INSULIN RESISTANCE, DEPRESSION, AND THE PROGRESSION TO

TYPE-2 DIABETES IN YOUTH

By

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ABSTRACT

Childhood obesity has become epidemic in the United States. Coinciding with this rapid increase in obesity is the development of type-2 diabetes in youth. Little is known about the progression of insulin resistance to type-2 diabetes or association of depressive symptoms and impaired glucose metabolism in at-risk obese youth.

A retrospective chart review and a secondary data analysis was done using a descriptive correlational design exploring the incidence of insulin resistance, hyperinsulinemia, impaired fasting glucose, impaired glucose tolerance, and progression to type-2 diabetes in a cohort of 78 high-risk obese youth age 11 to 17 years presenting to a pediatric endocrinology clinic from 2007 to 2009. Association between self-reported depressive symptom scores using the Center for Epidemiological Studies Depression Scale for Children (CES-DC) and measures above were also explored.

Of the 78 participants enrolled in the original study, 44 (56.4%) underwent oral glucose tolerance testing, and 4 (9.1%) were diagnosed with impaired glucose tolerance. None had a confirmed diagnosis of type-2 diabetes over the 6 year study period. Two hour oral glucose tolerance results significantly correlated with the initial HbA1c (r=.470, p=.007), the sum of insulin levels (r=.518, p=.001), and HOMA-IR (r=.429, p=.007). The insulin total correlated with HOMA-IR (r=.553, p=.001). The incidence of self-reported depressive symptoms was high in 35 (49 %) participants (n=71). None of the measures of impaired glucose metabolism correlated with depression scores.

These results indicate that even with a small sample of obese youth, 78 % met criteria for insulin resistance. The HbA1c correlated with 2-hour glucose tolerance test results. Glucose tolerance testing is used clinically for confirmatory diagnosis of impaired glucose tolerance and type-2 diabetes which support the use of HbA1c for screening youth. Despite lack of association

between depressive symptoms and impaired glucose metabolism, 49% reported symptoms of depression with 11% moderate or severe. It would be prudent to screen all obese youth for depressive symptoms as this may impact their ability to implement lifestyle changes. Future research is needed with a larger prospective sample of high-risk obese youth to identify those more likely to develop type-2 diabetes and benefit from lifestyle interventions.

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Chapter I
Introduction to the Research Problem

Over the past three decades in the United States (US), the prevalence of obesity in children and adolescents has nearly tripled (Centers for Disease Control and Prevention, 2013b). Approximately 17 percent of youth meet the diagnostic criteria for obesity based on the 2009 to 2010 National Health and Nutrition Examination Survey (NHANES) data (Ogden, Carroll, Kit, & Flegal, 2012b). When combining overweight and obese youth the prevalence is 31.7 percent or one third of US children (Ogden, Lamb, Carroll, & Flegal, 2010). Consistent with the rapid increase in childhood obesity is the development of insulin resistance and type-2 diabetes in youth as well as cardiovascular disease (CVD) in young adulthood. "Obesity is the most frequent cause of peripheral insulin resistance in childhood, yet this effect is non-linear, having the greatest metabolic impact in the higher obesity percentiles" (Weiss, 2007, p. 70). The more obese a child is the more likely he or she is to develop obesity-related insulin resistance, hyperinsulinemia, impaired fasting glucose, impaired glucose tolerance, or type-2 diabetes.

Psychopathology including depressive symptoms has been noted to be prevalent in obese youth when compared to the non-obese (Hasler et al., 2005; Kalarchian & Marcus, 2012). In a previous study conducted by the candidate, 51 percent of the overweight insulin resistant adolescents attending an outpatient endocrinology appointment for weight management and insulin resistance presented with depressive symptoms (Platt et al., 2013). In this study we examined the association between depressive symptoms and the development of hyperinsulinemia, insulin resistance, impaired fasting glucose, impaired glucose tolerance, or type-2 diabetes. We also examined differences in self-reported depressive symptoms in the

youth at presentation and the participants who developed hyperinsulinemia, impaired fasting glucose, impaired glucose tolerance, or type-2 diabetes over the past six years.

Research Questions

In a cohort of 78 obese youth 11-17 years of age who presented for an initial appointment for evaluation of obesity and insulin resistance and enrolled in an outpatient endocrine study from 2007 to 2009:

1. What is the incidence of abnormal ($\geq 5.7\%$) glycosylated hemoglobin (HbA1c) from June 2007 to March 2013?

2. What is the incidence rate of insulin resistance as measured by homeostasis model assessment of insulin resistance (HOMA-IR) during the study period of June 2007 to March 2013?

3. What are the incidence rates of elevated insulin response or hyperinsulinemia (a sum of the insulin results at 0, 30, 60, 90, and 120 minutes from the oral glucose tolerance test), impaired fasting glucose (fasting glucose 100mg/dl to 125mg/dl), impaired glucose tolerance (a two hour post challenge glucose of 140mg/dl to 199mg/dl), and type-2 diabetes (fasting glucose $\geq$ 126mg/dl or a two hour post challenge glucose of $\geq$ 200mg/dl) as measured by the two hour oral glucose tolerance test during the study period of June 2007 to March 2013?

4. Are depressive symptoms correlated with insulin resistance, hyperinsulinemia, impaired fasting glucose, impaired glucose tolerance, or HbA1c?

5. Are depressive symptoms significantly different in youth with type-2 diabetes than those without type-2 diabetes?

A secondary analysis method of inquiry was conducted to examine a database of 78 obese youth who were referred to an outpatient pediatric endocrinology clinic for evaluation and treatment of obesity and insulin resistance. These youth were enrolled in an earlier study evaluating changes in depressive symptoms from 2007 to 2009 and were followed for three visits over one year (Platt et al., 2013). Along with the secondary analysis of the database, a retrospective chart review of the same participants was conducted to answer the above research questions.

Background and Significance

Childhood obesity has become an epidemic in the United States with multiple health issues associated with excess weight (Centers for Disease Control and Prevention, 2012). Health risks in youth associated with overweight and obesity include hypertension and dyslipidemia which can lead to CVD in young adulthood (American Heart Association, 2013; Weiss, Bremer, & Lustig, 2013). Obese youth are at increased risk of developing impaired fasting glucose, impaired glucose tolerance, insulin resistance, and type-2 diabetes (Neef et al., 2013). They also have a greater risk of social and psychosocial problems such as discrimination, depression, and poor self-esteem (Centers for Disease Control and Prevention, 2012; Neef et al., 2013).

It is well documented that overweight and obese youth are at high risk for becoming overweight or obese adults (Singh, Mulder, Twisk, van Mechelen, & Chinapaw, 2008; R. C. Whitaker, Wright, Pepe, Seidel, & Dietz, 1997). According to S. Cook and Kavey (2011) there is an increase in cardiovascular mortality in middle age people which they attribute to the increase in childhood obesity and diabetes over the past four decades. By 2035, it is estimated that the prevalence of CVD will increase by a rate of 5 to 16% (Bibbins-Domingo, Coxson, Pletcher, Lightwood, & Goldman, 2007). Furthermore, they estimate more than 100,000 excess

cases of CVD will be attributable to increased obesity in young adulthood (Bibbins-Domingo et al., 2007).

Statement of the Problem

The availability of sugar sweetened beverages and snacks, fast food, and sedentary activities (video games and computers) have created an environment conducive to childhood obesity (Barlow & Expert, 2007). Genetics play a part in the childhood obesity epidemic as obesity and type-2 diabetes tends to run in families (Centers for Disease Control and Prevention, 2010). Heritability of adiposity traits has been studied in twins separated at birth and has been reported as high as 40-75 percent (O'Rahilly & Farooqi, 2008). It has been found that having two parents who are overweight as compared with normal weight parents doubles the risk of the child becoming obese (*OR 2.2; 95% CI 1.3,3.7)* and having two obese parents increased the likelihood of the child being obese with a 12 times greater risk (*OR 12.0; 95% CI 7.2, 20.1*) (K. L. Whitaker, Jarvis, Beeken, Boniface, & Wardle, 2010). According to the Centers for Disease Control and Prevention (2013c) "genetic changes in the human population develop too slowly to have caused the obesity epidemic" (para. 2). Obesity is most likely a "complex interaction among multiple genes and environmental factors that remain poorly understood" (Centers for Disease Control and Prevention, 2013c, p. para. 4). Thus the odds of youth developing obesity as cited earlier may be related to the environment in which the child lives and the genetics they inherit.

Coinciding with the increase in childhood obesity, the development of type-2 diabetes in both children and adults has also increased (De Ferranti & Osganian, 2007). A study following Danish adults with impaired glucose tolerance found that more than 10 percent of the participants developed type-2 diabetes per year over a five year period (Engberg et al., 2009). In

a study of children who were followed with impaired glucose tolerance eight percent progressed to develop type-2 diabetes (Cree-Green, Triolo, & Nadeau, 2013). It has been reported that youth develop type-2 diabetes at a faster pace than adults, in as little as 12 to 21 months from development of impaired glucose tolerance (Cree-Green et al., 2013; Mizokami-Stout, Cree-Green, & Nadeau, 2012).

The psychological toll of obesity in youth has been reported in the literature with conflicting findings. A secondary analysis of a large database of over 43,000 US children age 10 to 17 years was examined to explore the relationship between obesity and co-morbid mental health disorders including depression (Halfon, Larson, & Slusser, 2013). They reported obese children had three times the risk of co-morbid mental health disorders than normal weight children (Halfon et al., 2013). Yet in another study, there was no correlation reported between depression and increasing BMI among obese youth (Benson, Williams, & Novick, 2013). Few studies were found that assessed depression, insulin resistance, and the progression to type-2 diabetes (Jaser, Holl, Jefferson, & Grey, 2009; Owens-Gary & Allweiss, 2013).

Study Purpose

The purpose of this study was to explore the incident rates of hyperinsulinemia, insulin resistance, impaired fasting glucose, impaired glucose tolerance, and type-2 diabetes in a cohort of 78 obese youth who presented to an outpatient pediatric endocrinology clinic for treatment of insulin resistance and weight management from 2007 to 2009. A retrospective chart review was conducted to search for results from standardized pediatric oral glucose tolerance tests. The association of depression in youth was explored in those with insulin resistance, impaired fasting glucose, impaired glucose tolerance, and type-2 diabetes.

Conceptual Framework Guiding This Study

The investigator developed conceptual framework visually describes the proposed associations among the study variables and guides the analysis and interpretation of the results. Childhood obesity is the overarching problem. Elevated insulin response and insulin resistance are the origin of impaired fasting glucose and impaired glucose tolerance which are signs of beta cell failure and precursors to type-2 diabetes. Type-2 diabetes has become more prevalent in youth coinciding with the increasing rate of childhood obesity. Depressive symptoms have been reported in obese youth and will be further investigated (Figure 1).

Figure 1. **Factors Associated with Type-2 Diabetes in Obese Youth**

Demographic Variables (age, gender, race, & BMI)

Depressive Symptoms

Insulin Resistance & Abnormal HbA1c

Hyperinsulinemia, Impaired Fasting Glucose, & Impaired Glucose Tolerance

Type-2 Diabetes
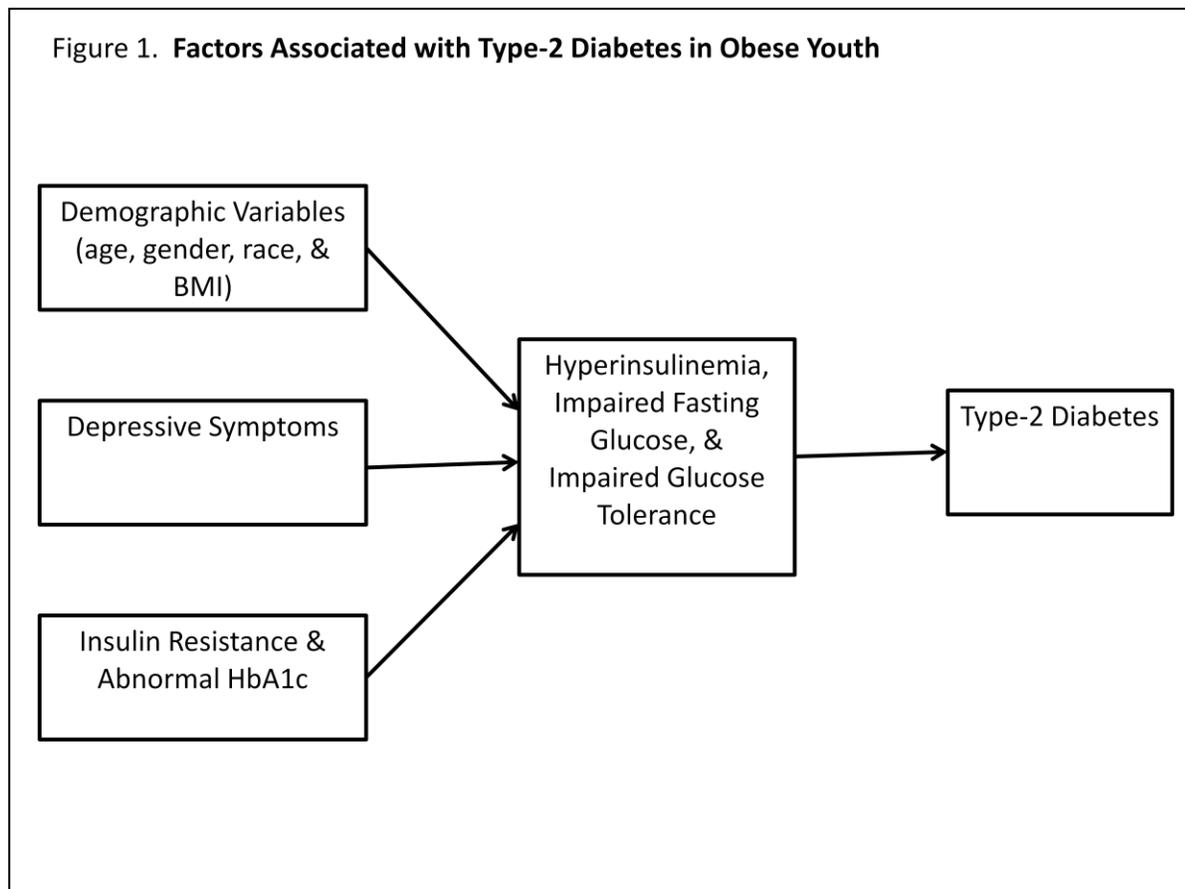
Theoretical Framework

The underlying theoretical framework of this study is psychoneuroimmunology. This is a relatively new field of science examining how emotional disorders such as depression can impact immunoregulatory processes and in turn have an effect on health status and the development or severity of chronic disease (M. Irwin, 2002). "Human psychoneuroimmunology emerged as interdisciplinary effort to understand the links between brain, behavior, and the immune system, as epidemiologic evidence demonstrate the influence of psychological stress and depression on morbidity and mortality risks" (M. R. Irwin, 2008, p. 129). In this study depressive symptoms are examined for correlations with impaired glucose metabolism and type-2 diabetes in obese youth.

Definition of Terms

Obesity

Obesity in youth is defined as a body mass index (BMI) greater than or equal to age and sex specific 95th percentiles when plotted on the 2000 Centers for Disease Control and Prevention (CDC) growth charts (Centers for Disease Control and Prevention, 2012). The definition is not comparable to adults. "A child's weight status is determined using an age and sex-specific percentile for BMI rather than the BMI categories used for adults because children's body composition varies as they age, and also vary between boys and girls" (Centers for Disease Control and Prevention, 2012). BMI is calculated as weight in kilograms divided by height in meters squared (Ogden, Carroll, Kit, & Flegal, 2012a). However, an issue with the percentiles is that this method does not discriminate between the obese and the very obese (greater than the 95th percentile). Thus BMI z-scores have been used as a comparison. They are the

transformation of the distribution of BMI for age and gender to a number representing the standard deviations above or below the mean on a normal distribution (Flegal & Ogden, 2011). According to the World Health Organization (WHO) obesity is classified as a child having a BMI z-score of $\geq$ 3 SD from the mean (de Onis & Lobstein, 2010). They separate children into two groups (less than 5 years of age and 5 to 19 years of age). The issue here is the difference in the growth of a 5 year old and a 19 year old. The concern related to an accurate measure of weight and obesity is the ability to identify the youth at highest risk for development of co-morbidities related to their weight (Daniels, 2009). The BMI percentiles were used as cut-offs for inclusion in this sample of youth as it is a widely accepted method and the z scores were computed to better describe the degree of obesity above the 95th percentile.

Glycosylated Hemoglobin (HbA1c)

HbA1c is a laboratory test averaging the blood glucose levels over the prior three months (Medline Plus, US National Library of Medicine, & National Institutes of Health, 2012). A result less than 5.7 percent is considered normal, 5.7 percent to 6.4 percent is considered pre-diabetes, and 6.5 percent and higher is diagnostic of diabetes with confirmatory testing (American Diabetes Association, 2013; Fajans, Herman, & Oral, 2011; Medline Plus et al., 2012).

Insulin Resistance

According to Levy-Marchal et al. (2010) there is no clear criteria for defining insulin resistance in children. Peripheral insulin resistance is most commonly associated with obesity and clinical features such as acanthosis nigricans (Guran, Turan, Akcay, & Bereket, 2008). During puberty there is an approximate 25-50 percent decrease in insulin sensitivity (Goran &

Gower, 2001) which contributes to the risk of the development of type-2 diabetes (S. Cook, Auinger, Li, & Ford, 2008; D'Adamo, Santoro, & Caprio, 2011). Insulin resistance can be measured using HOMA-IR from results obtained during an oral glucose tolerance test. This method has been found to be as sensitive as the gold standard: euglycemic clamp (Kurtoglu et al., 2010). The HOMA-IR is calculated by multiplying the fasting insulin (µU/ml) by the fasting glucose (mg/dl) and dividing by 405 (Kurtoglu et al., 2010).

Hyperinsulinemia

An elevated insulin response to glucose or hyperinsulinemia is the result of beta cell compensation secondary to a decrease in insulin sensitivity which in turn down regulates insulin receptor action and further complicates insulin action (D'Adamo et al., 2011; Lann & LeRoith, 2007; Neef et al., 2013). Hyperinsulinemia is the sum of the insulin results obtained at 0, 30, 60, 90, 120 minutes after a 75 gram glucose challenge during an oral glucose tolerance test. A level greater than or equal to 300 µU/ml of insulin is considered an elevated insulin response in obese children and adolescents (Kurtoglu et al., 2010; Maruhama & Abe, 1981).

Impaired Fasting Glucose

According to the latest guideline on treatment of youth with type-2 diabetes, impaired fasting glucose is defined as a fasting plasma glucose of $\geq$100-125 mg/dl (Copeland et al., 2013). This is the result of early beta cell failure as the pancreas responds to insulin resistance and makes large amounts of insulin to compensate and maintain euglycemia. The child begins to exhibit early glucose intolerance when the pancreas is unable to compensate for the insulin resistance (D'Adamo et al., 2011).

Impaired Glucose Tolerance.

Impaired glucose tolerance is defined as a plasma glucose of $\geq$140-199 mg/dl. two hours after an oral glucose challenge (Copeland et al., 2013). It is a further progression of beta cell failure or dysfunction and the inability to compensate for insulin resistance by making excess insulin to maintain euglycemia (D'Adamo et al., 2011). Youth with combined impaired fasting glucose and impaired glucose tolerance are at higher risk for developing type-2 diabetes which is similar to findings reported in adult longitudinal studies (Bacha, Lee, Gungor, & Arslanian, 2010; Meigs et al., 2003).

Type-2 Diabetes.

Type-2 diabetes is defined as having a fasting blood sugar $\geq$ 126mg/dl, a two hour glucose level $\geq$ 200mg/dl during and oral glucose tolerance test, or a random glucose $\geq$ to 200mg/dl (Copeland et al., 2013). It is the result of beta cell failure secondary to marked hyperinsulinemia which is in response to insulin resistance. The pancreas is unable to compensate by making large amounts of insulin to maintain euglycemia. The child's serum glucose levels rise and eventually the child develops type-2 diabetes (D'Adamo et al., 2011).

Depressive Symptoms

"Depressive symptoms, minor depression, dysthymia, and major depressive disorder have been suggested to represent a continuum of depressive symptom severity in unipolar major depressive disorder" (Ayuso-Mateos, Nuevo, Verdes, Naidoo, & Chatterji, 2010, p. 365). Some of the more prominent symptoms of depression are low mood, sadness, irritability, and a lack of pleasure in usual activities which lasts more than a couple days (Medline Plus, US National Library of Medicine, & National Institutes of Health, 2013). The presence of one or more core symptoms of depression could differentiate between depressive symptoms and persistent core

depressive symptoms which identifies an individual with a significant disorder (Ayuso-Mateos et al., 2010).

In the original study, the severity of depressive symptoms was measured using the Center for Epidemiological Studies Depression Scale for Children (CES-DC). It was originally adapted by Weissman, Orvaschel, and Padian (1980) and has been revalidated for use in adolescents several times (Faulstich, Carey, Ruggiero, Enyart, & Gresham, 1986; Fendrich, Weissman, & Warner, 1990). The CES-DC has been widely used as a screening instrument for depressive symptoms in youth as it is short (20 questions) and can easily be filled out by an 11 year old (Brown, Harris, Woods, Buman, & Cox, 2012; Rieck, Jackson, Martin, Petrie, & Greenleaf, 2013). It is also available at no cost by downloading it from the internet.

Assumptions

1. Data collected from the original research study was collected according to the research protocol and entered into the research database.
2. The Center for Epidemiological Studies; Depression Scale for Children (CES-DC) accurately measures depressive symptoms in youth.
3. Participants in the original study were accurately weighed and measured.

Summary

Obesity in youth has become an epidemic in the US with nearly 17 percent of children 2-19 years of age meeting criteria for obesity (Ogden et al., 2012b). There are many co-morbidities associated with obesity which impact the health of these youth and put them at greater risk than normal weight youth to develop impaired fasting glucose, impaired glucose tolerance, type-2 diabetes and CVD (Neef et al., 2013).

A co-morbidity of interest related to childhood obesity and insulin resistance is depressive symptoms. According to the literature there is little consensus as to a relationship between reported depressive symptoms and obesity (Kalarchian & Marcus, 2012). In this study we explored the association among reported depressive symptoms and insulin resistance, impaired fasting glucose, impaired glucose tolerance, and HbA1c. The depression scores were obtained using the CES-DC instrument.

This study is a secondary analysis and retrospective chart review using a descriptive correlational design to answer the research questions. This design provides a method to describe baseline characteristics of the sample and relationships among the variables. Pearson correlations were used to conduct the data analysis related to self-reported depressive symptoms, insulin resistance, impaired fasting glucose, impaired glucose tolerance, and HbA1c. Independent samples t-tests were used to explore depressive symptom mean differences in the youth who developed diabetes and those who did not.

Chapter II

Introduction to the Review of Literature

This review of literature introduces and describes the major concepts being investigated and provides in depth definitions of each variable. It includes recent literature related to insulin resistance, impaired fasting glucose, and impaired glucose tolerance as they relate to the development of type-2 diabetes in obese youth. The relationship of depressive symptoms and changes in glucose metabolism in youth will also be explored.

Review of the Main Concepts

Obesity in Youth and Insulin Resistance

Obesity in youth has become a major health concern, since it affects nearly 17 percent of the US population of children age 2 through 19 years of age (Ogden et al., 2012a). It was reported in a systematic review that overweight and obesity during adolescence presents a moderate risk for persistence into adulthood (Singh et al., 2008). Obesity is a multifactoral disease with the majority of early research focused on environmental and behavioral sources (Biro & Wien, 2010). However, recent research has been directed toward genetics, inflammatory biomarkers, and metabolic syndrome in youth (Biro & Wien, 2010; Rank et al., 2013; Santoro & Weiss, 2012). Regardless of the etiology, obesity predispose youth to develop insulin resistance with altered glucose metabolism leading to type-2 diabetes (Ghergherechi & Tabrizi, 2010).

In a normal state, hyperglycemia will cause a stimulation of the beta cells in the pancreas to secrete insulin and signal the liver to decrease glucagon production which in turn leads to an

increase in the uptake of glucose by muscle, liver, and adipose tissues. (Lann & LeRoith, 2007).

Under the condition of insulin resistance, the beta cells are dysfunctional and the first phase

insulin response to hyperglycemia does not occur causing an elevated postprandial glucose level

and an overwhelming second phase insulin response (Lann & LeRoith, 2007). This exaggerated

chronic hyperinsulinemia causes a down-regulation of the insulin receptors which subsequently

impairs normal insulin action (Lann & LeRoith). Insulin resistance is significantly associated

with obesity and cardiometabolic risk in youth; however, it does not only occur in the obese, as

some degree of insulin resistance normally occurs during puberty (J. S. Cook, Hoffman, Stene, &

Hansen, 1993; Cree-Green et al., 2013; D'Adamo et al., 2011; Goran, Shaibi, Weigensberg,

Davis, & Cruz, 2006; Levy-Marchal et al., 2010). The development of insulin resistance during

puberty may explain why many obese youth frequently present with impaired glucose

metabolism during adolescence. The combination of factors cited above can predispose obese

youth to a higher risk for development of impaired glucose metabolism such as impaired fasting

glucose, impaired glucose tolerance, or type-2 diabetes (Cree-Green et al., 2013; Kurtoglu et al.,

2010; Levy-Marchal et al., 2010; Raj, 2012).

Progression of Impaired Fasting Glucose and Impaired Glucose Tolerance to Type-2

Diabetes in Obese Youth

In a recent study examining insulin sensitivity and secretion in obese youth, the authors

reported a similar degree of beta cell dysfunction in a group of youth with impaired fasting

glucose in addition to impaired glucose tolerance and type-2 diabetes (Bacha et al., 2010). The

oral glucose tolerance test was most useful in the diagnosis of youth with impaired glucose

tolerance who have a high prevalence of insulin resistance and are at greatest risk for

development of type-2 diabetes (Ghergherechi & Tabrizi, 2010). These results support the

earlier explanation of insulin resistance and how it progressively worsens and causes impaired fasting glucose, impaired glucose tolerance, and in the worst case scenario, type-2 diabetes. However, impaired fasting glucose did not appear to be a sufficient measure on its own to assess glucose metabolic status (Bacha et al., 2010; Ghergherechi & Tabrizi, 2010). Impaired fasting glucose and impaired glucose tolerance are reported as independent pathways to the development of type-2 diabetes (Meigs et al., 2003). It is suggested that differences in the degree of insulin resistance or insulin secretion may produce discrete differences in how impaired fasting glucose or impaired glucose tolerance present (Meigs et al.).

Hyperinsulinemia appears to be associated with weight status, impaired fasting glucose, and impaired glucose tolerance (Li, Ford, Zhao, & Mokdad, 2009). Weiss et al. (2005) reported that eight obese adolescents (24 percent, n=33) progressed from impaired glucose tolerance to type-2 diabetes in 18 to 24 months which they state supports the hypothesis that the rate of beta cell failure in youth (and development of type-2 diabetes) may be a faster progression than in adults. Weight and African American ethnicity predicted a significant increase in the two hour glucose result on a second oral glucose tolerance test in a study looking at progression of insulin resistance to type-2 diabetes (Weiss et al., 2005). All of the youth with impaired glucose tolerance at baseline developed type-2 diabetes and seven of the eight were of African American decent (Weiss et al., 2005). In an adult study with a population of patients with newly acquired impaired fasting glucose, younger not older age predicted development of type-2 diabetes (Nichols, Hillier, & Brown, 2007). They report that the impaired fasting glucose subjects, based on adult literature, most likely had impaired glucose tolerance and developed type-2 diabetes in approximately 29 to 36 months (Nichols et al., 2007). A current study reported children with elevated triglycerides and hypertension in childhood were six times more likely to develop CVD

and type-2 diabetes in adulthood (Morrison, Glueck, Woo, & Wang, 2012). It is apparent that

impaired glucose tolerance in obese youth is a risk factor for development of type-2 diabetes and

the progression is a more rapid process than in adults. It is also notable that obese youth with a

large waist circumference, a family history of type-2 diabetes, and acanthosis nigricans were

more likely to have metabolic syndrome, impaired fasting glucose, or impaired glucose tolerance

(D'Adamo et al., 2011; Santoro et al., 2013). However, impaired glucose tolerance was reported

to be the best predictor in adolescents for development of type-2 diabetes (Weiss et al., 2005)..

Depressive Symptoms Associated with Obesity in Youth

Less than 30 years ago depression was viewed as an adult disorder and "children were

considered too developmentally immature to experience depressive disorders" (Maughan,

Collishaw, & Stringaris, 2013, p. 36). Now, few practitioners doubt the presence of depressive

disorders in youth, which can cause adverse social and educational outcomes when not treated.

The lifetime prevalence of experiencing a major depressive disorder in all youth 13-18 years is

11.2 percent, with 3.3 percent of these youth experiencing a severe debilitating depressive

disorder (National Institute of Mental Health, 2013).

In a study related to depressive symptoms and obesity, no relationship was found

between high levels of depressive symptoms and obesity in adolescents (Goodman & Must,

2011). The authors, however, did report that over time there was a significant association

between the depression screening scores and weight status. A recent study related to depressive

symptoms in overweight youth participating in a weight loss intervention over one year reported

that failure to lose weight was significantly associated with increased depressive symptoms (Pott,

Albayrak, Hebebrand, & Pauli-Pott, 2010). Another study found that overweight adolescents

self-reported more depressive symptoms than obese and normal weight adolescents (Ting, Huang, Tu, & Chien, 2012). In addition, they reported that "weight status on depressive symptoms was partially mediated by perceived overweight, greater weight concern, and dietary restraint" (Ting et al., 2012, p. 1252). It was reported that baseline depressive symptoms significantly influenced the rate of change in BMI, but the initial BMI did not influence the depressive symptoms (Needham, Epel, Adler, & Kiefe, 2010). Further, in a study with self-reported weights, adolescents reported differences in the measured BMI values and the self-reported values, which is concerning as many of the studies use self-reported data in this population (Rhew et al., 2008). The authors reported that the discrepancy in BMI measurements differed according to depressive symptoms, gender, and study visit (Rhew et al., 2008).

Depressive Symptoms in Youth Associated with Type-2 Diabetes

Studies evaluating depressive symptoms in youth with type-2 diabetes are not readily accessible even though there are many studies reporting depressive symptoms in youth with type-1 diabetes and youth with obesity (Ali, Fang, & Rizzo, 2010; Colton, Olmsted, Daneman, & Rodin, 2013; Richardson, Garrison, Drangsholt, Mancl, & LeResche, 2006; Wu, Hilliard, Rausch, Dolan, & Hood, 2013). Type-2 diabetes in youth has increased in prevalence over the past three decades which is most likely due to the increase in childhood obesity in the same period of time (Santoro, 2013; Van Name & Santoro, 2013). There is a gap in the literature related to the incidence of depressive symptoms in youth with altered glucose metabolism and type-2 diabetes.

According to the Centers for Disease Control and Prevention (2013a) it is well known that the prevalence of type-2 diabetes in the US is higher in non-white groups and especially

Native Americans. A study from Cincinnati, Ohio in 1994 reported an incidence rate for type-2 diabetes in youth at that time of 7.2 percent per 1000 in African American and white adolescents (Centers for Disease Control and Prevention, 2013a).

In a study focusing on depressive symptoms and type-2 diabetes in adults reported 52 percent higher odds of developing depressive symptoms (Golden et al., 2008). In addition, it was reported that individuals with higher depressive symptoms were less likely to follow lifestyle recommendations and subsequently develop poor outcomes (Golden et al., 2008). In a recent study of adolescents with insulin resistance, impaired fasting glucose, and impaired glucose tolerance, higher depressive symptoms were reported with a higher risk for development of type-2 diabetes in these youth (Hannon, Rofey, Lee, & Arslanian, 2013). Like depressive symptoms associated with obesity, the authors also state that the directionality of the association is unclear (Hannon et al., 2013).

Independent Variables and Childhood Obesity

Obesity is a risk factor for development of many co-morbidities associated with excess weight including impaired glucose metabolism which can lead to type-2 diabetes (Neef et al., 2013). NHANES data from 1999 to 2010 were indicated that 34 percent of type-2 diabetes in adolescents was undiagnosed (Demmer, Zuk, Rosenbaum, & Desvarieux, 2013). Hispanic, non-Hispanic black, Pima Indian, and Asian obese youth were more likely to develop type-2 diabetes than non-Hispanic White (Levy-Marchal et al., 2010; Ogden et al., 2012a).   Insulin resistance (decreased insulin sensitivity) can have multiple etiologies including obesity, ethnicity, family history, and pubertal hormones (Cree-Green et al., 2013; Levy-Marchal et al., 2010). When insulin resistance develops, the beta cells in the pancreas will maintain normoglycemia by

making exaggerated levels of insulin (hyperinsulinemia) to compensate (D'Adamo et al., 2011; Neef et al., 2013). At some point the beta cells fail and lose the ability to make the excess insulin to maintain serum glucose in the normal range. The child will progressively develop impaired fasting glucose or impaired glucose tolerance and eventually type-2 diabetes (D'Adamo et al., 2011). In another study it was reported that having both impaired fasting glucose and impaired glucose tolerance put a child at greater risk for development of type-2 diabetes (Bacha et al., 2010). It has also been reported that obese youth develop type-2 diabetes at a faster pace than adults (D'Adamo et al., 2011; Gungor & Arslanian, 2004; Weiss et al., 2005).

In 2010 the American Diabetes Association (ADA) endorsed the use of HbA1c to diagnose type-2 diabetes in adults and youth (American Diabetes, 2014). However, in youth the ADA acknowledges that there is a paucity of literature to support diagnosing youth based on HbA1c (American Diabetes, 2014). It has been reported that HbA1c has low sensitivity and specificity in youth and should be confirmed with oral glucose tolerance testing (Nowicka et al., 2011). The oral glucose tolerance test is completed after an eight hour fast. It measures the body's response to a glucose challenge. The fasting glucose and insulin levels are drawn, and then the child drinks 75 grams of glucose solution. Subsequent serum glucose and insulin levels are drawn at 30, 60, 90, and 120 minutes. An abbreviated glucose challenge omits the 30, 60, and 90 minute draws.

Overview of the Design

Secondary analysis is one method of research used to answer research questions utilizing an existing database, which can be more cost efficient and less time consuming than a research trial which involves recruitment and enrollment of subjects (Smith et al., 2011). A secondary

analysis can have disadvantages, such as no control over what data are collected (Smith et al., 2011). In this study a secondary analysis was completed from the existing dataset of a research study exploring depression in obese insulin resistant adolescents. A retrospective chart review was done on all participants to collect data over time (6 years) related to the progression of altered glucose metabolism.

Summary

The review of literature reveals that there is little information on the incidence rates of obesity and insulin resistance, impaired fasting glucose, impaired glucose tolerance, and the development of type-2 diabetes in youth over time. There is also little information related to the relationship between depressive symptoms and the above conditions.

Chapter III

Methodology

This chapter contains a description of the study design, the sample of youth who participated in the original study, the setting, procedures, measures, and the secondary data analyses and retrospective chart review. It also summarizes the details of the original study including the setting and a description of the participants over time. Finally, ethical considerations, possible limitations, and future research consideration are addressed.

Research Questions

In a cohort of 78 obese youth 11-17 years of age who presented for an initial appointment for evaluation of obesity and insulin resistance and enrolled in an outpatient endocrine study from 2007 to 2009:

1. What is the incidence of abnormal glycosylated hemoglobin (HbA1c) from June 2007 to March 2013?

2. What is the incidence rate of insulin resistance (measured by HOMA-IR) over the study period from June 2007 to March 2013?

3. What are the incidence rates of elevated insulin response (a sum of the insulin results at 0, 30, 60, 90, and 120 minutes from the oral glucose tolerance test), impaired fasting glucose (Fasting glucose 100mg/dl to 125mg/dl), impaired glucose tolerance (a two hour post challenge glucose of 140mg/dl to 199mg/dl), and type-2 diabetes (a fasting glucose $\geq$ 126mg/dl or a two hour post challenge glucose of $\geq$ 200mg/dl), as measured by a two hour oral glucose tolerance test (full or abbreviated) over the study period of June 2007 to March 2013?

4. Are depressive symptoms correlated with insulin resistance, hyperinsulinemia, impaired

 fasting glucose, impaired glucose tolerance, or HbA1c?

5. Are depressive symptoms significantly different in youth with type-2 diabetes than those

 without type-2 diabetes?

Overview of the Design

 A secondary data analysis is the examination and analysis of data collected for a different

purpose (Smith et al., 2011). Using a secondary analysis method allows researchers to answer

research questions with less time involved as subjects do not need to be enrolled. A

retrospective chart review is a method of data collection involving review of medical records and

data originally collected as part of a routine patient visit and not for research purposes (Gearing,

Mian, Barber, & Ickowicz, 2006).

 In this study, a secondary data analysis and a retrospective chart review was conducted

using the dataset and participant medical records from the study "Health-Related Quality of Life,

Depression, and the Impact on Successful Incorporation of Lifestyle Changes in Insulin Resistant

Adolescents as Evidenced by Changes in BMI, Waist Circumference, and Metabolic

Parameters". The original study was an evidence-based practice implementation project. There

was inadequate literature to support the project conducted at an urban medical center, thus a non-

randomized descriptive research study was conducted. The study was funded by the Dee Lyons

Foundation and The Children's Mercy Hospitals and Clinics in Kansas City, Missouri and the

Section of Endocrinology. The database includes overweight and obese participants (*n*=82)

presenting as newly referred patients to an outpatient pediatric endocrinology clinic. All

participants gave assent and their parents gave consent to allow participation in the study.

Enrollment was from June of 2007 to March of 2009. Each subject agreed to three visits over a

12 month time span. The primary aims of the original study were not met due to a high rate of attrition. In the proposed study, the incidence of precursors to diabetes were explored in the obese subjects without diabetes at baseline (*n*=78) using a secondary analysis method. The progression to type-two diabetes was investigated using a retrospective chart review method if the subjects had been followed in the endocrine clinic since participation in the study.

This methodology also provided longitudinal data to answer the research questions posed (Smith et al., 2011). The investigator for this study was familiar with the original study, the data collected, and the data collection methods (Smith et al., 2011). The data collected in a retrospective chart review are usually collected for clinical or administrative purposes (Gearing et al., 2006). However, this approach provides a rich source of data for clinical research, especially epidemiological studies (Gearing et al., 2006; Smith et al., 2011). One of the limitations of a secondary analysis research design is that the data collected might not be exactly what is needed to answer the research questions (Smith et al., 2011). In the original study database, waist circumference measurements were not available due to the difficulty the care assistant incurred trying to accurately measure the morbidly obese youth. In a retrospective chart review one of the limitations is incomplete documentation (Gearing et al., 2006). However, with the electronic medical record it is much simpler to obtain information by using templates to write letters during the visit, which create standardized notes and make it more efficient to collect data (Murphy, Ferris, & O'Donnell, 2007).

Secondary Analysis and Retrospective Chart Review Study Design

The study used a descriptive correlational design as the variables of this disease process were described but causal linkages were not identified. The connection between the disease in a

group (type-2 diabetes) and its relationship to the other dependent variables was also explored.

In this study the incidence rate of insulin resistance, hyperinsulinemia, impaired fasting glucose, impaired glucose tolerance, type-2 diabetes, and abnormal HbA1c levels was calculated in rates and percentages. Depression was correlated with all the continuous variables using Pearson's R Correlations, and independent t-tests were computed for the categorical variables. Differences in depression scores in youth with type-2 diabetes and those without were analyzed by using an independent samples t-test with an α of 0.05, as the data met normality assumptions. (See Figure 2.)

Figure 2. **Distribution of the Sample Sizes**
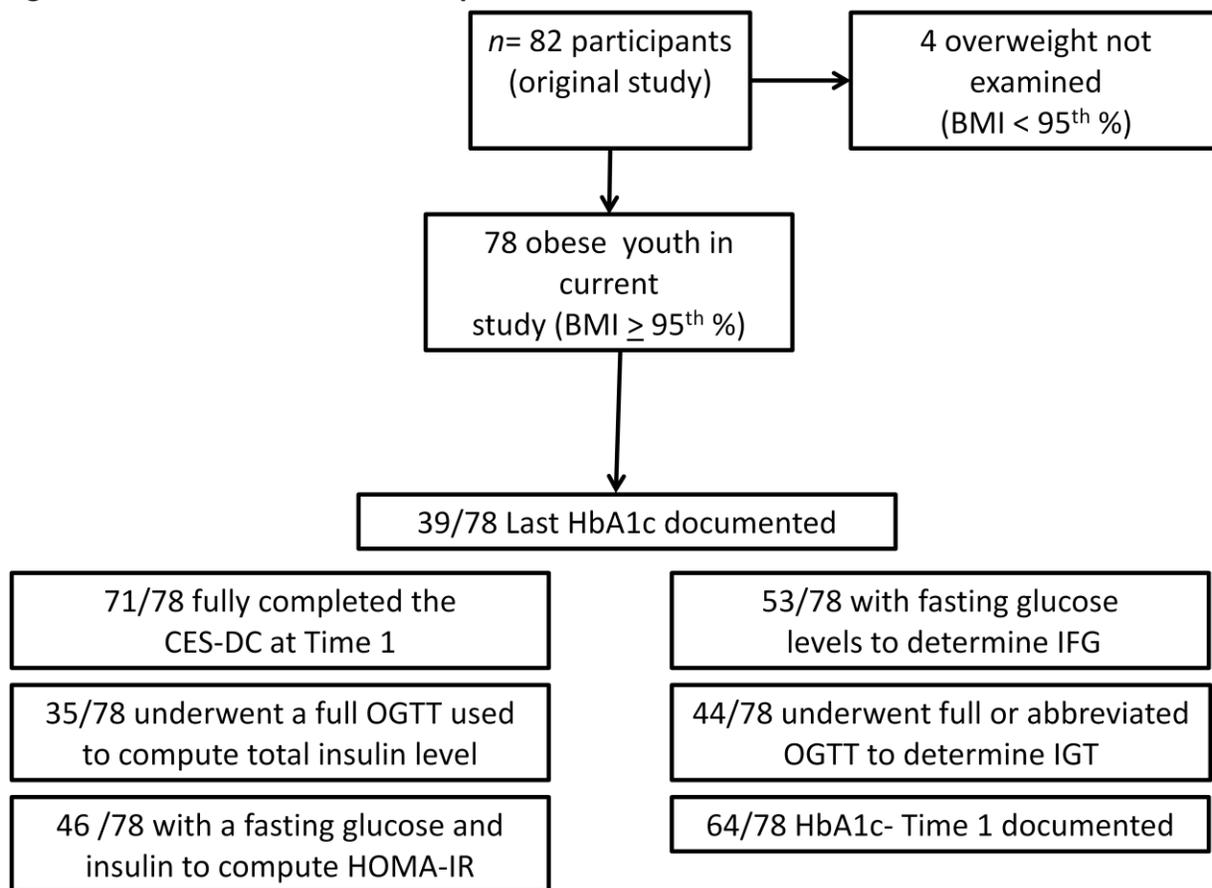
Secondary Descriptive Analysis

An advantage of conducting a secondary data analysis and retrospective chart review is it

provides a new perspective of existing data to answer new research questions. A report was

created with the raw data including a description of the sample (age, race, and gender),

frequencies of the variables, central tendencies, and potential outliers. New knowledge was

generated with the results related to the incidence rates of precursors to type-2 diabetes and type-

2 diabetes in youth which has not been published in the literature in obese youth. The HbA1c

percentage was helpful as a screening test to identify youth at risk for development of type-2

diabetes and to guide the providers in the identification of those who would benefit most from

the oral glucose tolerance test to confirm suspicions of type-2 diabetes (Fajans et al., 2011). The

central tendencies of the results were obtained along with a percentage of the sample in the

abnormal range. Depression has been associated with childhood obesity and new knowledge

was generated with correlations of depressive symptoms scores with altered glucose metabolism

and HbA1c to explore differences in this population. New hypotheses and new approaches to

screening high risk youth will be posed with this new information.

<div align="center">

Independent Variables and Type-2 Diabetes

</div>

Glycosylated Hemoglobin (HbA1c)

Results from oral glucose tolerance tests were reported to be better predictors of insulin

sensitivity and risk for development of type-2 diabetes than anthropometric characteristics

(Weiss et al., 2005). In 2010 a HbA1c of 6.5% or higher was recommended by the American

Diabetes Association as a more practical and reliable method for diagnosing type-2 diabetes

instead of the oral glucose tolerance test in adults. It is acknowledged that there is a lack of

literature supporting use of HbA1c for diagnosis in youth (American Diabetes, 2014). The oral

glucose tolerance test has been the "gold standard" to diagnose type-2 diabetes, but is lacking

validity and reproducibility in youth (Kapadia, 2013). The HbA1c has been dismissed as

unreliable because it doesn't always correlate with the results of the oral glucose tolerance test

(Kapadia, 2013; Nowicka et al., 2011). Yet, HbA1c is a less invasive method of screening youth

for impaired glucose tolerance and type-2 diabetes in the clinic setting and may increase early

detection of glucose impairment (Kapadia, 2013; Nowicka et al., 2011)

Insulin Resistance

Insulin resistance has an important role in the development of type-2 diabetes

(Mizokami-Stout et al., 2012). The progression of insulin resistance to overt type-2 diabetes is

related to a lack of insulin sensitivity and compensation by increasing the amount of insulin

secreted leading to beta cell failure or dysfunction and, subsequently, hyperglycemia develops

(Cali et al., 2009; Huan & Falkner, 2009; Mizokami-Stout et al., 2012). The rate of progression

from insulin resistance to type-2 diabetes appears to be more rapid in youth than in adults (Cree-

Green et al., 2013; Mizokami-Stout et al., 2012). In comparison with adults, however, not every

obese hyperglycemic adolescent will eventually develop type-2 diabetes (Cree-Green et al.,

2013). The increase in pediatric obesity and the prevalence of insulin resistance and type-2

diabetes makes it important to discern which obese youth will eventually progress to develop

diabetes so that treatments can be targeted toward this population (Cree-Green et al., 2013).

Hyperinsulinemia

Hyperinsulinemia calculated by the sum of the insulin responses (µU/ml) during a two

hour oral glucose tolerance test provides additional information related to the response of the

beta cells to a 75 gram glucose challenge (Kurtoglu et al., 2010). "Type 2 diabetes is often associated with basal hyperinsulinemia, reduced sensitivity to insulin, and disturbances in insulin release" (Shanik et al., 2008, p. s263). It is proposed that hyperinsulinemia reflects the level of insulin resistance and is related to "hypertension, obesity, and glucose intolerance in humans" (Shanik et al., 2008, p. s266). There is a paucity of literature related to hyperinsulinemia and insulin resistance in obese youth as hyperinsulinemia is usually associated with congenital hyperinsulinism and subsequent hypoglycemia in an infant or young child. Calculating the sum of the insulin responses from a two hour oral glucose tolerance test in obese youth is a simple method to identify those at higher risk for development of type-2 diabetes over time.

Impaired Fasting Glucose and Impaired Glucose Tolerance

Impaired fasting glucose and impaired glucose tolerance in youth have been linked to the development of type-2 diabetes in young adulthood (Bacha et al., 2010; Ghergherechi & Tabrizi, 2010; Nguyen, Srinivasan, Xu, Chen, & Berenson, 2010; Weiss et al., 2005). In a large population-based prevention study it was reported that youth with both impaired fasting glucose and impaired glucose tolerance had a 19 times higher rate of developing type-2 diabetes than a normal glucose tolerance group (Engberg et al., 2009).

Depressive Symptoms

Depressive symptoms and the association with type-2 diabetes in youth are not well reported in the literature which may be due to a lack of longitudinal studies (Springer et al., 2013). In the past, type-2 diabetes was labeled adult onset diabetes as it was not common in youth. However, with the increase in the prevalence of obesity there has been an increase in the prevalence of type-2 diabetes in youth (Demmer et al., 2013; Van Name & Santoro, 2013). A

secondary data analysis was conducted on NHANES data over the past 12 years and it was reported that type-2 diabetes accounted for approximately half the youth in the US with diabetes and one third of those youth were undiagnosed (Demmer et al., 2013). Subsequently, due to the lack of cases of type-2 diabetes diagnosed in youth, the association with depressive symptoms represents a gap in the literature.

Review of the Setting

The "Health-Related Quality of Life, Depression, and the Impact on Successful Incorporation of Lifestyle Changes in Insulin Resistant Adolescents as Evidenced by Changes in BMI and Metabolic Parameters" study was conducted in the outpatient endocrinology clinic at Children's Mercy Hospitals and Clinics (CMHC) main campus location in Kansas City, Missouri. The hospital is a free-standing pediatric facility well known for its excellence in care. The organization consists of two hospitals, five clinics, and multiple outreach clinics serving a 500 mile radius from downtown Kansas City.

Children's Mercy Hospitals and Clinics was the first hospital in Missouri and Kansas to earn Magnet Designation by the American Nurses Credentialing Center (ANCC). Developed by the ANCC, Magnet is the leading source of successful nursing practices and strategies worldwide" (American Nurses Credentialing Center, 2013). "The Magnet Recognition Program® recognizes healthcare organizations for quality patient care, nursing excellence and innovations in professional nursing practice. Consumers rely on Magnet designation as the ultimate credential for high quality nursing. Children's Mercy Hospitals and Clinics were redesignated in September 2012. There are currently ten hospitals in Missouri and Kansas with Magnet Designation.

There are currently 17 attending pediatric endocrinologists, seven fellows, and five nurse practitioners practicing in the section of endocrinology at CMHC. Research is a top priority at the hospital and in the section of endocrinology. This study was supported by the CMHC section of Endocrinology.

Review of the Original Study Enrollment

Institutional Review Board approval for the original study was obtained June 11, 2007 for two years and was extended one year for further enrollment purposes. Enrollment ended in March of 2010. Referred patients between the ages of 11 and 17 years inclusive, presenting to the Endocrinology Clinic for evaluation of obesity and insulin resistance and meeting inclusion and exclusion criteria were approached for enrollment into the study. Inclusion criteria were all new patients 11 to 17 years of age presenting for evaluation in the Insulin Resistance Syndrome Clinic within the section of endocrinology. All subjects and parents were required to speak, read, and write English fluently. Exclusion criteria were: 1) youth with a co-morbid syndrome making it unlikely they could fill out the forms themselves; 2) youth already diagnosed with type-2 diabetes; 3) youth taking metformin before the initial visit; 4) youth taking any medication for a psychiatric condition prior to the initial visit; and 5) youth with developmental delay. All screened patients meeting the inclusion and exclusion criteria were invited to participate in the study. All subjects were screened for depression and health-related quality of life at enrollment, four months, and 12 months. Independent variable data (HbA1c, cholesterol panel, height and weight to calculate BMI) were obtained from lab work drawn at the primary care provider's office, or on the day of the first visit.

Of the patients who were approached to participate in the study, a majority agreed to participate. The parent signed the consent form while the child assented to participation and also signed the consent form.   The historical control group (*n*=326) list was assembled from patients who had been evaluated for obesity and associated co-morbidities in the prior year in the Insulin Resistance Syndrome Clinic and could possibly serve as matched controls.

Review of the Sample

A sample of participants was recruited in this inner city, pediatric hospital affiliated outpatient clinic. At the initial recruitment, the number of youth who agreed to participate and enroll in the original study was 82 youth between the ages of 11 and 17 years (*M* = 14.2; *SD* = .76). Participants included 33 males (40.2%) and 49 females (59.8%). Participants were self-identified into one of four racial and ethnic groups including Caucasian (53.7%), African American (40.2 %), Hispanic (3.7%), and "other race" (2.4%). Forty-seven (57.3%) attended the three to four month follow up clinic appointment and continued to participate, and 30 (36.6%) attended the one year follow up appointment. Overall, 24 (29.3%) participated in all three visits. Six participated in the one year appointment, but did not attend the three to four month visit (Platt et al., 2013). Of the 78 youth who met criteria for obesity using the CDC body mass index percentile chart the mean weight was 100.2 kg (220 lbs) with a range of 58.2 kg (128 lbs) to 154.9 kg (341 lbs.).

Sample Representativeness

The sample of participants were recruited from all referred patients presenting to the clinic and meeting the inclusion and exclusion criteria thus avoiding a sampling bias (Rosenthal & Rosnow, 2008). Attrition rates of completers in this sample were high (70.7%), which is not

uncommon in weight management studies (Dolinsky, Armstrong, & Ostbye, 2012; Holzapfel et al., 2013). In a large study (n=983) examining predictors of attrition in a pediatric weight management program, the attrition rate was reported as 83 percent non-completers with race and public insurance significantly predicting dropout (Dolinsky et al., 2012). This particular sample had a low representation by Hispanic youth and "other race" which may be a reflection of the general population in this urban area. However, it could be related to the exclusion criteria that the family must be fluent in English to read, understand, and complete the consent forms and instruments. The data from the completers (n=30) and the non-completers (n=52) were analyzed for differences in demographics, health parameters, and psychological scores and no significant differences in the groups were found. Despite this potential limitation (low enrollment of Hispanic ethnicity and "other race"), the research questions being posed should still provide valuable information to nursing science.

Data Monitoring and Quality Management Controls

The institutional review board (IRB) at The Children's Mercy Hospitals and Clinics approved the study protocol prior to any research activities and required a written review of the study progress on an annual basis including samples of the last three consent forms. The IRB was notified of any personnel change or changes to the protocol (stopped measuring waist circumference due to inaccuracy of the measurements).

All data in the database were entered by a professional data entry research assistant. The data were reviewed by the primary investigator and a sub-investigator for accuracy at random intervals during the study. Calculations of BMI, BMI z-score, and depression screening scores were computed by the statistical software for accuracy.

Procedures and Methods for the Study

The current study utilized a copy of the original de-identified database. To ensure the accuracy of the original data, the primary investigator randomly selected 10 percent of the cases and verified the values. A copy of the verified database was cleaned to include only data needed for the proposed study. The variables from the retrospective chart review were added to this database. All data from the medical record was obtained and entered by the primary investigator as she is the only person with the master linking list which is filed on the password secured electronic medical record system at CMHC. A copy of the de-identified database was sent electronically to the committee chair and psychologist (Dr. Bosak and Dr. Egan) using the CMHC encrypted email system.

Due to the high attrition rate in the original study there is missing data. Consequently, the first visit data were used for the current study. We explored the participant medical records for oral glucose tolerance test results. Not all of the patients had this testing done as some only attended one visit. There was missing at random data (MAR) associated with the variables of interest such as calculating the incidence of type-2 diabetes (Rosenthal & Rosnow, 2008). As an approach to the missing data, we conducted a pairwise deletion procedure. We did not drop any of the participants in the study, as this could affect our study power with a small database. Additionally, the oral glucose tolerance test results were not required to answer all the research questions (Rosenthal & Rosnow, 2008). In the original study, any of the depression screens not completed were not included in the analyses (the total score would be inaccurate). A listwise deletion procedure was employed (Rosenthal & Rosnow, 2008).

Variables Included in the Secondary Data Analysis

The variables selected for the secondary data analysis were chosen after a review of the literature, based on the conceptual framework, and the availability of the data in the database or medical record. The variables in this analysis include the demographics of the sample (age, gender, and race/ethnicity), HbA1c, height, weight, BMI, BMI z score, results from the two hour oral glucose tolerance test, and depressive symptoms score which were obtained using the CES-DC instrument. All of these variables are continuous except for gender and race/ethnicity.

Study Instrumentation

The Center for Epidemiological Studies Depression Scale for Children (CES-DC) was adapted from the Center for Epidemiological Studies Depression Scale (CES-D) to screen youth for depressive symptoms (Faulstich et al., 1986; Weissman et al., 1980). It was selected for the original study as it is a widely recognized instrument with established psychometrics, relatively short, and the questions were worded with relevance to children. The CES-DC consists of 20 items answered with a 4-point Likert scale (0 to 3). It was designed to assess the level of psychological impairment in children and adolescents. A score of 15 or greater is indicative of depressive symptoms, 30 to 44 moderate depressive symptoms, and 45 and greater severe depressive symptoms (Weissman et al., 1980).

The CES-DC was piloted with a group of 148 children, eight to 17 years of age hospitalized in an inpatient psychiatric facility (Faulstich et al., 1986). The CES-DC was trialed a second time on a subset of these patients (n=78) for test re-test reliability (r= .51; $p < .005$). Internal consistency was good overall with a coefficient alpha of .84. The same sample of children were also screened with the Children's Depression Inventory (Beck, Steer, Ball, & Ranieri, 1996) for comparison and the concurrent validity was significant (r=.44). Factor

analysis was conducted using principal component analysis with a Varimax rotation and loaded best into a three factor solution (behavioral, cognitive, and happiness) which accounted for 44.32 percent of the variance (Faulstich et al., 1986).

The sample was divided into two groups based on ages, 8 to 12 years, and 13 to 17 years to look for developmental differences. The total scores on the CES-DC did not significantly differ between either group. The internal consistency in both groups measured by Cronbach's alpha was good at .77, and .86, respectively. However, the test-retest reliability was poor in the 8 to 12 year old group (r=.12), and good for the older group (r=.69). The Children's Depression Inventory test-retest for children was worse (r=.03) (Faulstich et al., 1986). It was tested in 1990 by another researcher who found the CES-DC to have good reliability ($r = .89$) and validity especially as a screening instrument for depressive symptoms in youth 12 to 18 years of age (Fendrich et al., 1990). This author recommended a score of 15 as a cut-off point for further clinical investigation (Fendrich et al., 1990). The CES-DC was revalidated more recently in a study evaluating depression in children living in Rwanda (Betancourt et al., 2012). The CES-DC was trialed on a group of 367 Rwandan children ages 10 to 17 years. Internal reliability was good (α=.86) and as was test-retest reliability (r =.85). When compared to the MINI KID (Sheehan et al., 2010), the CES-DC was able to identify the depressed from the non-depressed youth with an area under the curve of .825. A cut off of $\geq$30 was used as the diagnosis point for depression with a sensitivity of 81.9% and a specificity of 71.9%. This study validates the usefulness of the CES-DC in identifying depressed from non-depressed youth without psychiatric diagnoses.

In summary, the CES-DC was more accurate with screening adolescents for depressive symptoms than children, and was validated in 1990 and more recently in 2012 (Betancourt et al.,

2012; Faulstich et al., 1986; Fendrich et al., 1990). The sample of youth used for the pilot study were hospitalized psychiatric patients which may make the reported results less generalizable (Faulstich et al., 1986). The instrument was designed to identify adolescents exhibiting acute depressive symptoms who may need further consultation by a mental healthcare provider (Faulstich et al., 1986; Fendrich et al., 1990). It was not designed to be used as a diagnostic measure of depression (Faulstich et al., 1986). This instrument appears to be a valid and reliable instrument for screening adolescents for depressive symptoms. It is easy to use and is available at no cost in the public domain (Georgetown University, 2013).

Demographic Variables and Outcome Variables

The demographic variables used in this study were: age (in years and months calculated into years, for example 12 years and 3 months is equivalent to 12.25 years), race (self-reported), and gender (defined by biological sex). The outcome variables examined were (a) height was measured without shoes using a wall-mounted stadiometer (SECA, Birmingham, United Kingdom) with the head in the Frankfort plane position, back against the wall, and measured to 0.1 cm; (b) weight was also obtained without shoes using a digital scale (Scaletronix, White Plains, New York) and measured to the nearest 0.1 kg; (c) body mass index was calculated from the height and weight and was automatically calculated by the database software package (IBM Corp, 2011) to decrease calculation errors; (d) body mass index z-score was also calculated by the software package (IBM Corp, 2011) to standardize BMI for age and sex. It is the measure of the distance from the mean. (e) Glycosylated hemoglobin was obtained at the first visit or was recorded from lab work drawn at an outside facility no longer than two months before the first visit. (f) Oral glucose tolerance test results were obtained from the electronic medical records of the participants. The oral glucose tolerance test is conducted in the endocrinology clinic testing

area. Patients were instructed to fast for at least eight hours. If they had been taking metformin,

they were instructed to stop the medication at least two weeks prior to the study. When they

arrived to the clinic, an intravenous catheter (IV) was inserted and fasting lab work was drawn

including a baseline glucose and insulin level. The patient was then instructed to drink a 75

gram glucose drink in less than 10 minutes. After drinking the glucose drink, a glucose and

insulin level were drawn every 30 minutes for two hours (an abbreviated test measures fasting

and 2 hour post challenge glucose and insulin levels). (g) The other outcome variables as

previously defined in Chapter I were HbA1c, insulin resistance, hyperinsulinemia, impaired

fasting glucose, impaired glucose tolerance, type-2 diabetes, and depression scores from the

CES-DC.

Statistical Analysis

All data were analyzed using the Statistical Package for Social Science (SPSS) version 20

(IBM Corp, 2011). Cases were selected based on BMI % $\geq$95%. The dataset was reviewed for

missing data and outliers prior to analyses. The pairwise deletion procedure was used for the

missing data. Computations were conducted using the SPSS software (IBM Corp, 2011) and the

data available related to the parameters of interest (Rosenthal & Rosnow, 2008). Any outliers

were examined for accurate data entry. The computations were rerun without the outlier to

explore if the outlier was skewing the results, and consideration was made for dropping this

value. The outlier could have lead to a biased measure of central tendency (mean and median

would be affected). Statistical assumptions of normality and linearity were evaluated.

Descriptive statistics of each variable were conducted consisting of measures of central tendency

and frequency distributions.

Research Question Data Analysis

An analysis plan is described for each research question below. Descriptive statistics were conducted describing the sample of 78 obese adolescents as well as the outcome variables using SPSS version 20 (IBM Corp, 2011).

Research Question 1

1. *What is the incidence of abnormal glycosylated hemoglobin (HbA1c) from June 2007 to March 2013?*

The number of participants with HbA1c $\geq$ 5.7% was calculated as raw data. The percent of the individuals with an abnormal HbA1c was calculated (raw number divided by the total sample with HbA1c results documented).

Research Question 2

2. *What is the incidence rate of insulin resistance (measured by HOMA-IR) over the study period of June 2007 to March 2013?*

HOMA-IR was calculated by multiplying the fasting glucose (mg/dl) by the fasting insulin (μU/ml) and dividing by 504 (Kurtoglu et al., 2010). Descriptive analyses and measures of central tendency were conducted with the participants who met the definition of insulin resistance. Raw data of the number of participants with insulin resistance and the percent of the sample with insulin resistance were computed (raw number divided by the total sample).

Research Question 3

3. What are the incidence rates of elevated insulin response (a sum of the insulin results at 0, 30, 60, 90, and 120 minutes from the oral glucose tolerance test), impaired fasting glucose (fasting glucose 100mg/dl to 125mg/dl), impaired glucose tolerance (a two hour post challenge glucose of 140mg/dl to 199mg/dl), and type-2 diabetes (a fasting glucose $\geq$ 126mg/d, or a two-hour post challenge glucose of $\geq$ 200mg/dl) as measured by a two hour oral glucose tolerance test over the study period of June 2007 to March 2013?

Descriptive analyses were conducted on each dependent variable. Raw data of the number of participants with hyperinsulinemia, impaired fasting glucose, impaired glucose tolerance, and type-2 diabetes were calculated. The percent of the independent variables in the total sample were calculated (raw number divided by the total sample).

Research Question 4

4. Are depressive symptoms significantly correlated with HbA1c, insulin resistance (HOMA-IR $\geq$ to 2.7), hyperinsulinemia (summed insulin levels during oral glucose tolerance testing $\geq$ 300µU/ml), impaired fasting glucose (fasting glucose 100mg/dl to 125mg/dl), or impaired glucose tolerance (a two hour post challenge glucose of 140mg/dl to 199mg/dl)?

Descriptive statistics were conducted on the entire sample. T-tests were computed between depressive symptoms total score obtained from the CES-DC and each independent variable above using an alpha of 0.05.

Research Question 5

5.Are depressive symptoms significantly different in youth with type-2 diabetes than those without type-2 diabetes?

Independent samples t-tests were conducted on both groups to look for the distribution of the differences in the means of the sample with an alpha of 0.05. The *t* scores are normally distributed, thus median scores were not reported.

Power Analysis

Research Questions 1, 2, & 3

A power analysis was not necessary for research questions one, two, and three as these questions explore incidence rates and percentages. Causality was not assessed in this study.

Research Question 4

Chi square computations were conducted on the categorical variables of insulin resistance, hyperinsulinemia, impaired fasting glucose, impaired glucose tolerance, and type-2 diabetes. Independent t-tests were conducted to evaluate any significant associations between the continuous variables of age, BMI percentile, BMI z scores, HbA1c, HOMA-IR scores, the total insulin scores from the oral glucose tolerance test results, and the depressive symptoms scores (total scores from the CES-DC screening). Analysis of variance (one-way ANOVA) was computed to look for significant associations between the multi-level categorical variable of race/ethnicity and the continuous variables. A power analysis was conducted using G Power 3 (Faul, Erdfelder, Lang, & Buchner, 2007). A two-tailed exact test with an alpha of .05 will have 80 % power to detect a correlation of .5 when the null hypothesis is zero. The recommended sample size was 29.

Research Question 5

Independent samples t-tests were planned to be used to compare mean depression scores for the youth with type-2 diabetes and those without type-2 diabetes. A power analysis was conducted using G Power 3 (Faul et al., 2007) with a medium effect size of .5 (Cohen, 1992), an alpha of .05, and a power of .80 which requires a sample size of 64. However, non-parametric statistics were conducted as the sample size requirements were not met.

Strengths and Limitations

Secondary data analysis is an efficient and economic means to conduct research, as participants do not need to be enrolled and the expense of conducting the study is much less (Rew, Koniak-Griffin, Lewis, Miles, & O'Sullivan, 2000). The candidate helped recruit and enroll the participants. Access to the data was allowed once the IRB application was submitted and approved. The original data was available to double check data entry, as a retrospective chart review was also conducted. There are some limitations to this approach that must be taken into consideration. The data were collected to answer other research questions, thus not all of the variables were available to meet the criteria for more in depth questions (Rew et al., 2000). Another limitation was that the original dataset is small when compared with large national surveys (Rew et al., 2000). Attrition was one of the most difficult limitations encountered but not uncommon in this population of youth (Hampl et al., 2013). The strengths of the data, however, outweighed the limitations, especially with the additional data obtained from the retrospective chart review.

Ethical Considerations

A secondary data analysis is considered to be minimal risk research as the data in the database is de-identified. The data key has been locked in a cabinet in a locked office since the

original study was conducted. All data was transferred via the CMHC secure email. During the study all the data was stored on a password protected computer and automatically backed up on the hospital's "U" drive. No data was stored on any portable device. The IRB application for this study was approved by CMHC (primary review board) and the University of Kansas Medical Center Human Subject Committee (secondary review board).

Summary

A secondary analysis and retrospective chart review was conducted using a descriptive correlational design to answer the following research questions.

1. What is the incidence of abnormal glycosylated hemoglobin (HbA1c) from June 2007 to March 2013?

2. What is the incidence rate of insulin resistance (measured by HOMA-IR) over the study period of June 2007 to March 2013?

3. What are the incidence rates of hyperinsulinemia (a sum of the insulin results at 0, 30, 60, 90, and 120 minutes from the oral glucose tolerance test); impaired fasting glucose (fasting glucose 100mg/dl to 125mg/dl); impaired glucose tolerance (a two hour post challenge glucose of 140mg/dl to 199mg/dl), and type-2 diabetes (a fasting glucose $\geq$ 126mg/dl or a two hour post challenge glucose of $\geq$ 200mg/dl), as measured by a two hour oral glucose tolerance test (full and abbreviated) over the study period of June 2007 to March 2013?

4. Are depressive symptoms significantly correlated with insulin resistance, hyperinsulinemia, impaired fasting glucose, impaired glucose tolerance, or HbA1c?

5. Are depressive symptoms significantly different in youth with type-2 diabetes than those without type-2 diabetes?

Answering these questions provides insight into the co-morbidities of altered glucose metabolism and progression to type-2 diabetes as related to childhood obesity, and contributes to Nursing Science. The incidence of depressive symptoms in this sample of high-risk obese youth with glucose intolerance indicates an association that could be used to direct weight management interventions in the future from a mental health perspective.

Chapter IV

Results

In this chapter the results of this research study are reported and the findings are analyzed as related to the incidence rates of insulin resistance, hyperinsulinism, impaired fasting glucose, impaired glucose tolerance, abnormal HbA1c, and type-2 diabetes in a sample of 11 to 17 year old youth presenting to an outpatient endocrine clinic for treatment of obesity and insulin resistance. The association of depressive symptoms and the variables cited above are presented, along with the issues encountered with depressive symptoms and type-2 diabetes in this sample.

Data Preparation and Missing Data Management

As this was a secondary analysis of an already existing database with added variables from the retrospective chart review, data preparation was included. Timing of HbA1c levels were verified to ensure that they were recorded accurately. Ten percent of the existing data in the database were compared with the medical records to ensure reliability and validity of the sample before any statistical evaluation. The depression screens scores revealed some missing data (seven subjects did not complete the CES-DC). Subsequently, the participants with missing responses on the CES-DC instrument were dropped from the analysis using listwise deletion. The scores would not be accurate without all items completed. The database also has a lot of missing completely at random (MCAR) data as participants did not return for follow-up visits at the clinic. Not all participants underwent oral glucose tolerance testing which provided data for computation of several variables. The test was ordered at the provider's discretion. Due to the randomness of this missing data and the small sample size, pairwise deletion was employed and none of the obese participants were dropped from the analyses.

Description of the Sample

The original database consisted of 82 overweight and obese youth age 11 to 17 years of age who presented for an initial appointment for evaluation of obesity and insulin resistance to an outpatient pediatric endocrinology clinic. These participants all consented to participate and were enrolled from June 2007 to March 2009 in the research study related to depressive symptoms and health-related quality of life in overweight and obese youth. Subjects who were overweight (body mass index less than the 95th percentile for age and gender) were not included in the analysis *(n=4)*. One participant had an initial HbA1c of 6.5% and another 6.7% which is considered diagnostic of type-2 diabetes in adults by the American Diabetes Association (American Diabetes, 2014). However, type-2 diabetes was not confirmed in these participants as the participant with the HbA1c of 6.5% was lost to follow-up and the oral glucose tolerance test in question was not confirmatory in the participant with the HbA1c of 6.7%. Consequently, these participants were not excluded from the analyses. The demographic characteristics of the sample *(n=78)* consisted of 42% male, and 58% female. Race was divided into four categories which included Caucasian (54%), African American (40%), Hispanic (4 %), and "other race" (2%). The mean age of the sample was 14.22 *(SD=1.78)* years and the mean BMI was 36.4 *(SD= 5.93)*, (see Table 1).

Description of the Variables

BMI and BMI z score

Obesity in youth is defined as a BMI greater than or equal to age and sex specific 95th percentiles when plotted on the 2000 CDC growth charts (Centers for Disease Control and Prevention, 2012). However, once a child's BMI reaches the 99th percentile the percentile

plateaus. For example a 200 pound and 400 pound 12 year old will both plot at the 99th

percentile on the CDC BMI chart (Centers for Disease Control and Prevention, 2009). In

addition to the BMI and BMI percentile the BMI z score provides a value "based on a

normalizing transformation or a smoothed version of observed reference data" (Flegal & Ogden,

2011, p. 160S). The BMI z score is a reflection of the number of standard deviations above or

below the mean BMI score plots. The higher the z score the more obese the child (Daniels,

2009). According to the World Health Organization (2014) youth with a z score greater than 2 is

considered overweight and a z score greater than 3 is considered obese. However, if this criteria

were used none of the participants in this study would be considered obese including a

participant with a BMI of 50. The WHO BMI z score cut-offs for adults are recommended for

those 5 to 19 years of age (overweight is a z score greater than 1 and obese is a z score greater

than 2 (de Onis & Lobstein, 2010). Consequently, the extrapolation of the z scores should be

evaluated with caution (Flegal & Cole, 2013). The z score provides additional manner of

distributing the differences in weight in the higher percentiles. For this study we have reported

BMI z-scores but for inclusion criteria for the study we have used the Centers for Disease

Control and Prevention BMI percentiles to select the obese participants. In the sample of 78

participants in this study there is a significant difference in gender as associated to BMI %

(p=.016) and BMI z scores (p=.008). The males on average were heavier as measured by BMI

% (*M*=99.14; *SD* .71) than females (*M* =98.6; *SD* 1.18). The males were also heavier on average

as computed for BMI z scores (*M*=2.47; *SD* .28) than females (*M*=2.3; *SD* .29).

Glycosylated hemoglobin (HbA1c)

A normal HbA1c range is 4% to less than 5.7%. It is an average of the prior three

months serum glucose levels. A HbA1c $\geq$ 5.7% is considered abnormal (Copeland et al., 2013).

Of the 64 participants with HbA1c from the first visit, 25 (39%) had abnormal levels. Of the 39

participants with documented HbA1c at the last visit, 19 (29%) had abnormal levels (see Table

3). The HbA1c from the first visit and the last visit were significantly correlated (r = .806,

p=.001). Analysis of variance was computed using race/ethnicity as the independent variable.

The HbA1c from the last visit was significant indicating race was associated with the HbA1c

from the last visit (F=4.54, p= .006). Post hoc testing was done using a Tukey HSD to examine

pairwise differences among the means of the groups and there was a significant difference

between Caucasian, and African American (p=.010).

Family History of Type-2 Diabetes

The family history was documented in the initial history and physical obtained when the

participant presented for the first visit to the pediatric outpatient endocrinology clinic. Of the 78

participants, 75 (96%) had a documented family history and 55 (73%) had a family history of

type-2 diabetes. The categorical variables were compared for independence using Chi Square

testing and family history was not found to be significantly associated with any of the other

categorical variables. Independent samples t-test were computed using family history as the

independent variable which was not significantly associated with any of the continuous

variables. Of those with documented family history, 41 % were male and 59 % were female

which was not significantly different.

Insulin Resistance

Insulin resistance was calculated using the homeostasis model assessment for

insulin resistance (HOMA-IR). HOMA-IR is calculated by multiplying fasting insulin (µU/ml)

by fasting glucose (mg/dl) and dividing by 504 (Kurtoglu et al., 2010). Results greater than 2.7

are considered abnormal in obese children (Atabek & Pirgon, 2007). However, in a more recent

article the scores were divided by pubertal status as it is well known that children become more

insulin resistant during puberty (Kurtoglu et al., 2010). The scores reported in prepubertal males

and females respectively are 2.67 and 2.22. In pubertal youth the scores are 5.22 and 3.82

(Kurtoglu et al., 2010). In the sample of 46 participants (out of the original 78) who had

documented fasting glucose and insulin levels, the mean HOMA-IR was M =7.31 (SD 8.36).

Thirty-six of the 46 (65%) participants had abnormal HOMA-IR scores well above all levels

without available pubertal status. Insulin resistance correlated with the sum of the insulin levels

from oral glucose tolerance testing (r=.533, p= .001) which supports the literature related to the

mechanism of decreasing insulin sensitivity (increasing insulin resistance) as the beta cells of the

pancreas compensate by making exaggerated levels of insulin (Giannini et al., 2012; Lann &

LeRoith, 2007). Insulin resistance also correlated with the two hour serum glucose level (r=.429,

p= .007). The more insulin resistant a child becomes the more likely they are to have an elevated

2 hour serum glucose response after glucose challenge (see Table 4). Independent t-tests were

conducted to look for significant differences in insulin resistance and the continuous variables.

Insulin resistance was significantly different than BMI %, BMI z score, insulin total, and the

fasting glucose obtained during the oral glucose tolerance tests (see Table 5).

Hyperinsulinemia

Hyperinsulinemia was calculated by summing the insulin levels during an oral glucose

tolerance test at 0, 30, 60, 90, and 120 minutes (Kurtoglu et al., 2010). Of the 78 participants, 35

underwent full oral glucose tolerance testing. All insulin sums greater than or equal to

300μU/ml are considered hyperinsulinemic with 35 (66%) participants meeting the criteria.

More than half of the sample tested were already making excessive amounts of insulin in

response to profound insulin resistance, eventually leading to beta cell failure. The total insulin response from oral glucose tolerance testing correlated with the 2 hour serum glucose result (r=.518, p=.001) which again supports beta cell failure in these youth. Out of the sample of youth with hyperinsulinemia, 48 % were male and 52% were females which wasn't significantly different.

Impaired Fasting Glucose

Impaired fasting glucose is a fasting glucose of 100mg/dl to 125mg/dl. (Copeland et al., 2013). Of the sample of 78 participants, 46 had documented fasting glucose levels and four (7.5 %) had already developed impaired fasting glucose (see Table 3). All of the participants who developed impaired fasting glucose were female.

Impaired Glucose Tolerance

Impaired glucose tolerance was measured by a two hour post-prandial glucose level obtained after a 75 gm. glucose challenge. Of the sample of 78 participants, 44 underwent oral glucose tolerance testing (full or abbreviated) and 4 (9.1%) met criteria for impaired glucose tolerance (see Table 3). Of the 44 participants tested, four developed impaired glucose tolerance, two were female and two were male. It has been reported that once obese youth develop impaired glucose tolerance they have developed an approximate 20 % failure of their beta cells (Cali et al., 2009).

Type-2 Diabetes

Type-2 diabetes is described as a fasting glucose level greater than 126mg/dl., a two-hour post-prandial glucose level obtained during an oral glucose tolerance test after a 75gm. glucose

challenge, or a random glucose greater than 200mg/dl (Copeland et al., 2013). In the sample of 78 participants, none met criteria for diagnosis of type-2 diabetes.

Depressive Symptoms Total Score

Depression screening was completed by 71 of the 78 participants at their initial visit, 44 of 78 at the second visit (3 to 4 months), and 29 of 78 at the one year visit. At the initial visit (*n* = 71) 49 % of the sample met criteria for elevated depressive symptoms (27 individuals with mild symptoms, 7 moderate symptoms, and 1 with severe symptoms). At the second visit (*n* = 44) 50 % met criteria for elevated depressive symptoms (19 had mild, 2 had moderate, and 1 had severe symptoms). At the final visit (*n* = 29) 41 % of the sample reported depressive symptoms (7 with mild, 4 with moderate, and 1 with severe), (see Table 6). When t-tests were conducted between the impaired glucose metabolism variables and total depression scores none of the results were significant.

<div align="center">

Description of the Relationships in the Study Framework

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Demographic Variables and Impaired Glucose Metabolism

Demographic variables of age, gender, race/ethnicity, and BMI describe this sample of obese youth. Age was not associated with impaired glucose metabolism. Chi square testing was conducted to look for associations between gender and impaired glucose metabolism variables. An elevated HbA1c was assessed in 10 males and 9 females with 64 (30%) greater or equal to 5.7%. Insulin resistance was assessed in 13 males and 17 females with 46 (65%) meeting criteria for diagnosis. Hyperinsulinemia was assessed in 11 males and 12 females with 35 (52%) meeting criteria for diagnosis. Impaired fasting glucose was assessed in four female participants and not in males. Impaired glucose tolerance was assessed in two male and two female

participants. Hyperinsulinemia was the only variable significantly associated with gender ($X^2 =$ 8.37(1), *p*=.004).

Demographic Variables and Type-2 Diabetes

The demographic variables of age, gender, race, and BMI describe the sample in general but age and BMI (continuous variables) were not able to be tested for association to type-2 diabetes since no participants developed type-2 diabetes over the six year period of time since the original study was conducted.

Depressive Symptoms and Impaired Glucose Metabolism

Hyperinsulinemia was prevalent in this high risk obese sample 35 (66%) of youth. Hyperinsulinemia had a strong association with the two hour glucose response after challenge (*r* = .518, *p*= .001) and the HOMA-IR (*r* = .533, *p*=.001). However, there were no correlations with the depressive symptoms scores. Insulin resistance was prevalent as 46 of the 78 obese youth were tested and 46 (65%) had elevated levels. Insulin resistance was associated with the two hour glucose response after challenge (*r* = .429, *p*= .007)). Insulin resistance scores and depressive symptom scores were not correlated. Of the youth with documented fasting glucose levels (53 of the 78 participants) only 4 (7.5%) met criteria for impaired fasting glucose. Impaired fasting glucose and depression scores were not associated. Impaired glucose tolerance was found in 4 (9.1%) participants in the sample of 44 who underwent glucose tolerance tests. Impaired glucose tolerance and depression scores were not associated. Independent t-tests were computed to look for differences in the means among impaired glucose metabolism (categorical variables) and depression scores and none were significant.

Depressive Symptoms and Type-2 Diabetes

The association between depressive symptoms and type-2 diabetes was unable to be tested as none of the participants developed type-2 diabetes over the six years since initial presentation.

Impaired Glucose Metabolism and Type-2 Diabetes

Type-2 diabetes was not found in any of the participants (*n*=78) thus the possible association with any of the variables was not tested.

Hypothesis Testing

1. *What is the incidence of abnormal ($\geq$ to 5.7%) glycosylated hemoglobin (HbA1c) between June 2007 and March 2013?*

    Of the 78 participants 61 had documented HbA1c results after the original study was completed. The Mean score was 5.5% (*SD* .38) with a range from 4.3 % to 6.4 % [19 (31%) were abnormal]. None met criteria for a diagnosis of type-2 diabetes according to the ADA criteria (American Diabetes Association, 2013).

2. *What is the incidence rate of insulin resistance (measured by HOMA-IR) during the study period of June 2007 to March 2013?*

    Of the 78 participants in the database, 46 had recorded fasting glucose and insulin levels. Some were obtained from results of the oral glucose tolerance test, some were obtained by an abbreviated glucose tolerance test (fasting levels and 2 hours after the glucose bolus), and some had recorded fasting glucose and insulin levels only. Thirty-six (78%) of the participants met criteria for diagnosis of insulin resistance with a range of results from 1 to 40. The Mean value was 7.31 (*SD* 8.36). A general score greater than 2.7 is considered insulin resistant (Atabek & Pirgon, 2007). However, in a more recent

article the scores were divided by pubertal status, as it is well known that youth become more insulin resistant during puberty (Kurtoglu et al., 2010). The scores reported in prepubertal males and females respectively are 2.67 and 2.22. In pubertal youth the scores are 5.22 and 3.82 (Kurtoglu et al., 2010).

3. *What are the incidence rates of hyperinsulinemia (a sum of the insulin results at 0, 30, 60, 90, and 120 minutes from the oral glucose tolerance test), impaired fasting glucose (Fasting glucose 100mg/dl to 125mg/dl), impaired glucose tolerance (a two hour post challenge glucose of 140mg/dl to 199mg/dl), and type-2 diabetes (a fasting glucose ≥ 126mg/dl or a two hour post challenge glucose of ≥ 200mg/dl), as measured by a two hour oral glucose tolerance test during the study period of June 2007 to March 2013?*

   Hyperinsulinemia was tested in 35 participants who underwent a full oral glucose tolerance test out of the sample of 78 participants and 23 (66%) of the sample were abnormal. The range of results was from 125 µU/ml to 1513 µU/ml. A result ≥ 300µU/ml is considered hyperinsulinemic (Kurtoglu et al., 2010). The score of 1513µU/ml is markedly elevated which together with insulin resistance raises concerns for development of beta cell failure. Impaired fasting glucose was tested in 53 participants of 78 and 4 (7.5%) met the criteria. Impaired glucose tolerance was tested in 44 of the 78 participants and 4 (9.1%) met criteria for diagnosis.

4. *Are depressive symptoms correlated with hyperinsulinemia (a sum of the insulin results at 0, 30, 60, 90, and 120 minutes from the oral glucose tolerance test), impaired fasting glucose (Fasting glucose 100mg/dl to 125mg/dl), impaired glucose tolerance (a two hour post challenge glucose of 140mg/dl to 199mg/dl)?*

Insulin resistance, hyperinsulinemia, impaired fasting glucose, impaired glucose tolerance and HbA1c did not have a significant association with depressive symptoms.

5. *Are depressive symptoms significantly different in youth with type-2 diabetes than those without type-2 diabetes?*

This research question was not able to be answered with the available data as the participants who returned for follow-up over the six year period did not develop type-2 diabetes.

Summary

None of the participants in the sample of high risk obese youth developed diabetes over the six year follow-up time period. Consequently the association of diabetes and depressive symptoms was not able to be tested. Despite the sample revealing a large total number of participants (n=71; 49 %) with elevated depressive symptoms at presentation, depressive symptoms were not statistically associated with impaired glucose metabolism or abnormal insulin levels. Investigation of these same questions in a larger prospective sample is needed.

Chapter V

Discussion, Recommendations, and Conclusions

The primary purpose of this study was to explore the incidence of abnormal HbA1c, altered glucose metabolism, and progression to type-2 diabetes in a sample of high risk obese adolescents. The participants were 11 to 17 years of age and presented to an outpatient endocrinology clinic for assessment of their risk for development of type-2 diabetes. The secondary purpose was to evaluate associations with depressive symptom scores from self-reported data collected using the CES-DC with the above variables. This chapter discusses the results and their implications to direct future treatment of obese youth, identifies study limitations, and make recommendations for future research.

Characteristics of the Sample

The sample of obese youth investigated in this study presented at the Children's Mercy Hospital Outpatient Pediatric Endocrine Clinic for an initial evaluation of obesity, co-morbidities, and risk for development of type-2 diabetes. The majority of the participants were referred by a primary care provider due to their high risk for development of diabetes. Of the original sample (*n*= 82) all who had a BMI in the obese range were selected for inclusion in this secondary analysis (*n* = 78). In the general population, measured by NHANES data from 2009 to 2010, approximately 17 percent of youth are obese (Ogden et al., 2012a). This sample of youth had BMI score in the obese range (*M*= 36.4, *SD* 5.91) placing them at higher risk for development of type-2 diabetes. Although not considered in the research questions of this study, family history of type-2 diabetes was present in 73% (*n*=78) of the sample.

Of the entire sample (*n*= 78), 44 (56%) of the participants who underwent oral glucose tolerance testing, four were diagnosed with impaired fasting glucose and four were diagnosed with impaired glucose tolerance. Progression to type-2 diabetes in youth is reported to occur at a faster pace than in adults, is associated with continued weight gain, and with a higher incidence in minority youth in the lower socioeconomic populations (Finkelstein et al., 2012; Mizokami-Stout et al., 2012). Despite the high risk status for development of type-2 diabetes in this sample of obese youth, none of the participants were diagnosed over the six year follow-up period.

Consistent with other studies, the participants in this study had a high rate of attrition (63%). Some were recruited and enrolled, missed the 3 to 4 month visit, and returned a year later. Others enrolled and never returned despite making a follow-up appointment and receiving a reminder call which is not uncommon in this population of urban youth. In a recent study related to attrition at weight management appointments, attrition rates ranged from 27 to 73 percent with an average of greater than 50 percent (Hampl et al., 2013).

Insulin Resistance

In the current study 65 % (*n*=46) of the participants met criteria for insulin resistance using the HOMA-IR method with a mean score of 7.31 (*SD* 8.36). In a similar study with 68 obese adolescents referred to an endocrine clinic, using the same method as the current study 31.8 % of the participants met criteria for insulin resistance and none developed type-2 diabetes (Ghergherechi & Tabrizi, 2010). In another study with 150 early-adolescent participants (some obese and some normal weight), insulin resistance was calculated for the obese group (*n*=39) and the authors reported a mean HOMA-IR of 4.66 (*SD* 3.38) (Bindler, Bindler, & Daratha, 2013). The authors did not report the percent of participants with insulin resistance in the obese group.

With 65% (*n=46*) of the sample and a range of insulin resistance HOMA-IR scores from 1 to 40 in this study, it appears that these participants were highly insulin resistant. Insulin resistance is a precursor to the development of impaired glucose tolerance and type-2 diabetes (Levy-Marchal et al., 2010) which once more supports the description of the high-risk obese youth in this sample.

Hyperinsulinemia

An insulin hypersecretion phenomena was described in adults in the 1960's and reported in a study of obese Japanese adolescents of obese parents (Maruhama & Abe, 1981). The obese offspring less than 10 years of age exhibited a normal insulin response to glucose challenge making it unlikely that inherited hyperinsulinemia was a cause for the development of the obesity (Maruhama & Abe, 1981). In a more recent study of 268 obese youth referred to a pediatric endocrinology clinic, oral glucose tolerance tests were conducted to evaluate differences in impaired glucose metabolism in prepubertal and pubertal participants who were hyperinsulinemic and those who were not (Kurtoglu et al., 2010). In the pubertal group 65 % (*n=186*) were hyperinsulinemic which is congruent with our study findings (66%; *n=35*). The mean sum of the insulin results in pubertal youth was 600µU/ml (male) and 655µU/ml (female) with the highest result in the males of 2136µU/ml and in females 3628µU/ml (Kurtoglu et al., 2010). These results are similar to the current study as the mean insulin total for all participants was 641µU/ml (*SD* 297). The range of insulin sums in the current study were not as elevated as reported in the earlier study by Ghergherechi and Tabrizi (2010). However an insulin sum of 1513µU/ml (*n=23*) is still noteworthy as hyperinsulinemia has been described as the demise of the beta cell and one subsequent cause of type-2 diabetes. "Hyperinsulinemia, insulin resistance, and impairment of glucose-stimulated insulin release are intertwined biologically" (Shanik et al.,

2008, p. S266). In the current study the sum of the insulin levels was significantly associated (*r*= .553, *p*=.001) with the HOMA-IR scores (*n*=35). They were also associated with the two hour glucose result from the oral glucose tolerance test (*r*=.518, *p*=.001).

Impaired Fasting Glucose

In a retrospective cohort of the Bogalusa Heart Study children with fasting glucose levels from 86 to 99 mg/dl were twice as likely to develop impaired fasting glucose or diabetes as adults than the group with a fasting glucose of less than 86mg/dl (Nguyen et al., 2010). We expected similar results in the current study, however, the Bogalusa Heart Study was conducted over 21 years and our study was conducted over a 6 year period of time. In the current study 16 of the participants had a fasting glucose level between 86 to 99mg/dl. Over time, most obese youth will develop type-2 diabetes. The youth in the current study received intensive multi-disciplinary services to support lifestyle modifications which may have changed the disease trajectory and must be taken into consideration in the analysis of this data.

Impaired Glucose Tolerance

Obese youth with impaired glucose tolerance are at a high risk for development of type-2 diabetes associated with the impact of increased insulin resistance (decreased insulin sensitivity) and the subsequent beta cell failure (Cali et al., 2009). However, this was not found in the current study as 4 (9.1%) of the 44 participants tested were found to have impaired glucose tolerance and none developed diabetes in the six year follow-up. In a previous study of obese children and adolescents the authors report a prevalence of 14.7 % (*n*=68) impaired glucose tolerance in an adolescent sample (Ghergherechi & Tabrizi, 2010). According to a current

report, youth with impaired glucose tolerance or impaired fasting glucose developed type-2 diabetes at a more rapid pace when compared to adults (Cree-Green et al., 2013).

Depressive Symptoms

The association with depressive symptoms and type-2 diabetes in adults and in obese youth has been widely investigated; however the association with depressive symptoms and youth with type-2 diabetes have not received the research attention. This may be in part related to the more recent increase in childhood acquired type-2 diabetes. It has been reported that youth with higher depressive symptoms scores also exhibited lower insulin secretion in relation to insulin sensitivity (Hannon et al., 2013). In future prospective studies measuring the insulin secretion levels may be a more precise method of computing insulin resistance. In the current study 49% (n=71) of the sample met criteria for elevated depressive symptoms scores (38 % mild, 10 % moderate, and 1% severe). However, depressive symptoms scores were not statistically associated with any of the variables of glucose metabolism measured in this study.

Summary of the Associations Among the Concepts in the Revised Research Model

The research model was revised based on results of this study and the associations with recent literature (see Figure 3).

Figure 3. **Factors Related to the Development of Type-2 Diabetes**
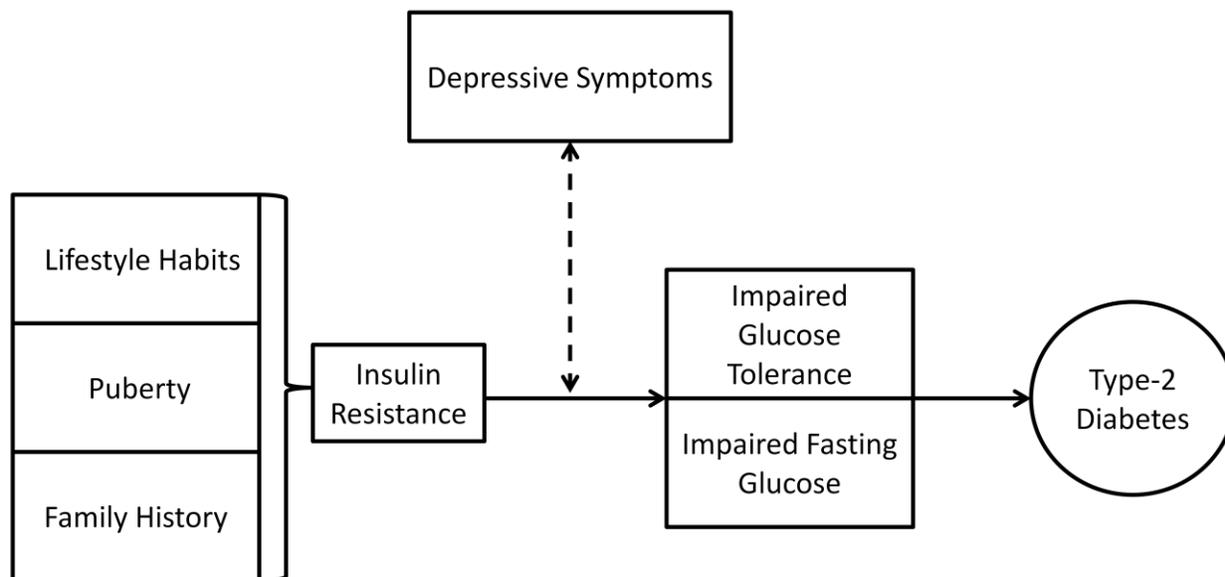
Summary of the Associations Among the Concepts in the Revised Research Model

The revised model illustrates how the increase in insulin resistance as a child

progresses through puberty and can be compounded by a family history of type-2 diabetes and

lifestyle habits. It is well documented that during puberty youth develop less insulin sensitivity

(Cree-Green et al., 2013; D'Adamo et al., 2011; Goran & Gower, 2001; Levy-Marchal et al.,

2010). In addition 73% of the obese participants in the current study had a family history of

type-2 diabetes which places them at a higher risk in the future for development of type-2

diabetes (Bianco et al., 2013; Brandao, Lopes, & Ramos, 2013; Cree-Green et al., 2013; Levy-

Marchal et al., 2010; Maruhama & Abe, 1981). Lifestyle habits have been the crux of the

development of obesity and the main focus of weight management treatment (Bianco et al.,

2013; Forbes et al., 2013). Poor lifestyle habits when added to lower insulin sensitivity and a

family history of diabetes can create exaggerated insulin resistance. If left untreated these factors combined can lead to impaired glucose metabolism and subsequent type-2 diabetes.

Another variable impacting this process may be depressive symptoms. Of the sample of obese adolescents in the current study 71 (49 %) reported a high level of depressive symptoms ($\geq$15 on the CES-DC). In the revised model it is posited that abnormal levels of reported depressive symptoms may have an impact on the association between insulin resistance in obese youth and impaired fasting glucose or impaired glucose tolerance. In the literature there is not a consensus related to whether obese youth develop depressive symptoms associated with their weight or whether the child exhibits depressive symptoms and subsequently becomes overweight or obese. There is a paucity of literature related to depressive symptoms and type-2 diabetes in youth.

There are several places in the revised model where interventions could be directed. The primary focus for treating childhood obesity must be weight management with a focus on changing the lifestyle habits of the obese child as well as their families. According to the Childhood Obesity Action Network, step 1 for treating childhood obesity is assessing and preventing obesity at child well visits (Barlow & Expert, 2007). The expert recommendations in step 2 are focused on making lifestyle changes and referring the child to a healthcare provider with experience in weight management for children or a weight management program designed for youth (Barlow & Expert, 2007). The final step includes recommendations for community action to support healthy lifestyles and it also describes a staged plan of action for overweight and obese youth which doesn't include treatment with medication or surgery until the last stage (Barlow & Expert, 2007). Depressive symptoms may have an impact on how successful a child and their family are at making lifestyle changes (Jaser et al., 2009). Once a child develops

impaired fasting glucose or impaired glucose tolerance (confirmed by oral glucose tolerance testing) most providers in the endocrinology clinic where these participants were recruited will consider treating the child with medication in an attempt to slow or prevent the development of type-2 diabetes. However, it is proposed in the revised model that depressive symptoms moderate the association between insulin resistance and impaired fasting glucose, impaired glucose tolerance, and type-2 diabetes. Interventions to decrease the depressive symptoms may have the potential to improve the future outcomes of the obese insulin resistant child.

Item Analysis and Reliability Analysis of the

Center for Epidemiological Studies Depression Scale for Children (CES-DC)

The CES-DC was evaluated for reliability (internal consistency) with a strong Chronbach's alpha (α= .81) indicating the amount of total variance in the scale can be attributed to the same source (Pett, Lackey, & Sullivan, 2003). It has been validated in the past with strong overall internal consistency (α=.86) and test-retest reliability was good when testing adolescents (r=.69). The factor analysis loaded on to three distinct dimensions [behavioral (r=.74), cognitive (r=.80), and happiness (r=70)], (Faulstich et al., 1986). It was revalidated in 1990 revealing strong internal consistency (α=.89),(Fendrich et al.). Most recently it was validated for children in Rwanda after translation with a strong overall internal consistency (α=.86), and a good test-retest reliability (r=.85), (Betancourt et al., 2012).

Implications for Practice

The results of the current study reveal a high incidence of insulin resistance, depressive symptoms, and family history of type-2 diabetes in a sample of high risk obese youth. The literature supports the importance of making lifestyle changes to slow the progression of insulin

resistance to type-2 diabetes in youth. Lifestyle changes should remain the first intervention

directed toward weight loss as family history and puberty cannot be changed. Medication should

be considered only after completing an oral glucose tolerance test to determine the risk for

development of type-2 diabetes (IGT or type-2 diabetes) and prescribed in conjunction with

lifestyle changes (Dileepan & Feldt, 2013). Screening and referral to a mental healthcare

provider if needed should be standard care as in the current sample 49% (*n*=71) of the obese

youth scored in the abnormal range for depressive symptoms. Healthcare providers must

document a thorough family history on all youth presenting for obesity as it has been noted that

genetics can play a large role in the development of the disease (Bianco et al., 2013; Dileepan &

Feldt, 2013). Fasting blood glucose levels and HbA1c should also be monitored in obese youth

as it has been reported that with a fasting glucose between 86 and 99 mg/dl they are twice as

likely to develop type-2 diabetes as adults (Nguyen et al., 2010). In the current study 38%

(*n*=53) of the participants met this criteria for fasting blood glucose level.

Study Limitations

One of the limitations of this study was the high attrition rates which led to a reduced

sample size. Attrition is common in this population of youth referred for weight management

clinical services (Hampl et al., 2013; Jensen, Aylward, & Steele, 2012). Despite the high

attrition rate, 35 participants underwent oral glucose tolerance testing which provided data to

calculate the incidence of hyperinsulinemia, insulin resistance, impaired fasting glucose, and

impaired glucose tolerance. In future prospective studies of obese adolescents referred to an

endocrinology clinic, calling patients to remind them of their appointment instead of using an

automated call system may decrease attrition rates (Hampl et al., 2013). Parents then have the

opportunity to reschedule the appointment if needed. This may be a good approach to address

the high attrition rates in an endocrinology outpatient setting. Patients with abnormal HbA1c's

could be scheduled for oral glucose tolerance testing as soon as possible to assess patient risk for

development of type-2 diabetes as standard care. Interventions could then be directed based on

risk assessment using a multidisciplinary approach. Social workers in the endocrinology

department could meet with the families at the first appointment to assess barriers to follow-up

(Hampl et al., 2013). Depressive symptoms have been reported to have an impact on

appointment attendance (Jensen et al., 2012). Being proactive and having the social workers

assistance at the first appointment may decrease attrition and improve patient outcomes. High

rates of attrition or large gaps in between appointments tend to lead to less patient adherence to

the treatment plan and an inability to implement or remember goals. These are both complex

multi-factorial issues which cannot be solved in one visit.

A limitation not considered in the current study was treatment of the participants at

highest risk for development of type-2 diabetes (IGT) with metformin. This is a limitation as it

has been reported that metformin has been modestly beneficial in decreasing the BMI in youth

when compared to lifestyle changes alone (McDonagh, Selph, Ozpinar, & Foley, 2014). This

may have had an effect on the metabolic outcomes of this sample of high-risk youth.

Another consideration is that all participants received lifestyle education including self

directed goal creation by the patient. These sessions were led by a Dietician or Certified

Diabetes Educator coinciding with their appointment with the health care provider.   Follow-up

testing was not conducted to evaluate change in knowledge and self care skills.

A secondary analysis of an already existing database places limitations on what can be

assessed as the data were collected for a different study reflecting other hypotheses (Rew et al.,

2000). However, in the original study there was a rich amount of data collected on high risk obese youth. With the addition of the available data obtained by retrospective chart review, a large enough sample of the original participants who followed-up in the endocrinology clinic provided longitudinal data for the current study.

Conclusions and Recommendations

The sample of obese youth recruited from an endocrinology ambulatory clinic provided rich data despite the incomplete documentation associated with the high attrition rate. There were many participants at high risk for development of diabetes with high summed insulin levels (maximum of 1513 µU/ml), high HOMA-IR results (insulin resistance), impaired fasting glucose, and impaired glucose tolerance despite receiving treatment for these conditions over the relatively short follow-up time frame of 6 years.

The high incidence of depressive symptoms (49%; *n*=71) in this study supports the need for more research related to depression and childhood acquired type-2 diabetes. The high rate of attrition along with the high incidence of depressive symptoms in this cohort of youth are compelling, and further investigation directed at how depressive symptoms may affect appointment attendance is needed.

As the incidence rate of obesity has increased in youth, the co-morbidities associated with the obesity have also increased. There will be a greater need for mental health services in this population of high risk youth referred to an ambulatory endocrinology clinic for evaluation and recommendations. Although depressive symptoms were not associated with impaired glucose metabolism in this sample of youth, and an association between these variables is

posited. A larger prospective study investigating the pathway of association of these variables should be considered.

Lastly, childhood obesity is a national problem with complex health disorders previously occurring only in adults. Obesity in childhood is becoming more common as the children become obese at younger ages and are obese for most of their childhood. A future larger prospective study is needed to explore new and innovative strategies for lifestyle and behavior changes incorporating a focus on optimal mental health in obese youth.   Efforts are needed to address this epidemic and research is needed to predict and explain how best to direct those efforts and improve the health outcomes of the nation's children.

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APPENDIX

Tables of Statistical Results

Table 1

Descriptive Variables

Variables	*M* (*SD)*	Min.	Max.	*n**
Age (yrs.)	14.2 (1.78)	11.08	17.75	78
Height (cm)	165.5 (8.8)	145.8	190.3	78
Weight (kg)	100.2 (20.5)	58.2	154.9	78
Weight (lbs)	220.4 (45.2)	128	341	78
BMI (kg/m^2)	36.4 (5.91)	25.4	50.5	78
BMI %	98.8 (1.03)	95	99.9	78
BMI z	2.37 (.295)	1.65	2.98	78

Note. * Gender 42 % male and 58% female

Table 2

Demographic Variables and Gender

	Male		Female	
	M (SD)	*n* (total)	*M (SD)*	*n* (total)
Age (years)	14 (1.65)	33	14.4 (1.86)	45
Height (cm)	168.2 (10.4)	33	163.6 (6.9)	45
Weight (kg)	103.4 (21.5)	33	97.8 (19.7)	45
BMI	36.4 (6)	33	36.4 (5.9)	45
BMI %	99.1 (.71)	33	98.6 (1.2)	45
BMI z	2.47 (.28)	33	2.3 (.29)	45

Table 3

Measures of Glucose Metabolism

Variables	*M* (*SD)*	Minimum	Maximum	*n* (total)
IR	9.42 (9.1)	2.85	40.35	33 (46)
HYPERIN (μU/ml)	641 (297)	304	1513	23 (35)
IFG (mg/dl)	111 (5.35)	106	117	4 (53)
IGT (mg/dl)	154 (13.45)	141	169	4 (44)
DM2 (mg/dl)	0	0	0	0 (78)
Elevated HbA1c (Time 1)	6 % (2.66)	5.7 %	6.7 %	25 (64)
Elevated HbA1c (Last)	6 % (.174)	5.7 %	6.4 %	19 (39)

Note. IR = insulin resistance. HYPERIN =Hyperinsulinemia. IFG = Impaired fasting glucose.
IGT= Impaired glucose tolerance. DM2 = type-2 diabetes.

Table 4

Correlations Among Variables of Glucose Metabolism

Variables	Pearson r	p (significance)	n (total)
2 hr. Glucose tol. & First HbA1c	.470	.007	32
2 hr. Glucose tol. & Last HbA1c	.404	.011	39
2 hr. Glucose tol. & Insulin total	.518	.001	35
2 hr. Glucose tol. & HOMA-IR	.429	.007	38
Insulin total & HOMA-IR	.553	.001	35

Table 5

Insulin Resistance

Variable	*t*-test (*df*)	Sig. (2-tailed)	*M* (SD)	95% *CI* LL	UL
Last HbA1c	1.66 (38)	.104	.172 (.103)	-.037	.381
BMI %	2.95 (22)	* .007	1.08 (.365)	.321	1.835
BMI z	3.64 (44)	*.001	.321 (.088)	.143	.499
Insulin Total	3.56 (33)	*.001	311 (88.4)	130.6	490.8
0 min. Glucose tol.	2.17 (44)	*.035	6.28 (2.89)	.458	12.1
2 hr. Glucose tol.	1.97 (36)	.057	16.1 (8.16)	-.495	32.6

Note. * Significance at an α of .05

Table 6

Depressive Symptoms Measured by the CES-DC

Depression Scores	0-14 (none)	15-29 (mild)	30-44 (moderate)	45-60 (severe*)*	*n* (total in sample)
Time 1	36 (46%)	27 (35%)	7 (9%)	1 (1%)	71 (78)
Time 2	22 (28%)	19 (24%)	2 (2.6%)	1 (1%)	44 (78)
Time 3	17 (22%)	7 (9%)	4 (5%)	1 (1%)	29 (78)

Note. CES-DC (Centers for Epidemiological Studies-Depression Scale for Children)