptoms (Lenz, E. R, Pugh, L.C., Milligan, R. A., Gift, A. G., & Suppe, F. (1997). The middle-range theory of unpleasant symptoms: An update. *Advances in Nursing Science, 19*(3), 17).

Two unidirectional arrows from the physiologic factors indicate VAT levels influence adiponectin levels and IL-18 levels. Conversely, the bidirectional arrow suggests that adiponectin levels and IL-18 levels potentially influence each other despite levels of VAT.

Medina-Torne, Araneta, Macera, Kern and Ji (2011) report that in FA women without diabetes, that adiponectin levels are half the concentration compared to Caucasian women; therefore, it is theorized that although VAT may decrease adiponectin and increase IL-18 in other ethnic populations, in FAs existing levels of adiponectin and possibly IL-18, have an influence on each other in a bi-directional manner.

Furthermore, the physiological factors of VAT levels, adiponectin levels, and IL-18 levels mutually influence the presence of non-diabetes, pre-diabetes, or type 2 diabetes. In the figure, the resulting clinical state of non-diabetes, pre-diabetes, or type 2 diabetes further shapes the existing/co-existing physiologic factors, environmental factors, and psychologic factors of the individual.

Significance to Nursing

Diabetes is a public health problem and therefore, besides clinical management, needs public health approaches (Albright, 2008). From the healthcare viewpoint, the prevention of diabetes and its complications is the ultimate aim (ADA, 1999). Type 2 diabetes is a progressive disease that results from defects in insulin action, insulin secretion, or both (Franz, 2007). The prevalence of the disease has become endemic resulting in numerous health-related complications. Many of the complications related to type 2 diabetes, including the disease itself, have been attributed to endothelial dysfunction because of a pro-inflammatory state (Tabit, Chung, Hamburg, & Vita, 2010).

Exercise along with a prescribed nutritional plan has been shown to be favorable interventions/measures in preventing type 2 diabetes. The role of nurses is particularly important in emphasizing the role of diet and behavioral changes in diabetes prevention and as a

complement to medical intervention (Lazarou, Pangiotakos, & Matalas, 2012). Despite these unique and complementary approaches to the prevention of type 2 diabetes the American Diabetes Association [ADA] (2008) cautions recommending the same approach to prevention for all individuals. The caution is particularly true regarding recommendations for supplementation of micronutrients that have been known to reduce pro-inflammatory markers (ADA, 2008).

Individualized plans for prevention and or treatment of type 2 diabetes are paramount to ensure success in ameliorating its effect not only individuals but within special populations such as with FAs.

Screening

Screening according to the ADA (2007) is used to identify asymptomatic individuals who are most likely to have diabetes. The ADA (2007) suggests that several key conditions must be met as it applies to screening. The key conditions referenced include the premise that the disease being screened is a significant health burden in that particular population, there is a recognizable preclinical stage of the disease that can be identified, reliable and valid tests exists that can aid in identifying the disease, treatment after early detection outweighs treatment after clinical symptoms present, and screening is ongoing rather than an isolated event (ADA, 2007).

It is already established that type 2 diabetes is a health burden for all populations within the U.S., but even more so in the FA population. Early identification of what is referred to as micro-symptoms, symptoms that the patient does not outwardly express or feel, occur within the body such as through increased VAT, IL-18, and decreased adiponectin. These symptoms are what are considered the preclinical stage of the disease. These “symptoms” can be easily assessed using reliable and valid methods of measurement and analysis in the clinical and

laboratory setting. By treating these “symptoms,” through methods such as exercise, micronutrient supplementation, and patient education, nurses are capable of preventing and or treating the disease.

CHAPTER 2: BACKGROUND AND LITERATURE REVIEW

The TOUS was the framework for the literature review discussing the factors influencing type 2 diabetes first followed by the concepts of interest in this study.

Physiological Factors Contributing to the Pathogenesis of Type 2 Diabetes

Diabetes occurs in an inflammatory state and has often been described as an inflammatory disease. According to Straczkowski, Kowalska, Nikolajuk, Otziomek, Adamska, Karolczuk-Zarachowicz, and Gorska (2007), there has been growing evidence that chronic inflammation leads to the development of insulin resistance and atherogenesis, contributing to the prevalence of type 2 diabetes. Wongeakin, Bhattarakosol, and Paturmraj (2014) describe the pathogenesis "Diabetes-induced hyperglycemia can disturb the vascular homeostasis that is characterized by decreased vascular blood perfusion, increased vascular permeability, and enhanced vascular inflammation leading to diabetic vascular complications" (p. 1).

Researchers refer to what Wongeakin et al (2014) describe as endothelial dysfunction. Because of endothelial dysfunction, micro and macrovascular complications are common especially in individuals affected by type 2 diabetes. Diabetes is further characterized by a chronic hyperglycemic state resulting in an increased production of reactive oxygen species (ROS), inactivating the production of nitric oxide (NO), and resulting in a decreased bioavailability of NO (Rungseesantivanon, Thenchaisri, Ruangvejvorachai, & Patumraj, 2010). In recent years, there has been an upsurge in research focused in ameliorating the effects of type 2 diabetes on the endothelium such as studying mechanisms to increase the bioavailability of NO and reduction of ROS through therapies focused on reducing inflammatory processes within the body.

Several studies have looked at the contribution of CRP, interleukin-6, interleukin-18, and adiponectin in several populations; however, contributing factors such as these have not been extensively researched in Filipino Americans.

Psychosocial Factors Contributing to Prevention of Type 2 Diabetes

Randomized controlled studies show that lifestyle interventions can be effective in preventing or delaying the onset of type 2 diabetes in high-risk individuals with impaired glycemic control (Unger & Moriarty, 2008). Because of inactivity, obesity has become commonplace amongst Americans leading to a greater incidence of decreased insulin sensitivity. Physical inactivity is an independent risk factor for type 2 diabetes (Hawley & Houmard, 2004). Lifestyle measures/interventions such as exercise have been researched and compared to its effect on insulin sensitivity and prevention/progression of type 2 diabetes.

One such study that compared exercise to insulin sensitivity, combined endurance and resistance exercise, was shown to contribute to improved glucose control (Segerstrom et al., 2010). Repeated bouts of contractile activity (i.e., exercise training) improve glucose tolerance and insulin action in individuals with insulin resistance, obesity, and patients with type 2 diabetes (Hawley & Houmard, 2004). The molecular mechanisms for enhanced glucose uptake and insulin sensitivity with exercise training are related to the increased expression and/or activity of key signaling proteins involved in skeletal muscle glucose metabolism (Zierath, 2002).

The Diabetes Prevention Program Trials found that the lifestyle intervention group (individuals who maintained a weight reduction of 7%, consumed a low-fat diet, and engaged in moderate-intensity exercise) reduced their risk of developing type 2 diabetes by 58%, across both genders and all ethnic groups (Unger & Moriarty, 2008). Conversely, Segerstrom et al. (2010)

argue the intensity of exercise rather than duration is related to improved insulin sensitivity. Overall, exercise training increases insulin sensitivity in individuals with prediabetes (Malin et al., 2012).

Despite the promising effects of exercise in increasing insulin sensitivity, it appears exercise alone is not sufficient. In the Diabetes Prevention Program Trials, it was discussed that combination exercise and a prescribed nutritional program were necessary to achieve significant results (Diabetes Prevention Program Research Group, 2002). Based on research indications the aims of nutritional interventions for the management and prevention of diabetes are to maintain normal blood glucose levels, healthy weight, normal lipid blood levels, and normal arterial pressure (Franz et al., 2008). Nutrition influences not only the outcome but also the gravity of diabetes (Berdanier, 2001).

Over the years, the diabetes literature has provided numerous recommendations for fulfilling the aims stated above. Researchers have also examined the effects of carbohydrates, fiber, fat, and micronutrients in the prevention of type 2 diabetes. It is generally recommended that carbohydrates should provide 45-65% of energy intake (Wheeler & Pi-Sunyer, 2008). Diets that are rich in carbohydrate have been observed to increase glucose and insulin levels by 12% and 9% respectively (Parillo et al,. 1992). Increased consumption of food of low glycemic index, according to metabolic studies and randomized trials, improves glucose levels (Thomas and Elliott, 2009). Despite this known fact, the overall quantity of intake of carbohydrates is of greater importance than the individual types of carbohydrates consumed (Franz et al., 2008).

Fiber is another important food source that has been proven to aid in the prevention of diabetes. To prevent type 2 diabetes, individuals are encouraged to achieve the recommendation

for dietary fiber of 14g fiber/1000 kcal (ADA, 2008). Fiber is known to improve overall glucose control and blood lipids (Slavin, 2008). According to the current evidence, soluble fiber has immediate results on glucose levels (Lazarou & Matalas, 2012). Interventions high in soluble fibers resulted in the decrease of insulin and plasma glucose, in pre-diabetics and type 2 diabetics (Aller et al, 2004).

Contrary to the use of fiber, diets high in fat have been related to insulin-resistance (Lovejoy, 1999). High intake of saturated fatty acids has been related to the increased risk of the development of diabetes as well as its progression (Vessby et al., 1994). Recommendations are that total fat should represent 25-35% and saturated fat less than 7% of total calories, while the main sources of fat should be monounsaturated fatty acids and fish oil (Franz, 2008). Although saturated fats can be detrimental, their replacement with mono-unsaturated fatty acids has been shown to aid in the prevention of type 2 diabetes. Once carbohydrates and saturated fatty acids are replaced with mono-unsaturated fatty acids, improvement of glucose tolerance and insulin sensitivity has been observed (Hu et al., 2001).

The final suggestion for prevention and or progression of type 2 diabetes relates to the use of micronutrients. As diabetes seems to be a state of increased oxidative stress, an increased intake of antioxidants is being deemed as an important an approach, supported by epidemiological evidence, showing a beneficial influence on type 2 diabetes with antioxidant intake (Bartlett & Esperjesi, 2008). However, a deficiency of specific minerals, such as potassium, magnesium, and possibly zinc and chromium, can aggravate intolerance to carbohydrates (Franz et al., 2002). Other research studies, although limited, examined the effects of Vitamins C, D, and E on glucose control and insulin sensitivity with mixed results reported.

Therefore, based on the available scientific evidence, the American Diabetes Association (ADA) states that supplementation with micronutrients does not provide any added benefit and cannot be recommended in the present stage (ADA, 2008).

Environmental Factors Contributing to Pathogenesis of Type 2 Diabetes

There are several known factors contributing to the pathogenesis of type 2 diabetes. Environmental factors have recently been mentioned in the healthcare literature and are not yet fully understood. Several environmental factors exist that researchers believe contribute to the pathogenesis of the disease. The environmental factors contributing to type 2 diabetes are described mainly as pollution. Pollution consists of exposure to noise and fine airborne particulate matter such as pesticides and herbicides. Traffic noise, when at least 10dB, overtime increases the risk for type 2 diabetes by 20-40% for individuals exposed (Kolb & Martin, 2017). An assumption can be made that individuals living in urban areas may have an increased risk of developing type 2 diabetes because of their greater exposure to noise.

Furthermore, chronic exposure to pesticides and herbicides induces insulin resistance through disturbed glucose metabolism (Murea, Ma, & Freedman, 2012). Murea, Ma, and Freedman (2012) discovered a significant dose-dependent relationship between exposure to pesticides and prevalence of diabetes. The authors mention there is a greater association in overweight individuals due to the lipophilic nature of pesticides (Murea, Ma, & Freedman, 2012). Murea, Ma, and Freedman (2012) suggest that the excess fat acts as a storage for the pesticides contributing to non-effective metabolism resulting in insulin resistance and as time passes to the development of type 2 diabetes.

Concepts

Type 2 Diabetes

According to the Mayo Clinic (2015) type 2 diabetes is a chronic condition is influenced by many factors that affect the way the body metabolizes glucose in which there is no cure but can be managed through diet, exercise, and medications. Much research has been done regarding type 2 diabetes but the exact pathophysiology of the disease is still unknown. Initially, type 2 diabetes was characterized as a disease caused by a defect in both insulin secretion and insulin action whose interaction leads to a progressive increase in plasma glucose levels (Scheen, 2003). Several studies throughout the last two decades have suggested that the development of type 2 diabetes is a result of the interaction between an individual's genetic makeup and their environment (Gerich, 1998). Several organs such as the pancreas, liver, skeletal muscle, adipose tissue, gut, and central nervous system are implicated in the pathophysiology of type 2 diabetes in which there is disrupted communication between them causing an alteration of glucose homeostasis and ultimately leading to the development of type 2 diabetes (Reaven, 1995).

Epidemiology of Type 2 Diabetes in Asian Population

Ramachandran, Ma, and Snehlatha (2010) describe Asia as the fastest growing site for the prevalence of diabetes. By 2030, all Asian countries combined will have over 113 million people affected by diabetes (Ramachandran, Ma, & Snehalatha, 2010). The increase in the prevalence of diabetes in Asian countries is associated with countries that are undergoing the most rapid economic growth and include countries such as China, India, Pakistan, Indonesia, Bangladesh, and the Philippines (Ramachandran, Ma, & Snehlatha, 2010). Studies in Asian countries have indicated that the prevalence of type 2 diabetes is high in both urban and rural

areas and more likely a consequence of impaired glucose tolerance (Ramachandran, Ma, & Snehlatha, 2010).

Surprisingly, not only are countries where Asians are the majority being affected by the rates of diabetes amongst the population but so are countries that have high rates of Asian immigrants. In the United States (US) Asians and Pacific Islanders comprised 5% of the total US population in 2010 (Karter, Schillinger, Adams, Moffet, Liu, Adler, & Kanaya, 2012). Of this population, Filipino Americans are the second largest population in the US with over 2.6 million individuals (Cuasay, Lee, Orlander, Steffen-Batey, & Hanis, 2001). The states with the largest percentage of FAs are California, Hawaii, and Nevada (Dalusung-Angosta & Gutierrez, 2013). Researchers in the US have suggested that Asians as a whole have a greater risk of type 2 diabetes compared to non-Hispanic whites (Karter et al., 2012).

Mechanisms of Type 2 Diabetes

Role of Adipose Tissue

Adipose tissue has become known as a complex, multicellular organ that has the ability to influence the function of several other organ systems through adipocytes, a primary cell type of adipose tissue (Rutkowski, Stern, & Scherer, 2015). There are several subtypes of adipocytes and are primarily classified by color from white to brown (Rutkowski et al., 2015). According to Rutkowski et al. (2015) white adipocytes represent the majority of cells in visceral and subcutaneous adipose depots within the body and are responsible for the release of adipokines such as adiponectin (Rutkwoski et al., 2015).

There is a unique relationship between the level of obesity and adipocyte growth, with adipose tissue undergoing molecular and cellular alterations thus causing systemic metabolism

changes (Greenberg & Obin, 2006). During the process, fasting whole-body free fatty acids and glycerol are released from adipocytes promoting insulin resistance (Greenberg & Obin, 2006). Small adipocytes in lean individuals promote metabolic homeostasis while enlarged adipocytes in obese individual's recruit macrophages and promote inflammation (Greenberg & Obin, 2006).

Inflammation in Type 2 Diabetes

Systemic inflammatory markers are risk factors for the development of type 2 diabetes with adipose tissue being a site of inflammation in the presence of obesity (Esser, Legrand-Poels, Piette, Scheen, & Paquot, 2014). In animal models of obesity and diabetes, there is an obvious infiltration of macrophages into adipose tissue, which is crucial for the production of adipose tissue-derived pro-inflammatory cytokines (Esser et al., 2014). Furthermore, the phenotypic, physiological, and functional attributes of subcutaneous fat versus visceral fat are evident with visceral adipose tissues containing more macrophages, T lymphocytes, and inflammatory molecules (Esser et al., 2014).

There are several biomarkers associated with inflammation in type 2 diabetes. According to Lyons and Basu (2012), biomarkers can often be direct endpoints of the disease or surrogate endpoints. In diabetes, biomarkers may indicate the presence or severity of hyperglycemia or the presence and severity of vascular complications of diabetes (Lyons & Basu, 2012). Furthermore, biomarkers allow identifying individuals with subclinical disease prior to the development of overt clinical disease (Lyons & Basu, 2012). As such, identification of these biomarkers may enable clinicians to apply preventative measures to prevent the disease from fully manifesting (Lyons & Basu, 2012).

Biomarkers that have been identified to help monitor diabetes and its associated micro- and macrovascular complications are classified as genomic, transcriptomic, proteomic, metabolites, markers of subclinical disease, and metabolic end-products (Lyons & Basu, 2012). In recent studies, substantial evidence suggests that interleukin 6 (IL-6) and C-reactive protein (CRP) are such biomarkers that may predict subclinical disease in diabetes, primarily inflammation (Pradhan, Manson, Rifai, Buring, & Ridaker, 2001).

Interleukin 6, a major proinflammatory cytokine, is produced in a variety of tissues, including activated leukocytes, adipocytes, and endothelial cells. C-reactive protein is the principal downstream mediator of the acute phase response and is primarily derived via IL-6–dependent hepatic biosynthesis (Pradhan et al., 2001). Furthermore, Hodgkin (2011) described a positive association between interleukin 6 (IL-6) and new-onset diabetes independent of obesity and presence of insulin resistance. In mice models of glucose metabolism, infusion of human recombinant IL-6 has been shown to induce gluconeogenesis, subsequent hyperglycemia, and compensatory hyperinsulinemia (Pradhan et al., 2001). These biomarkers appear to be promising in predicting underlying disease; however, other biomarkers have also been associated with inflammation in type 2 diabetes including adiponectin and interleukin-18.

Adiponectin

Adiponectin is a protein secreted by adipose tissue that has an insulin-sensitizing, antiatherogenic and anti-inflammatory effect and is a promising therapeutic target for the management of diabetes (Paz-Pacheco, Lim-Abraham, Sy, Jasul, Sison, & Laurel, 2009; Straczkowski et al., 2007). Adiponectin displays a vascular protective effect by inhibiting the expression of adhesion molecules on endothelial cells, the transformation of macrophages into

foam cells, and the proliferation of smooth muscle (Ouchi et al., 2001). Furthermore, several studies have suggested that adiponectin acts as an insulin sensitizer by mechanisms unknown (Bastard et al., 2006). It is also known that adiponectin is decreased in the presence of obesity, type 2 diabetes, and lean children of individuals' affected by type 2 diabetes despite its synthesis in adipose tissue (Straczkowski, 2007). The inverse relationship between IL-18 and adiponectin remains unknown (Staczkowski, 2007).

The Mayo Clinic Medical Laboratories (2017) published the following reference ranges for adiponectin measures in blood using body mass index with comparisons to sex.

TABLE 1. *Mayo Clinic Laboratories reference range for adiponectin.*

Body Mass Index	**Adiponectin mcg/mL**
Body Mass Index <25	Males 4-26; Females 5-37
Body Mass Index 25-30	Males 4-20; Females 5-28
Body Mass Index >30	Males 2-20; Females 4-22

Paz-Pacheco et al. (2009) state that investigations conducted in Filipinos living in San Diego suggest that decreased adiponectin levels may help explain ethnic differences in their propensity for diabetes. According to Medina-Torne, Arpanet, Madera, Kern, and Ji (2011), normoglycemic Filipino women have half the adiponectin concentration compared to non-Filipino women, independent of body size or level of insulin resistance. Conversely, when adiponectin was stratified according to gender, Filipino men had lower levels of adiponectin compared to Filipino women (Paz-Pacheco et al., 2009). Furthermore, lower levels of adiponectin were seen in Filipino women with higher BMI and waist circumference (Medina-Torne et al., 2011). As a subgroup of the Asian population, Filipinos with Type 2 diabetes have

significantly lower levels of adiponectin compared with normoglycemic non-Filipino individuals (Paz-Pacheco et al., 2009).

In a meta-analysis of prospective studies investigating the relationship between adiponectin and the development of type 2 diabetes the authors consistently reported that there was a lower risk of type 2 diabetes in individuals with higher levels of circulating adiponectin levels thus hypothesizing that adiponectin is preventative for progression of the type 2 diabetes (Li, Shin, Ding, & van Dam, 2009). According to Yamamotto, Matsushita, Nakagawa, Hayashi, Noda, and Mizoue (2014) mechanistic studies have indicated that adiponectin improves insulin sensitivity by stimulating glucose utilization and fatty acid oxidation in skeletal muscle and liver.

Interleukin-18

Straczkowski et al. (2007) suggest that interleukin-18 (IL-18) has a possible metabolic function that may contribute to type 2 diabetes as consequence of expression in adipocytes. IL-18 is a pro-inflammatory cytokine that acts similar to interleukin-1 within the body. IL-18 enhances T cell and natural killer cell maturation, in conjunction with the production of cytokines, chemokines and cell adhesion molecules (Troseid, Seljeflot, & Arnesen, 2010). Normal plasma values in healthy adults for IL-18 are 81.5-344 (R & D Systems Inc., 2018). In metabolic syndrome and type 2 diabetes, it has been reported via several studies that IL-18 is found in excess in individuals affected by these diseases (Troseid, Seljeflot, & Arnesent, 2010)

In studies mentioned by Straczkowski et al. (2007) IL-18 is present in large amounts in individuals affected by obesity, polycystic ovary syndrome, metabolic syndrome, and type 2 diabetes. From these studies, it was proposed that elevated IL-18 levels were a predictor of type 2 diabetes independent of the presence of Interleukin-6 and TNF-alpha (Straczkowski et al.,

2007). The link between IL-18 and insulin resistance has a systematic basis involving the activation of c-Jun N-terminal kinase 1(JNK1)/signal transducer and activator of transcription (STAT) kinase pathway and phosphorylation of the serine/threonine IRS1 (McKie, Reid, Mistry, DeWall, Abberley, Ambery, & Gil-Extremera, 2016).

Two prospective studies, report baseline IL-18 levels to be predictive of new-onset type 2 diabetes even when controlling for multiple risk factors and other inflammatory markers and adipokines (Hivert, Sun, Shrader, Mantzoros, Meigs, & Hu, 2009; Thorand, Kold, Baumert, Koenig, Chambles, Meisinger, Illig, Martin & Herder, 2005). A decrease in IL-18 was also observed to be an independent predictor of improvement in insulin sensitivity in patients treated with rosiglitazone or metformin (Kim, Kang, Kim, Kim, Ahn, Cha, Nam, Chung, Lee, Nam, & Lee, 2007). Furthermore, one study shows that lifestyle modification has the ability to modify IL-18 levels, with exercise interventions reducing plasma IL-18 levels in either low-level or extreme exercise conditions including in patients with type 2 diabetes (Kadoglou, Perrea, Iliadis, Angelopoulou, Liapis & Alevizos, 2007).

It is hypothesized that IL-18 may be the inhibiting factor for adiponectin secretion from adipose contributing to decreased levels of adiponectin in obese individuals (Straczkowski et al., 2007). Conversely, in a study by Harms, Yarde, Guinn, Lorenzo-Arteaga, Corley, Cabrera and Servetnick (2015) it was shown that in non-obese diabetic mice, pancreatic beta-cells can produce IL-18 resulting in destructive insulitis because of an enhanced expression of IL-18. This leads to the theory that truncal or visceral adiposity in Filipino Americans may lead to an increase in presence of IL-18 thus contributing to their prevalence of type 2 diabetes.

Traditional Measurement of VAT

Adipose tissue is distributed in different proportions throughout the body and is traditionally compartmentalized into two different types of fat to include subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT) (Shuster, Patlas, Pinthus, & Mourtzakis, 2012). VAT has been known to release several bioactive molecules and hormones resulting in potentially adverse pathogenesis such in the case of type 2 diabetes (Shuster et al., 2012). Both SAT and VAT have several methods of assessment in live individuals. These methods include indirect measures that are the most clinically expedient and quickly performed without extensive technical training. These indirect measures include anthropometric techniques, bioelectrical impedance analysis (BIA), dual energy x-ray absorptiometry and air displacement plethysmography (DXA).

These indirect methods for VAT measurement all have their advantages and disadvantages. Anthropometric techniques primarily use body mass index (BMI) to assess levels of fat. This method tends to be the easiest technique for a clinician to use in an office to measure overall body fat. BMI is calculated using a person's weight in kilograms divided by the square of height in meters. According to the World Health Organization, a BMI greater than 25kg m^2 is classified as obese (Shuster et al., 2012). Despite the ease of assessing BMI, the measure fails to distinguish the difference between SAT and VAT.

Another accessible method for assessing body fat is the use of BIA. BIA measures fat by sending a low level, imperceptible electrical current through the body (Shuster et al., 2012). The flow of the current is affected by the amount of water in the body and the device measures how this signal is impeded through different types of tissue (Shuster et al., 2012). As BIA determines

the resistance to flow of the current as it passes through the body, it provides estimates of body water from which body fat is calculated using selected equations (Shuster et al, 2012). Shuster et al. (2012) explain that despite the ease of use of BIA, the method lacks specificity consequently having to use prediction equations to assess the differences in resistance attributed to lean and fat components of the body.

The most precise and rapid assessment of VAT using an indirect approach is that of the DXA. DXA is based on pressure-volume relationships to estimate volume and density (Shuster et al., 2012). Shuster et al. (2012) describe DXA as measuring the attenuation of two "energies" emitted to help distinguish fat, lean, and bone mineral in content. In a recent study conducted by Micklesfield, Goedecke, Punyanitya, Wilson, and Kelly (2012) explained that DXA-VAT measurement performed as well as a clinical read of VAT from a computed tomography (CT) scan. Furthermore, DXA accurately and precisely measures the whole body and regional distribution of fat and lean tissue and the x-ray radiation associated with a DXA scan is very low (equivalent to about 1 day of natural background radiation) and the cost is relatively modest (Micklesfield et al, 2012). Because of the ease of use and accuracy of DXA, this has become the gold standard alongside CT and magnetic resonance imaging in assisting clinicians in assessing VAT.

Body Mass Index

In Asian subgroups, especially Filipinos, the average Body Mass Index (BMI) was below the threshold for obesity based on the National Heart, Lung, and Blood Institute standards (Karter, Schillinger, Adams, Moffet, Liu, Adler, & Kanaya, 2012). Because of identifying the low BMI in Filipinos affected by type 2 diabetes, compared to national standards, the World

Health Organization suggested lowering BMI standards for Asian populations (Karter et al., 2012). By lowering the BMI standards, it is suggested that clinicians can better identify Asian individuals at risk for type 2 diabetes helping provide prevention and treatment measures, and in turn reducing the risk for morbidity and mortality (Hsu et al., 2015). Diagnostic considerations for type 2 diabetes are important in Asian Americans because they often do not present with obvious signs of obesity and may be underdiagnosed or go undiagnosed (Hsu, Boyko, Fujimoto, Kanaya, Karmally, Karter, King, Look, Maskarinec, Misra, Tavake-Pasi, & Arakaki, 2012).

The development of type 2 diabetes has been thought to be closely associated with increased body weight, obesity, sedentary lifestyles, inflammation, and insulin resistance; however, the relationship between excess adiposity and diabetes is not straightforward in Asian Americans (Hsu et al, 2012). The Japanese American Community Diabetes Study demonstrated the importance of visceral fat as a risk factor for cardiometabolic outcomes (Hsu et al, 2012). In a cross-sectional comparison of Filipino women in California with an adjusted BMI of less than 23kg/m2, they had a similar volume of intra-abdominal fat when compared with Caucasian and African American women with a BMI less than 25kg/m2 (Hsu et al, 2012). It is suggested that these two studies indicate that individuals of Asian ethnicity have a greater propensity for deposition of fat in the visceral depot.

Body Fat Distribution

It is known that increased body weight is a risk for type 2 diabetes; however, it is suggested that the relationship between body weight and type 2 diabetes is more than likely a consequence of the quantity and distribution of body fat (Hsu et al., 2015). It is thought that visceral adipose tissue (VAT) is a source of proinflammatory cytokines especially in Filipino

women who have been shown to have a higher proportion of VAT compared to non-Filipino women with the same level of waist circumference (McDade, Rutherford, Adair, & Kuzawa, 2008). Arenata, Wingard, and Barrett-Connor (2002) revealed Filipinas had larger waist circumference, waist to height ratio, and percentage of truncal fat; however, were shorter and weighed less than their Caucasian counterparts. Arenata et al. (2002) also discovered that Filipinas had more VAT after adjusting for total body fat, but truncal and waist girth did not differ by ethnicity after adjustment for BMI.

Furthermore, the study by Arenata et al. (2002) proposed Filipina ethnicity, age, higher percent of truncal fat, use of anti-hypertensives, and dyslipidemia were independently associated with diabetes. The propensity for the development of visceral fat is consistent with higher risk of diabetes; however, in Filipinas, there may be diabetogenic factors that occur even in non-obese individuals (Arenata et al., 2002).

It is known that Asians develop more visceral adiposity versus peripheral adiposity and distribute it differently thus contributing to insulin resistance and type 2 diabetes (Hsu et al., 2015). Hsu et al. (2015) suggest that Asians of both sexes have a higher percentage of body fat at any given BMI level compared to non-Asian counterparts increasing their prevalence of diabetes. Interesting factors such as levels of interleukin-18 and adiponectin have been suggested to contribute to Type 2 diabetes but not researched well in Filipino Americans.

CHAPTER 3: METHODOLOGY

Design

The proposed study was non-experimental and utilized a descriptive comparative design.

Setting

The setting for this study occurred in several community clinics and centers in Northern California.

Sample

The participants consisted of a convenience sample of FA adults ages 18-100+. Filipino American participants were recruited from community clinics, social center, churches, and other locations within Solano County using a snowball effect.

The self-reported inclusion criteria for this study included the following:

1. Self- identified FAs
2. Adults 18 or older who are English speaking

The self-reported exclusion criteria for this study included the following:

1. FAs with Type 1 diabetes
2. FAs who are pregnant
3. FAs with active infections
4. FAs with recent infection within the last 3 months
5. FAs currently taking corticosteroids

Recruitment Strategy

The strategy for recruitment of Filipino Americans living in Solano County California was accomplished via flyer/handouts/posters and brief talks at community centers, churches,

schools and clinics/hospitals. The flyer contained the contact information for the investigator and included the investigator's phone number and University of Arizona email. The flyer asked the prospective participant to contact the investigator to set up a date, time, and location to obtain the prospective participant's information/measurements for the study if they choose to participate.

The primary locations for participation in the study occurred at Touro University California School of Nursing Building (Vallejo, California), North Bay Medical Center Campus (Fairfield, California), and Vaca Valley Hospital Campus (Vacaville, California). When the prospective study participant decided he/she was willing to participate, 40-60 minute appointments were made at the location of their choosing based on the flyer. Appointments with the participants were made on a first come first served basis. During this appointment, consent was reviewed and signed if the individual chose to participate.

Sample Size

Power calculations for one-way independent ANOVAs were performed using power analysis and sample size using G*Power Version 3.1.7 (computer software). The power analysis for one-way ANOVA with three groups was conducted in G*Power to determine a sufficient sample size using an alpha of 0.05, and a power of 0.80, and an effect size of 0.5 Based on the aforementioned assumptions, the desired sample size for each group is 25 participants for each group for a power of 0.9743.

Study Procedures

At the time of study enrollment, the investigator obtained a complete medical and personal health history and baseline physiologic variables (height, weight, waist circumference, BMI, VAT). All subjects had a hemoglobin A1C serum sample obtained and stratified into one

group defined as non-diabetes, pre-diabetes, or diabetes group. The stratification of subjects was done using criteria as set forth by the American Diabetes Association Standards of medical care in diabetes (2016):

- Non-diabetes was classified by a HgBA1c of: $\leq$ 5.6%
- Pre-diabetes was classified by a HgbA1c of: 5.7-6.4%
- Diabetes was classified by a HgBA1c of: $\geq$ 6.5%

In addition, the participants were assessed for baseline inflammatory markers IL-18 and adiponectin.

Medical and Personal History Questionnaire

A demographic and medical questionnaire was administered prior to obtaining any measurements or blood samples (Appendix A). A data tool designed specifically for this study to collect demographic, personal history, familial and individual health history was developed.

Physiological Measures

Weight

Weight was obtained on each subject without shoes and measured in kilograms using the InBody® 570 to the nearest 0.1 kilograms (Kg).

Height

Height was measured to the nearest centimeter using a Hopkins Road Rod® with participant's shoes off and the results documented to the nearest centimeter.

Waist Circumference

Waist circumference was obtained using a Seca 201 Girth Measuring Tape® and results reported to the nearest centimeter. The World Health Organization (2008) protocol for waist

measurement was used for this study. The protocol for measurement was be conducted as follows:

1. The subject was measured while standing upright, with arms relaxed at the side, feet evenly spread apart and body weight evenly distributed.
2. The waist circumference was measured at the end of several consecutive natural breaths, at a level parallel to the floor, the midpoint between the top of the iliac crest and the lower margin of the last palpable rib in the mid-axillary line.

Body Mass Index (BMI)

BMI was calculated according to National Heart, Lung, and Blood Institute (2018) methods as weight in kilograms divided by height in meters squared.

Visceral Adipose Tissue (VAT)

VAT was indirectly analyzed using the InBody® 570 Body Composition Analyzer. The body composition analyzer measured how much fat and muscle the participant had but was also measured total body water divided into intracellular water and extracellular water. The method for body composition measurement by the device was completed through impedance. The device does not use statistical data or empirical equations to predict body composition.

To analyze body composition the device used safe, low-level currents sent through hand and foot electrodes. The impedance currents were measured with resulting body composition results provided. To measure body composition, the participant followed the steps below:

1. The participant was asked to remove shoes and socks and asked to stand on the unit. The heels were aligned with the rear round electrodes, and placed the rest of their feet on sole electrodes.

2. The participant was then asked to stand still for the unit to capture weight in kilograms.
3. Once the weight had been computed, a random ID was entered along with age, height, and gender into the device.
4. As soon as all information was input into the device, the patient was asked to grab the hand electrodes. The participant placed their thumbs on the top oval electrodes and wrapped their fingers around it.
5. The participant was then asked to extend their arms downward and away from their torso and allowed 45 seconds for the device to analyze body composition.

FIGURE 2. Picture of InBody® 570

Blood Collection

The blood sampling procedure included the collection of blood from a vein in an upper extremity. An easily visualized vein was selected after placing a tourniquet around the arm, inspecting and palpating the vein, and sterilizing the site with isopropyl alcohol. The needle was inserted into the skin with the bevel upward, smoothly and quickly into the vein to avoid risk for

hemolysis of the sample. Immediately after insertion of the needle, the tourniquet was released. Vacuum tubes were used for blood collection. Once complete, the needle was withdrawn and pressure held to the site with a Band-Aid or simple pressure dressing applied over the area. Before leaving the examination site, the tubes were properly labeled with the participant's identification code.

Hemoglobin A1C Analysis

Hemoglobin A1c (HbA1c) was analyzed using a fasting sample of a drop of whole blood collected and analyzed using a portable HbA1c device and results were provided within less than 10 minutes. The device is a point-of-care immunoassay analyzer manufactured by Siemens. The name of the product is DCA Vantage Analyzer. The analyzer performs quantitative tests of HbA1c (whole blood): Range: 2.5% to 14% (4mmol/mol to 130mmol/mol). The device uses self-contained immunoassay cartridges and is single use.

The analyzer uses a monoclonal antibody agglutination reaction test method to assess HbA1c. The required sample volume is at least 1 microliter of whole blood. There is no pretreatment required for the sample. According to manufacturer specifications, time to results takes 6 minutes or less. Calibration of the device is done via a Lot-specific calibration card that provides automatic calibration with every cartridge. According to manufacturer recommendations for quality control, the machine provides automatic reminders for quality controls (QC). When QC reminders occurred during the timeframe of testing of the sample QC was be done according to prompts and manufacturer guidelines by the researcher.

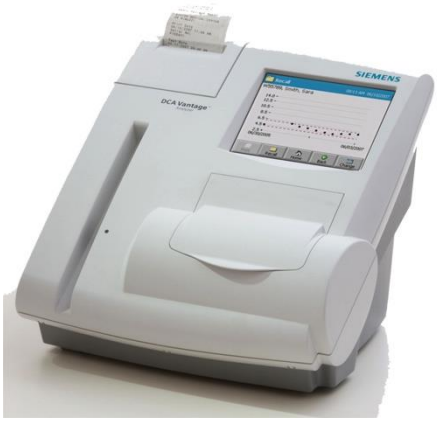

FIGURE 3. Picture of Siemens DCA Vantage™

Biomarker Analysis

Adiponectin

Adiponectin was analyzed by first obtaining a fasting sample of at least 1mL of whole blood collected into an Ethylenediaminetetraactic acid (EDTA) red top tube. The tube was centrifuged at for 10 minutes at 1,000 x g within 30 minutes of collection and stored at -20° C until they were shipped to the laboratory of Dr. Thaddeus Pace at the University of Arizona for analysis via enzyme-linked immunosorbent assay (ELISA). Plasma concentrations of adiponectin were measured using ELISA from R & D Systems (Minneapolis, MN) following manufacturer instructions. Intra- and inter-assay coefficients of variation for the adiponectin ELISAs were 5.9 and 16.0%, respectively.

IL-18

Interleukin-18 was analyzed by first obtaining a fasting sample of at least 3mL of whole blood collected into an EDTA red top/gold tube. The tube was centrifuged at for 10 minutes at 1,000 x g within 30 minutes of collection and stored at -20° C until they were shipped to the laboratory of Dr. Thaddeus Pace at the University of Arizona for analysis via ELISA. Plasma IL-

18 concentrations were determined using enzyme-linked immunosorbent assay (ELISA) from R & D Systems (Minneapolis, MN) according to manufacturer instructions. Intra- and inter-assay coefficients of variation for the IL-18 ELISAs were 2.4 and 3.7%, respectively.

Data Analysis and Management

Data Analysis Plan

Descriptive statistics for all study variables was generated for the overall group and then for each individual inflammatory biomarker. Data between groups were expressed as means and standard deviation (SD) where appropriate. Means and SD was determined for each inflammatory marker. Values for each inflammatory marker was compared between groups along with diabetes characteristics (non-diabetes, pre-diabetes, diabetes) using a R, considering a p-value < 0.05 as significant.

- For Aim 1, to quantify VAT, IL-18, and adiponectin and describe the values in relation to known reference ranges, the percentage of men, women, and total group sample were calculated for VAT, IL-18, and by non-diabetes, pre-diabetes, and diabetes groups.
- For Aim 2, to determine relationships between VAT, IL-18, and adiponectin, Pearson's Correlations were calculated separately for participants in the non-diabetes, pre-diabetes, diabetes groups.
- For Aim 3, to determine if VAT, IL-18, and adiponectin were significantly different among groups, one-way ANOVAs were used.

Protection of Human Subjects

Human Involvement and Characteristics

The study was approved by the University of Arizona Institutional Review Board as such to conform to the rules and regulations of human subject protection.

Security of materials. To protect the privacy of participants, each participant was assigned an accession number. Confidentiality was maintained by coding all specimens and questionnaire results with the participant's identification number. All data from this study was kept in a 1) paper notebook and 2) a computer spreadsheet in the investigator's locked office. The computer was password protected. In the notebook and the computer spreadsheet, only numbers were used to identify patients.

Only the principal investigator (PI) had access to the list of participant initials and numbers, which were kept in a separate locked file in the investigator's office (located at Touro University California, School of Nursing, Vallejo, CA). All identifying information was shredded and destroyed at the completion of the study.

Only qualified research personnel had access to the database containing the participant's information. All of the participant's data entered into statistical analyses and publication reports only referred to individuals by number rather than name. This procedure maintained confidentiality. Only the primary investigator was aware of participant's identity. All blood samples were drawn by the PI. Participants were advised that they were free to stop the study procedures and exit the study at any time without penalty.

Potential Risks

The risk of venipuncture was minimally invasive. There was a possibility of minor discomfort and risk of mild bruising during venipuncture. Bruises from venipuncture would likely heal in several days. Discomfort associated with the venipuncture procedure included needle insertion, blood withdrawal, and needle withdrawal. There was a potential for bleeding to occur at the puncture site but was alleviated with direct pressure and a Band-Aid if it did occur.

Adequacy of Protection Against Risks

All laboratory tests were conducted under the supervision of trained personnel. Since the tests were not inherently hazardous, the only identified hazard more than likely to have occurred would be the result of impaired participant confidence or sudden unwillingness to complete the test. To avoid such hazards, study personnel thoroughly explained all tests to the potential participant before the participant is offered the consent form to sign.

Handling of Blood Samples

All blood component and materials were handled as potentially hazardous with universal precautions followed per established guidelines by the Center for Disease Control and Prevention and Occupational Safety and Health Standards (Occupational Safety and Health Administration).

Recruitment and Informed Consent

The strategy for recruitment of patients was accomplished via handouts/flyers/posters in the community clinic. A phone number for the investigator was provided for contact. An informed consent form was made available for participants. The information provided to each participant included the purpose of the study and routine and potential risks associated with the study procedures. All risks, costs, and benefits were discussed. The participant was assured of

their right to withdraw at any time without prejudice to their care. The participant was assured of confidentiality in maintaining records and reporting of results.

Protection Against Risk

Prior to beginning this study, the investigator obtained approval from the University of Arizona Institutional Review Boards. All materials including questionnaires and consent forms were reviewed and approved by the Institutional Review Board. Data collection will be for the sole purpose of the proposed study. No adverse effects of the participants occurred during the study, therefore, nothing was reported to the University of Arizona Institutional Review Board.

Potential Benefits for the Participants

From this study, the participant could gain personal satisfaction in contributing to knowledge leading to improved, ethnic-specific means for understanding type 2 diabetes. In addition, participants received information regarding their hemoglobin A1C, adiponectin, and IL-18 and VAT levels, if requested. There was no direct personal benefit to the participant for being in this study.

Inclusion of Women, Children, and Minorities

The entire sample of participants was from self- identified FAs of both genders. The investigator selected an under representative research population due to the high incidence of type 2 diabetes within the population. Children were not included in this study as the focus will be on FA adults. Enrollment of study participants was evaluated monthly. During the course of the study, the sample did not diverge from the planned enrollment, and alternative strategies were not explored.

Summary

This study tested levels of adiponectin and IL-18 in individuals who self-identified as Filipino American who fit into three categories (non-diabetes, pre-diabetes, and diabetes); furthermore, these levels were compared to levels of visceral fat and other standard anthropometric measures. The process for obtaining these measures was minimally invasive to the participants and required only a small sample of whole blood for analysis. In the clinical setting, levels of adiponectin and IL-18 are not routinely obtained; however, it was hypothesized that as VAT increased the levels of adiponectin and IL-18 would also be affected. This study contributed to the body of knowledge regarding the pathogenesis of type 2 diabetes as applicable to Filipino Americans. No previous studies have examined the possible correlation between VAT and these two biomarkers in Filipino Americans.

CHAPTER 4: RESULTS

This chapter presents the results of the study aims including a description of the study population. The purpose of this study was to determine if adiponectin and IL-18 were associated with VAT in adult Filipino Americans in those with no diabetes, with pre-diabetes or with diabetes.

Description of Sample Participants

Participants were recruited from four main locations within Solano County. These sites included two outpatient clinics, one academic site, and one community site. The two outpatient clinics are part of a community healthcare system, the academic site was at a local university, and the community site was part of a care center for adult clients. From these sites, initial participants were recruited through group talks and using flyers for recruitment. An indirect method for recruitment occurred when the community healthcare system printed a story about the study in their biweekly internal employee newsletter. The majority of participants were recruited by word of mouth and snowball sampling.

Demographics of the participants are described in Table 2. A total of 75 adult FAs participated in the study. The mean age of all participants was 41.6 years (SD = 13.51). By group, the mean age was 35.96 years (SD = 0.31) for those classified as non-diabetes, 40.12 years (SD = 12.89) for those classified as pre-diabetes, and 48.72 years (SD = 14.22) for those classified as having diabetes. Overall, 51/75 (68%) of the participants were female. By group, there were 20 (80%) females in the non-diabetes group, 17 (68%) in the pre-diabetes group and 14 (56%) in the diabetes group.

BMI (kg/m^2) by group, the mean was 25.37 (SD = 5.23) in the non-diabetes group, 27.69 (5.36) in the pre-diabetes group, and 28.62 (SD = 5.78) in the diabetes group. Waist circumference (cm) was 86.04 (SD = 15.2) in the non-diabetes group, 95.64 (SD = 10.89) in the pre-diabetes group, and 96.32 (SD = 11.77) in the diabetes group. Furthermore, height (inches) was 62.84 (SD = 2.56) in the non-diabetes group, 64.60 (SD = 3.86) in the pre-diabetes group, and 63.20 (SD = 3.61) in the diabetes group.

Self-reported exercise and range of minutes of exercise weekly by each group were similar among groups; 21 (84%) participants in the non-diabetes group participated in 30-420 minutes of exercise weekly, 16 (64%) participants in the pre-diabetes group participated in 10-420 minutes of exercise weekly, 18 (72%) participants in the diabetes group participated in 20-300 minutes of exercise weekly. Only 33 (44%) participants reported whether they ate out during the week. Of those who self-reported eating out more than two times per week were 12 (48%) participants in both the non-diabetes and pre-diabetes group while only 9 (36%) participants responded they eat out more than two times per week in the diabetes group.

The most common comorbidities reported in all three groups were hypertension, hyperlipidemia, and depression. In the non-diabetes group, 7 (28%) participants reported having hypertension while in the pre-diabetes group only one (4%) reported having hypertension; furthermore, in the diabetes group, 12 (48%) participants reported having hypertension. Six (24%) participants in the non-diabetes group, none in the pre-diabetes group, and 8 (32%) in the diabetes group reported hyperlipidemia. In all groups, 2 (2%) participants per group reported having depression.

The most common diseases reported in the participant's family history, which included parents, siblings, grandparents, and children, included hypertension, type 2 diabetes, and hyperlipidemia. By groups, in the non-diabetes group 20 (80%) participants reported hypertension, 12 (48%) type 2 diabetes, and 2 (8%) hyperlipidemia; in the pre-diabetes group 15 (60%) participants reported hypertension, 9 (36%) type 2 diabetes, and 1 (4%) hyperlipidemia; in the diabetes group 14 (56%) reported hypertension, 14 (56%) type 2 diabetes, and 5 (20%) hyperlipidemia.

TABLE 2. *Demographics of participants.*

	Non-Diabetes (N = 25)	***Pre-Diabetes (N = 25)***	***Diabetes (N = 25)***
Age (M/SD)	35.96 (10.31)	40.12 (12.89)	48.72 (14.22)
Age Range (years)	19-59	21-64	23-71
Gender (female)	N = 20 (80%)	N = 17 (68%)	N = 14 (56%)
BMI (kg/m^2)	25.37 (5.23)	27.69 (5.36)	28.62 (5.78)
Waist Circumference (cm)	86.04 (15.2)	95.64 (10.89)	96.32 (11.77)
Height (inches)	62.84 (2.56)	64.60 (3.86)	63.20 (3.61)
Self Report Exercise	N = 21(84%)	N = 16 (64%)	N= 18 (72%)
Exercise Range (minutes)/week	30-420	10-420	20-300
Eats out > 2x/week	N = 12 (48%)	N= 12 (48%)	N = 9 (36%)
Self-reported Medical History			
Hypertension			
Hyperlipidemia	N = 7 (28%)	N = 1 (4%)	N = 12 (56%)
Depression	N = 6 (24%)	N = 0	N = 8 (32%)
	N = 2 (8%)	N = 2 (8%)	N = 2 (8%)
Family History			
Hypertension	N = 20 (80%)	N = 15 (60%)	N = 14 (88%)
Type 2 DM	N = 12 (56%)	N = 9 (36%)	N = 14 (88%)
Hyperlipidemia	N= 2 (8%)	N = 1 (4%)	N = 5 (20%)
Depression	N = 2 (8%)	N = 2 (8%)	N = 2 (8%)

In addition to VAT, the variable of primary interest to this study, the InBody® 570 provided measurements of participants in computation of VAT (Table 3.). These measures included body mass index (BMI), body fat mass (BFM), and lean body mass (LBM). BMI is defined as a person's weight in kilograms divided by square of height in meters and is used as a

screening tool but not a diagnostic in determining an individual's body fatness (CDC, 2016). Interestingly, BMI did not appear different among groups.

Further, InBody® USA (2018) defines BFM as the total mass of fat divided by total body mass multiplied by 100. The BFM includes fat that is essential body fat and storage body fat (InBody® USA, 2018). Similar to VAT, BFM appeared to increase in the pre-diabetes and diabetes groups compared to non-diabetes group. Additionally, LBM is the total weight of the body without the weight due to fat (InBody® USA, 2018). Surprisingly, when compared to VAT, as VAT increased in the non-diabetes and pre-diabetes groups the LBM remained almost unchanged but in the diabetes group LBM increased.

TABLE 3. *VAT to body mass index, body fat mass, and lean body mass according to DM status.*

	Non-Diabetes, N=25 (M/SD)	***Pre-Diabetes, N=25 (M/SD)***	***Diabetes, N-25 (M/SD)***
VAT (cm^2)	78.0 (43.6)	109.2 (46.8)	108.8 (57.2)
Body Mass Index (kg/m^2)	25.37 (5.23)	27.69 (5.36)	28.62 (5.78)
Body Fat Mass (kg)	19.25 (8.97)	25.28 (10.71)	25.37 (12.26)
Lean Body Mass (kg)	41.6 (11.82)	41.15 (16.15)	47.61 (10.97)

M = Mean; SD = Standard Deviation

Aim 1: Results

Aim 1: Quantify VAT, IL-18, and Adiponectin and describe the values in relation to known reference ranges. The standard deviations in each of the biomarkers were large, making any comparisons to normal values difficult. Therefore, an additional analysis of the biomarkers was performed and presented as the percentage of the biomarkers that fell within or above the known reference range was calculated for each group, separated by gender and total group sample (Table 4.).

Interestingly, for VAT in the non-diabetes group, 80% of the men but only 20% of the women fell *within* known reference range. When looking across groups for those who fell *above*

the known reference range, it was notable that the percentages above normal for men increased from 20% in non-diabetes to 50% in pre-diabetes, but fell to 27% in the diabetes group. In contrast, the percentages of VAT above normal values in women increased from 25% in the non-diabetes group, to 53% in pre-diabetes group and remained at a high value of 57% in diabetes group. Of further interest is that in the diabetes group 57% of women but only 27 % of men had values above the known reference range.

For IL-18, several interesting comparisons are noted, despite no reported standard range for IL-18 in clinical practice. First, in the non-diabetes group, 80% of the men but only 35% of the women had values above the known reference range. This pattern persisted in the pre diabetes group, but not in the diabetes group. Furthermore, as a total group sample, the percentage of participants with an IL-18 above the known reference range was greatest in the pre-diabetes (68%) and diabetes groups (64%) versus the non-diabetes group (40%), and this pattern was largely attributed to the greater values in men, as noted above.

Interestingly, 90-100% of the adiponectin values were well above known reference range (RR) for men and women (and total group sample). There was little difference in percentage among the groups. In the non-diabetes and pre-diabetes groups, for men, women, and total sample group, levels above SV were at 100% as compared to the diabetes group where 91% of men and 93% of women were above the SV.

In the total group, the percent of VAT values above the SV was 52% in the pre-diabetes group and 44% in the diabetes group; these values were approximately twice the percentage of those above the range in the non-diabetes group (24%). The total group percentage that fell above known reference range mirrored the percentages in women, but not men (in women non-

diabetes = 25%, pre-diabetes = 53%, diabetes = 57%). With respect to IL-18, again, in the total group, the percentage of values above the MFR SV was greater in the pre-diabetes group (68%) and diabetes (64%) groups than the non-diabetes group (40%) and these values were consistent with those in women, but not men.

TABLE 4. *VAT, IL-18, and adiponectin to known reference range.*

	RR	***ND* Within RR**	***ND* Above RR**	***PD* Within RR**	***PD* Above RR**	***D* Within RR**	***D* Above RR**
VAT (cm^2)	10-100						
Men (%)		80	20	50	50	73	27
Women (%)		20	25	47	53	43	57
TGS (%)		76	24	48	52	56	44
IL-18 (pg/mL)	36.1 –						
Men (%)	257.8	20	80	12	88	18	63
Women (%)		65	35	29	59	36	64
TGS (%)		60	40	28	68	32	64
Adiponectin (mcg/mL)	1.2-2.0						
Men (%)		-	100	-	100	9	91
Women (%)		-	100	-	100	7	93
TGS (%)		-	100	-	100	8	92

RR = Reference Range; ND = Non-Diabetes; PD = Pre-Diabetes; D = Diabetes; TGS = Total Group Sample

To extend the description of the three biomarkers across the groups studied, the distribution of VAT, IL-18, and adiponectin values were also analyzed, as seen in Figures 5-7. In Figure 5, the distribution of VAT by group is presented. As seen in Figure 5, the majority of participants in the non-diabetes group (21/25) and pre-diabetes group (21/25) had VAT values that were below 109cm^2 and non-diabetes (4/25) and pre-diabetes (4/25) above 109, respectively. In contrast, the level of VAT in the diabetes group was skewed to the right, with a total of 15/25 below 109cm^2 and 10/25 above 109cm^2.

In Figure 6, the distribution of IL-18 is skewed slightly to the right, to the mid-range of values, in the pre-diabetes and diabetes groups while the non-diabetes group tended to cluster in

the lowest range of the values. In Figure 7, the distribution of adiponectin seems to be similar among groups.

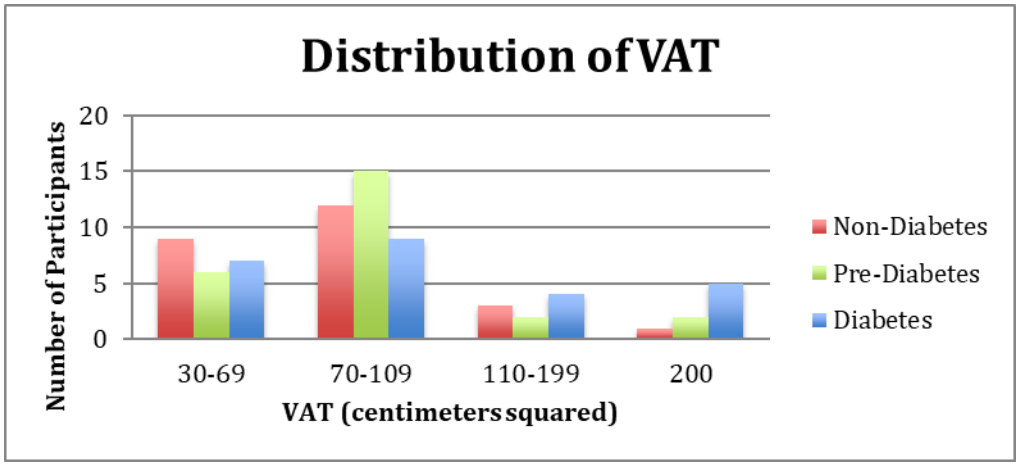

FIGURE 4. Distribution of VAT

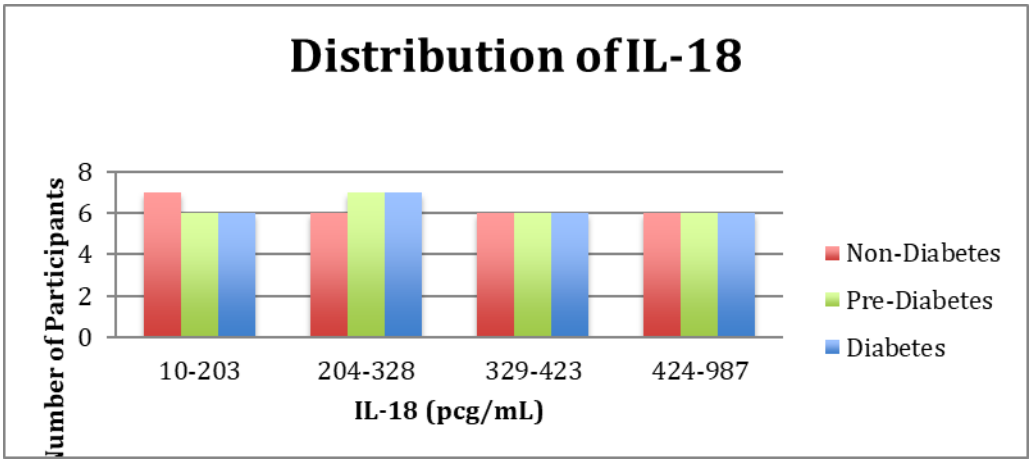

FIGURE 5. Distribution of IL-18

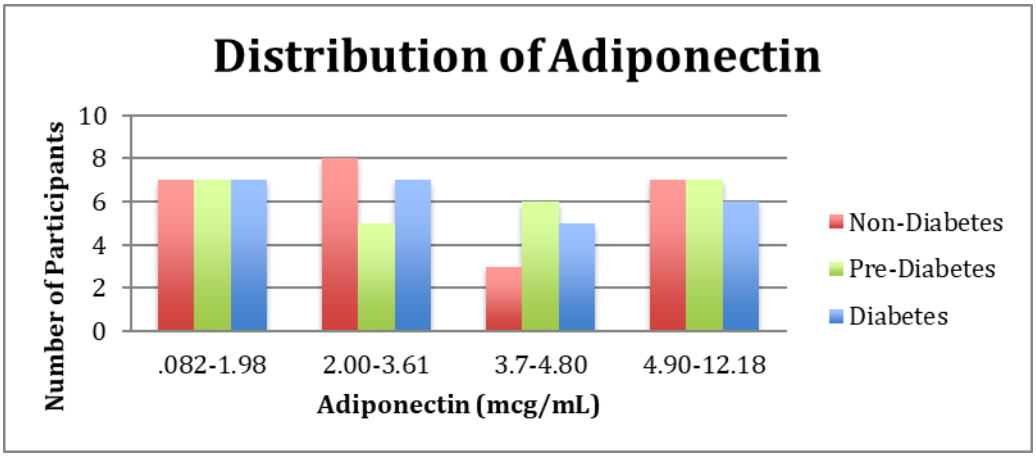

FIGURE 6. Distribution of adiponectin

Aim 2: Results

Aim 2: Determine the relationship of VAT, IL-18, and adiponectin within each of the three groups of FAs. ***Hypothesis 1****: postulated that VAT and Il-18 would be significantly increased and adiponectin will be significantly decreased in FAs with type 2 diabetes.* ***Hypothesis 2****: suggested VAT would be significantly increased and IL-18 and adiponectin will be within normal range in FAs with pre-diabetes.* ***Hypothesis 3****: predicted VAT, IL-18, and adiponectin would be within normal range in FAs without diabetes.*

Pearson product-moment correlations were computed using an alpha of 0.05 for each single group (non-diabetes, pre-diabetes, diabetes) to determine if a relationship existed among VAT, adiponectin, and IL-18. In the non-diabetes groups (Table 5) when comparing VAT to adiponectin there was a weak positive correlation (r = 0.17, p = 0.41) and a weak negative correlation with IL-18 (r = -0.02, p = 0.09). Furthermore, when comparing adiponectin to IL-18 there was a weak negative relationship (r = -0.30, p = 0.14) between these variables.

TABLE 5. *Pearson correlation matrix non-diabetes group.*

	VAT **(*r* value, *p* value)**	***Adiponectin*** **(*r* value, *p* value)**	***IL-18*** **(*r* value, *p* value)**
VAT	1	0.17, 0.41	-0.02, 0.09
Adiponectin	0.17, 0.41	1	-0.30, 0.14
IL-18	-0.02, 0.09	-0.30, 0.14	1

In the pre-diabetes group (Table 6.), when comparing VAT to adiponectin there was a weak positive correlation ($r = 0.04$, $p = 0.86$) and a weak positive correlation when comparing to IL-18 ($r = 0.3$, $p = 0.13$). In comparing IL-18 to adiponectin, there is a weak negative correlation ($r = -0.26$, $p = 0.20$).

TABLE 6. *Pearson correlation matrix pre-diabetes group.*

	VAT **(*r* value, *p* value)**	***Adiponectin*** **(*r* value, *p* value)**	***IL-18*** **(*r* value, *p* value)**
VAT	1	0.04, 0.86	0.31, 0.13
Adiponectin	0.04, 0.86	1	-0.26, 0.20
IL-18	0.31, 0.13	-0.26, 0.20	1

In the diabetes group (Table 7.), comparing VAT to adiponectin there is a weak negative relationship ($r = -.13$, p = 0.53) and compared to IL-18 a weak positive relationship ($r = 0.01$, p = 0.97). When comparing IL-18 to adiponectin within this group there was a weak positive effect relationship ($r = 0.004$, $p = 0.98$).

TABLE 7. *Pearson correlation matrix diabetes group.*

	VAT **(*r* value, *p* value)**	***Adiponectin*** **(*r* value, *p* value)**	***IL-18*** **(*r* value, *p* value)**
VAT	1	-.13, 0.53	0.01, 0.97
Adiponectin	-.13, 0.53	1	0.004, 0.98
IL-18	0.01, 0.97	0.004, 0.98	1

Aim 3: Results

Aim 3: Determine if VAT, IL-18, and Adiponectin are significantly different among the three groups. ***Hypothesis 1:*** *predicted VAT would be significantly greater in type 2 diabetes than*

in pre-diabetes and no diabetes groups. ***Hypothesis 2:*** *anticipated IL-18 would be significantly greater in type 2 diabetes than in pre-diabetes and no diabetes groups.* ***Hypothesis 3:*** *proposed adiponectin would be significantly lower in type 2 diabetes than in pre-diabetes and no diabetes groups.*

VAT, IL-18 and adiponectin were compared among the three groups (Table 8.). VAT appeared to be lower in the non-diabetes group (M = 78, SD = 43.6) compared to the pre-diabetes (M = 109.2, SD = 46.8) and diabetes group (M = 108.8, SD = 57.2).

One-way ANOVAs were conducted for VAT, IL-18, and adiponectin respectively (Table 9.). When evaluating VAT among groups there was no significance ($F_{2,72} = 1.614$, $p = 0.206$) in the levels of VAT in all three groups. This result is contrary to hypothesis 1 that predicted there would be a significant increase in VAT levels in the pre-diabetes and diabetes groups compared to the non-diabetes group. For IL-18, there was also no significant difference ($F_{2,72} = 0.791$, $p = 0.457$) among groups. The results failed to support hypothesis 2 that suggested there would be higher levels of IL-18 in the diabetes group compared to the pre-diabetes and non-diabetes groups.

Counter to the findings of the one-way ANOVAs for VAT and IL-18 among groups, the analysis of adiponectin as the dependent variable, there was a significant difference amongst the groups ($F = 3.789$, $p = 0.027$). In a post hoc analysis, Tukey's Honest Significant Difference (HSD) (Table 10) determined the significant difference amongst the three groups was between the non-diabetes and diabetes groups ($p = .02$). This finding partially agrees with hypothesis 3 that suggested that adiponectin would be significantly increased in the non-diabetes group

compared to the diabetes group; however, did not meet the significance for the difference between the non-diabetes group and pre-diabetes group.

TABLE 8. *VAT, IL-18, and adiponectin amongst groups.*

	***Non Diabetes* (M/SD)**	***Pre-Diabetes* (M/SD)**	***Diabetes* (M/SD)**
VAT (cm^2)	78.0 (43.6)	109.2 (46.8)	108.8 (57.2)
IL-18 (pg/mL)	304.8 (171.0)	287.1 (154.2)	348.7 (205.1)
Adiponectin (mcg/mL)	7.2 (5.0)	5.2 (3.7)	4.1 (2.9*)

M = Mean; SD = Standard Deviation; * significantly different than non-diabetes group using one-way ANOVA and Post-hoc Tukey HSD

TABLE 9. *One-way ANOVA for each variable.*

	Dif. effect	***Dif. error***	***F***	***p value***
VAT				
Groups	2	72	1.614	0.206
IL-18				
Groups	2	72	0.791	0.457
Adiponectin				
Groups	2	72	3.789	0.027

TABLE 10. *Tukey HSD for adiponectin.*

Contrast	**Difference**	**Standardized difference**	**Critical value**	**p. value**	**Significant**
ND vs D	3046.049	2.708	2.393	**0.023**	Yes
ND vs PD	2005.014	1.783	2.393	0.183	No
PD vs D	1041.035	0.926	2.393	0.626	No

ND = non-diabetes, PD = pre-diabetes, D = Diabetes

CHAPTER 5: CONCLUSIONS

Introduction

It is well observed in the clinical setting and through studies that as a subpopulation of Asians in the U.S., FAs have the second highest incidence of diabetes, next to Chinese Americans (Karter et al., 2012). Further, several studies suggest that VAT and inflammatory biomarkers are involved in the development and/or progression of diabetes in this population, and that VAT may have a unique role to play in FAs (Araneta et al, 2005). Several studies have examined VAT and adiponectin, a protective protein that reduces inflammation, compared to biomarkers such as C-reactive protein (Putz, Goldner, Bar, Haynes, & Sivitz, 2004) and TNF-alpha (Alberti, Girola, Gilardini, Conti, Cattaldo, Micheletto, & Invitti, 2007) in different populations.

In addition, studies indicate IL-18, an inflammatory cytokine, is associated with chronic low-grade inflammation and thought to play a role in predicting cardiovascular events and precedes the development of type 2 diabetes (Troseid et al., 2010). However, no research has been done examining VAT, IL 18 and adiponectin in FAs. Therefore, the purpose of this study was to examine VAT, IL-18, and adiponectin in FAs with type 2 diabetes, FAs with pre-diabetes and FAs without diabetes. The specific aims were to 1) quantify VAT, IL-18, and adiponectin and describe the values in relation to known reference ranges 2) determine the relationship of VAT, IL-18, and adiponectin within each of the three groups of FA and 3) determine if there was a significant difference in VAT, IL-18, and adiponectin amongst the three groups.

The findings of the study indicate that there was both a greater distribution of VAT in the higher ranges and a greater percentage of VAT and IL-18 values that were above known

reference ranges in the pre-diabetes and diabetes groups than in the non-diabetes group. No statistically significant correlations among VAT, IL-18 and adiponectin were detected within any of the groups. Importantly, the results indicate that there was a significantly lower level of adiponectin in the diabetes group compared to the non-diabetes group. This study is the first of its kind to describe a significant difference in levels of adiponectin in FAs with diabetes compared to FAs without diabetes. This novel findings points to the need for larger scale studies to determine whether important and unique relationships among these biomarkers exist in FAs without diabetes, with pre-diabetes, and diabetes.

Discussion of Findings

The triad of VAT, IL-18 and adiponectin were selected for this study based on evidence indicating that intermittent elevations in glucose levels cause a subsequent elevation of IL-18 and decrease in adiponectin (Xu, Dai, & Sun, 2009). Further, other studies indicate that the level of VAT influences the release of IL-18 and adiponectin (Hiler, Cheema, & Bahouth (2004). VAT versus subcutaneous fat is more metabolically active resulting in an increase in insulin resistance and progression to type 2 diabetes (Hiler et al., 2004). It has also been suggested that the accumulation of VAT, rather than subcutaneous fat, contributes to the development of metabolic syndrome (Sadashiv, Paul, Kumar, Dhananjai, & Negi, 2012; He, Rodriguez-Colon, Fernandez-Mendoza, Vgontzas, Bixler, Berg, Kawasawa, Sawyer, & Liao, 2015). Further, as mentioned earlier, it has been suggested that VAT may play a unique role in the development and/or progression of diabetes in FAs. The following discussion will focus on this study's specific aims relative to these three biomarkers in FAs without diabetes, with pre-diabetes or with diabetes.

VAT

VAT is a type of fat present in the abdominal cavity, mainly in the mesentery and omentum draining directly through the portal circulation to the liver (Ibrahim, 2010). When compared to subcutaneous fat, VAT is more cellular, vascular and contains a vast amount of inflammatory and immune cells (Ibrahim, 2010). VAT also tends to be more metabolically active and more sensitive to insulin resistance compared to subcutaneous tissue (Ibrahim, 2010). Further, it has been suggested that Filipino women have a greater amount of VAT than do Caucasian women (Araneta, Wingard, & Barrett-Connor, 2002). The sensitivity to insulin resistance and presence of large amounts of inflammatory and immune cells, and the findings in studies that VAT tends to be higher in FAs, informed the decision to select VAT as a biomarker for this study.

For Aim 1, we quantified and described all biomarkers, including VAT, relative to known reference ranges using a relatively inexpensive and convenient user-friendly and validated bio-impedance analyzer. We found that more FAs with diabetes had VAT values above 110cm^2 than in the other groups. In addition, the percentage of VAT increased across non-diabetes to pre-diabetes to diabetes groups and this increase was observed in men, women, and the group as a whole. Considering the total group with diabetes, the percentage of VAT values that fell above the known reference ranges (100cm^2) was approximately double the values observed in FAs without diabetes. These findings in FAs are consistent with the findings by Premanath, Basavanagowdappa, Mahes, and Suresh (2014) who reported that South Asian Indian individuals with diabetes had significantly higher levels of VAT compared to those without diabetes, when using ultrasound to measure VAT.

When considering FA women alone, a study by Araneta and Barrett-Connor (2005) found that Filipino women had higher levels of VAT compared to African-American and white women despite similar BMI and waist circumference. In addition, they found that the prevalence of type 2 diabetes was elevated among Filipino women at all levels of VAT (Araneta & Barrett-Connor, 2005). The risk of type 2 diabetes did not differ after adjusting for VAT between African-American (AA) and white women (Araneta & Barrett-Connor, 2005). However, for Filipino women the prevalence of type 2 diabetes was significantly higher in Filipinos than in AA and white women across all levels of VAT (Araneta & Barrett-Connor, 2005). Consistent with these findings, we found that the percentage of VAT values that fell above the known reference range in FA women with pre-diabetes and diabetes was double that of those with no diabetes. Furthermore, with the assistance of the body impedance analyzer, BMI obtained appeared to have no bearing on levels of VAT within groups in this sample. In this study, the mean of BMI observed in all groups (Table 3.) varied little among groups, which was similar to the findings reported by Araneta and Barrett-Connor (2005).

In Investigating Aim 2, it was hypothesized that there would be a correlation among VAT and the other biomarkers, postulating that compared to FAs with no diabetes, VAT would correlate with an increase in IL-18 and a decrease in adiponectin in FAs with pre-diabetes and diabetes. However, we did not detect a correlation among VAT and other biomarkers in the groups studied. This is contrary to findings reported by Bruun, Stallknecht, Helge, and Richelsen (2007) who concluded that increased VAT is associated with increased incidence of insulin resistance and elevated of levels of IL-18. In addition, Cho, Joo, Cho, Lee, Park, Hong, Yu, and

Lim (2017) who recently reported that metabolic syndrome was the highest in individuals with low serum adiponectin and elevated visceral fat.

For Aim 3, VAT means among all groups, despite gender, was not significantly different. We suspect that our findings for Aims 2 and 3 may have been influenced by a small sample size and the relatively young age of the groups, especially in the diabetes group. The average age for participants in this study was younger, when compared the participants in the study by Araneta and Barrett-Connor (2005) whose average participant age was 65 years of age. Further, it may be that those in the diabetes group may have been controlled with medication and thus may have affected the ability to detect a correlation within a group or significant differences across groups. Another factor is that 55 out of 75 participants in the study exercised weekly and less than half of participants ate out more than two times per week, thus potentially decreasing overall levels of VAT within the sample.

IL-18

IL-18 is a member of the IL-1 superfamily of cytokines and in older literature is described as interferon gamma inducing factor (Troseid et al., 2010). This biomarker is produced in many types of cells to include macrophages, endothelial cells, and adipocytes (Troseid et al., 2010). IL-18 is a significant proinflammatory cytokine that enhances T cells and natural killer cell maturation (Troseid, 2010). IL-18 has been shown to be increased in individuals with metabolic syndrome despite adjustments for other biomarkers such as IL-6 and CRP (Troseid et al., 2010). The assumption that levels of IL-18 can predict the progression to type 2 diabetes such as described in studies like Troseid et al. (2010) and Thorand et al. (2005), and the fact that

IL-18 had not been characterized in FAs with pre-diabetes and diabetes, prompted the selection of this biomarker for this study.

For Aim 1, interestingly, the percentage of women and total group sample had IL-18 levels above the known reference range. The percentage of women in the non-diabetes group (35%) had levels above the known reference range compared those in the pre-diabetes (59%) and the diabetes (64%) groups. This observation extends results from a previous study by Thorand et al (2005) who reported that individuals with type 2 diabetes compared to those without have elevated concentrations of IL-18 by demonstrating that increased levels are already present before onset of diabetes but more so in women.

In contrast to the findings of others, in this study, IL-18 in all groups indicated no relationship to VAT or adiponectin (Aim 2). These findings could be attributed to the fact that there was a greater participation in exercise in all groups compared to other studies. This possibility is supported by Troseid, Lappegard, Mollnes, Arnesen, and Seljeflot (2009) who found that exercise has the propensity to decrease levels of IL-18.

Of note is that the standard range of IL-18 values for this study was large. This wide range of normal values is in keeping with studies that are reported in the literature. Studies such as those by Welsh, Woodward, Rumley and Lowe (2007) explain that levels of IL-18 in the general population varies due to age and has shown to be higher in males than females. In this study, men had a greater percentage of values above the known reference range than women did. This data could be skewed due to the smaller percentage of men in the study; however, it does confirm studies like Welsh et al. (2007). In addition, a young average age (41) of those men who did participate could have affected the findings. Support for an age-related effect is provided by a

laboratory study from Abu Elhija, Lunefeld, and Huleihel (2008) who reported that in male mice, levels of IL-18 are higher during adolescents and young adulthood compared to decreased levels in elderly males and that this effect is mainly driven by levels of circulating testosterone.

Adiponectin

Adiponectin is a protective protein thought to slow the progression of type 2 diabetes in individuals (Iqbal, 2007). According to Yamamoto, Matsushita, Nakagawa, Hayashi, Noda and Mizoue (2014) adiponectin has anti-inflammatory and insulin-sensitizing properties. It has been reported that plasma levels of adiponectin are significantly lower in Japanese individuals with type 2 diabetes (Chandran, Phillips, Ciaraldi, & Henry, 2003). The presumed ability of adiponectin to exert anti-inflammatory effects in individuals who may have pre-diabetes or diabetes, the previous reports that FA women with diabetes have low adiponectin and its unknown relationship to VAT and IL-18 in FAs, prompted the use of this biomarker in this study.

For Aim 1, adiponectin was examined among groups and we were surprised to find that the levels were actually elevated above known reference ranges (as specified by Mayo Clinic) in all three groups and did not seem to differ by gender. Again, for Aim 2, we found no correlation of adiponectin to VAT or IL-18. These findings are contrary to studies such as Kim, Park, Park, Kang, Ahn, Cha, Lim, Kim, and Lee (2012) who reported that levels of visceral fat were a strong predictor for adiponectin levels especially in individuals with type 2 diabetes. Furthermore, the lack of correlation also contradicts a meta-analysis by Liu, Feng, Li, Wang, Li, and Hua (2016) who reported that the risk for type 2 diabetes as a whole was strongly associated with increased levels of IL-18 and low levels of adiponectin.

For Aim 3, an important finding of this study is that compared to FAs with no diabetes, the mean adiponectin level was significantly less than in those with diabetes ($p< 0.05$). To our knowledge, this is the first time that adiponectin has been compared in a population of both men and women FAs with no diabetes, with pre-diabetes and with diabetes. Our findings, in part, are similar to those of Paz-Pacheco et al. (2009) who reported that Filipino men and women with diabetes have significantly lower adiponectin levels compared to those without diabetes. While we did not see any gender differences, others have found that Jordanian women with diabetes have higher levels of adiponectin compared to men (Aleidi, Issa, Bustanji, Khalil, & Bustanji, 2015).

A previous study by Araneta and Barrett-Connor (2007) found that Filipino American women have significantly lower levels of adiponectin compared to white women independent of body size or presence of insulin-resistance. In this study, the majority of participants were women and when considering only this subset of the sample, we similarly found that the percentage of adiponectin was lower in the diabetes group than in the non-diabetes group (Table 4). Interestingly, in our study, adiponectin levels were higher in women with diabetes than in men with diabetes, a finding that was also reported by Aleidi et al. (2015). The reasons for this gender difference in adiponectin in those with diabetes has not be explained or explored well in studies that exist.

Strengths of the Study

The plasma biomarker adiponectin has potential for use in the clinical setting to help determine risk for progression to type 2 diabetes in FAs. Recruitment for this population was relatively easy due to ease of communication with participants and the overall commitment from

them to appear for the study at their selected time for participation. The test is minimally invasive and can be included in routine screening labs making this a practical tool for providers. In this study, the primary investigator obtained all samples and measures minimizing the risk for errors in data collection. Further, the equipment used was calibrated per manufacturer recommendations to ensure consistency between participants and all laboratory samples were processed in a laboratory that is familiar with the processing of ELISA samples.

The investigator considers the method for measuring the VAT a strength of the study. While the "gold standard" for VAT measurement is dual-energy X-ray absorptiometry (DEXA), this method is costly, not readily available to practitioners (Miller et al., 2016). On the other hand, body impedance analyzers are less expensive, are portable and can be used in any setting.

Previous studies have compared the use of indirect measures of VAT with body impedance analyzers to DEXA and suggested that they are a valid measure of fat compared to DEXA especially for assessment in community-based research (Beeson, Batech, Schultz, Salto, Firek, DeLeon, Balcazar, & Cordero-MacIntyre, 2010; Ling, de Craen, Slagboom, Gunn, Stokkel, Westendorp, & Maier, 2011). This study utilized the InBody® 570. Studies such as Kim, Choi, and Yum (2006) and Hancu and Radulian (2015) have confirmed that with the use of commercially available body impedance analyzers, individuals with greater than 100 cm^2 of VAT is a predictor for increased cardiovascular risks, elevated lipids, glucose, and alanine aminotransferase. The use of the InBody® 570 compared to DEXA is strongly correlated when evaluating body fat and can be deemed a comparable measure due to its versatility, affordability, and valid measurement (Miller, Chambers, & Burns, 2016). Further, VAT less than 100 cm^2 is considered normal and indicates a decreased risk of obesity-related disorders (InBody® USA,

2018). The portability and ease of use of this machine, coupled with the knowledge that VAT can be accurately measured, makes this a method that could potentially be used in the practice setting.

Limitations of the Study

The samples for the study were gathered from four main locations within Solano County. The locations included two community hospitals, one academic center, and one community center. This has limited the ability for the results of this study to be generalized amongst Filipinos who may live outside of Solano County or those who are not familiar with the locations from where participants were recruited. The sample included mostly women and thus may not be representative of the general population. Furthermore, participation in this study mainly occurred through a snowball sampling that may have contributed to a less diverse pool of participants according to age and gender.

In conversation with participants regarding their participation in the study it was discovered that a large majority of participants feared participating in the study not because of the blood draw but more so for finding out if they had diabetes and being told that they may be "fat" as the result of the body fat analysis. Additionally, when participants were asked if they could assist in referring other people to the study many of them mentioned that they would try but they believed that because I was not Filipino and was a nurse practitioner, they didn't believe that they could be successful in helping with recruiting others.

Another limitation of the study with respect to recruitment was the idea of using biomarkers, specifically VAT IL-18 and Adiponectin, to understand diabetes progression as they are not widely known by the layperson as potential contributors for disease.

In discussion with participants who were classified in the diabetes group, most participants did mention that they were on medications for their diabetes. Unfortunately, in this study medications related to type 2 diabetes were not documented. Because most of the participants who were in the diabetes group were on medications, the effects of these medications may have been confounders in the amounts of VAT, IL-18 and adiponectin observed in this group. In addition, a greater female to male participant ratio, failure to control for exercise and young mean age may have confounded the results.

Finally, the lack of relationship between all three biomarkers (Aim 2) and the lack of significance among a single biomarker among groups (Aim 3) may have been due to an inadequate sample size, despite a power analysis prior to data collection indicating that a sample of 75 participants (25 in each group) would detect overall differences with an alpha of 0.05.

Generalizability

Because the sample population was limited in setting, age and gender diversity, the information obtained from the study cannot be generalized into the greater population including the sub-population of Filipino Americans.

Implications for Nursing Practice

Currently, the literature supporting the use of these biomarkers as contributors to type 2 diabetes is not sufficient to support their everyday use by diabetes practitioners. However, the information from this study does add to the body of knowledge regarding the potential use of biomarkers in diabetes risk assessment and management. In clinical practice, FAs appear to be much slenderer even in the presence of type 2 diabetes compared to other ethnic groups such as Caucasians, African Americans, and Hispanics who usually have a visually larger appearance

(Fuller-Thomson, Roy, Chan, & Kobayashi, 2017; Lorenzo, Okoloise, Williams, Stern & Haffner, 2003). The idea for using these novel biomarkers was to help identify tangible precursor to type 2 diabetes with the expectation that clinicians could mitigate their presence through concentrated recommendations such as appropriate diet, exercise, and medications that could reduce VAT and IL-18 and increase adiponectin.

Had these results shown a statistically significant correlation, the implications for nursing would have been much more defined. Nurses would have had literature to support the use of biomarkers to assist in assessing, testing, and managing diabetes to complement the more common lab or point of care tests such as hemoglobin A1C and fasting blood sugar. The use of the body impedance analyzer would have also been important in its use in the clinical setting. With the costs associated with running clinical lab tests on patients, IL-18 and adiponectin would not necessarily need to be obtained routinely; rather the body impedance analyzer could predict levels based solely on levels of VAT.

The findings of this study suggest that maybe other biomarkers could predict the progression and severity of type 2 diabetes. Surprisingly, having higher levels of adiponectin in this ethnic group, who tends to have a higher incidence of type 2 diabetes, should be further assessed. The supposition is that there is a physiological explanation that adiponectin, a protective protein, despite being elevated in non-diabetes, pre-diabetes, and diabetes may possibly be inhibited by another biomarker in this population. The overall implications for nursing hold promise for further research specific to use body impedance analysis and biomarkers in predicting type 2 diabetes.

Future Research

Many opportunities exist for future research particularly adiponectin as a biomarker for predicting type 2 diabetes in FAs. In addition, investigations as to why FAs seem to have higher levels of adiponectin above known reference ranges would be warranted. Recommendations to validate or refute this study would be to increase the sample size to minimize variability in the sample. Furthermore, future studies should consider controlling for exercise and use of diabetes medications that could have contributed to the present results.

We know that more research studies exist specific to FA women and diabetes compared to men. Recommendations would be to assess these same levels in men compared to women. Additionally, IL-18 in men was elevated in this sample compared to women. The presence of elevated IL-18 and adiponectin despite the presence of type 2 diabetes in men could be further investigated. Future researchers could also consider other common biomarkers to compare in this population to include levels of CRP or TNF-alpha.

Conclusion

Type 2 diabetes is an endemic issue throughout the world but more so in developed countries where individuals have easy access to high calorie foods and do not participate in routine physical exercise. Biomarkers exist in the body that are still unknown or insufficient research has been conducted to compare them to the progression of type 2 diabetes. This study elucidates the variance of the VAT, IL-18, and adiponectin especially in FAs. These biomarkers, as evidenced by several studies, vary based on age, gender, and ethnicity.

Understanding physiological biomarkers, in this subgroup of the Asian population, as it applies to type 2 diabetes is imperative to understand to ensure that the risk for the development

of the disease is mitigated. Future research is necessary to validate findings of this study and more so to advance the understanding of type 2 diabetes in FAs. It is in understanding the physiology of these biomarkers in FAs, that clinicians will be better armed to provide appropriate treatments to reverse or prevent type 2 diabetes.

APPENDIX A:

THE UNIVERSITY OF ARIZONA INSTITUTIONAL REVIEW BOARD APPROVAL LETTER

Research
Office for Research & Discovery

Date:	May 23, 2017
Principal Investigator:	Julian Leandro Gallegos
Protocol Number:	1705469588
Protocol Title:	Hidden Risks: Relationships among VAT, IL-18 and adiponectin in the development of Type 2 Diabetes in Filipino Americans
Level of Review:	Expedited
Determination:	Approved
Expiration Date:	May 21, 2018

Documents Reviewed

Concurrently:

Data Collection Tools: *Health History Form 5_16_17.docx*
HSPP Forms/Correspondence: *f107_form Julian Gallegos.doc*
HSPP Forms/Correspondence: *Julian Gallegos UA IRB JG 5_17_17.doc*
HSPP Forms/Correspondence: *Signature page.pdf*
Informed Consent/PHI Forms: *Informed Consent 5_16_17.doc*
Informed Consent/PHI Forms: *Informed Consent 5_16_17.pdf*
Other Approvals and Authorizations: *NorthBay Letter for space use .pdf* **Other Approvals and Authorizations:** *Touro Letter for space use.pdf* **Recruitment Material:** *Recruitment Flyer_Talking Points*

APPENDIX B:

PARTICIPANT HISTORY AND DATA FORM

Participant History Form/Data Form

Participant Number: _____ **Consent signed:** □Yes □ No

Hemoglobin A1C: _____ **Group Assigned:** □NonT2DM □PreT2DM □T2DM

Height		**Body Fat Mass**	
Weight		**Lean Body Mass**	
Waist Circumference		**Visceral Fat Level**	
Body Mass Index		**Adiponectin Level**	
Segmental Fat Analysis (Trunk)		**Interleukin-18 Level**	

Social History:

Age: _____

Marital Status: □ Single □ Married □ Divorced

Tobacco (chew/smoke): _____per day
Caffeine (coffee/tea/soda):_____per day
Alcohol (spirits/beer/wine): _____per day
Street Drugs (marijuana, etc.): _____

Habits:

What do you do for exercise? _____
How many minutes of exercise per week? _____
Describe your eating habits: (Poor, Well-balanced, Vegetarian, gluten-free, etc.)_____
Do you eat out more than twice per week? □Yes □ No

Medical History: Have you ever been treated for any of the following medical conditions?

□ Arthritis □ Depression/anxiety □ Diabetes
□ Heart problems □ High blood pressure □ High cholesterol

Please list any additional medical conditions:

Do you take any supplements (calcium/vitamin D/fish oil/multivitamin)? □Yes □ No, if yes what type:

Family History: Please list any known medical problems for the individuals below:

Mother:
Father:
Brother/Sister:
Children:

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