ASSESSMENT OF PREDIABETES AND MEDICAL INTERVENTIONS IN A SAMPLE OF OVERWEIGHT MICHIGAN YOUTH

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ABSTRACT

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Study Objectives – The objectives of this study were to 1) assess current screening practices for prediabetes in youth, 2) determine the existence of prediabetes in a sample of overweight youth, 3) describe associative factors related to prediabetes in youth, and 4) asses current clinical recommendations provided, including medical nutrition therapy, physical activity, and the prescription of metformin.

Study Design – A cross-sectional, retrospective medical record review of subjects aged 6 to 18 years with a body mass index percentile 85th percentile seeking care for their overweight condition with pediatric endocrinologist.

Results – 53% of the sample received screening for prediabetes. Greater than 60% of the sample met the criteria for metablolic syndrome. Prediabetes was detected in 13.5% of those screened. Youth with prediabetes had significantly higher levels of fasting blood glucose ($p>0.001$), serum insulin ($p<0.001$), insulin-to-glucose ratio ($p<0.01$), and systolic blood pressure ($p<0.001$). The majority of youth seen for prediabetes received nutrition education similar to that prescribed to adults.

Conclusion – Overweight youth under the care of endocrinologists are not being adequately screened for prediabetes. The majority of youth presenting for care have documented metabolic disturbances. Those with prediabetes have significantly higher levels of biomarkers indicative of insulin resistance and abnormal glucose tolerance.

DEDICATION

This thesis is dedicated to the health and well being of future generations of young people.

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CHAPTER 1
Introduction

The incidence and prevalence of childhood and adolescent overweight in the United States and worldwide is increasing, such that the Centers for Disease Control and Prevention (CDC) have proclaimed it a global epidemic (CDC, 2002.) The prevalence of overweight and at-risk for overweight in youth aged 6 to19 years in the United States is estimated to be 16% (defined by the CDC Growth Charts as a Body Mass Index (BMI)-for-age ≥ 95th percentile) and 15% (BMI-for-age <95th percentile but ≥85th percentile) (Hedly *et al.*, 2004.) One in five children in the United States is overweight (Evantson *et al.*, 1998), with the prevalence nearly tripling from the period of 1976 to 1980 (NHANES II) to that of 1999 to 2000 (NHANES III) (CDC, 2003.) The 2003 Youth Behavior Risk Survey (YRBS) data shows that 12% of those10 to 24 years in Michigan are overweight, and 13% are at risk for overweight (YRBS, 2003.) A more recent report names Michigan youth as the 3rd most overweight in the country (Cotton *et al.*, 2005.)

As the number of overweight youth increases, the risk for weight-related health conditions also increases. Diagnosed cases of type 2 diabetes, hypertension, and hyperlipidemia in youth are also on the rise, and of considerable alarm to health care and public health professionals (Sinha *et al*, 2002; Freedman *et al.*, 1999.) The development of type 2 diabetes in youth corresponds highly with trends of overweight (Pinhas *et al.*, 1996). Type 2 diabetes (previously referred to as Adult Onset Diabetes Mellitus (AODM) or Non Insulin Dependent Diabetes (NIDDM)) was formerly thought to be an exclusively "adult" chronic disease. However, this condition has recently been detected as a "new disease" in youth 19 years of age and younger (Rosenbloom *et al.*, 1999,

Fagot-Campagna *et al.*, 2000.) Once, representing fewer than 1% of all newly diagnosed cases of diabetes in youth by pediatric endocrinologists (Arslanian *et al.*, 1994), current studies estimate that 8 to 45% of youth diagnosed with diabetes have type 2 (American Diabetes Assocation [ADA], 2003; Fagot-Campagna *et al.*, 2000.) However, since type 2 diabetes in youth is a relatively new phenomenon, accurate statistics on national prevalence have not yet been generated (ADA, 2003.)

Diabetes is a burdensome, costly chronic disease with potentially devastating end results, especially when left undiagnosed or poorly managed. The total annual economic cost of diabetes in 2002 was estimated to be $132 billion, or one out of every 10 health care dollars spent in the United States (ADA, 2003.) The estimated costs of diabetes-related medical care in Michigan exceeded $2.9 billion in 2000 (ADA, 1998.) Poorly managed diabetes mellitus, both type 1 or type 2, may lead to organ damage, negatively affecting the function of the kidneys, eyes, and nerves (United Kingdom Prospective Diabetes Study [UKPDS], 2003; Diabetes Complications and Control Trial [DCCT], 2003.) In the year 2000, diabetes was the leading cause of blindness and kidney disease in Michigan according to the Michigan Department of Community Health (MDCH), and a major factor in hypertension, cardiovascular disease, and non-traumatic lower limb amputations (MDCH, 2002.)

Being overweight or obese, having a sedentary lifestyle, a strong family history of diabetes, and having glucose levels above normal, yet below the diagnostic level for true diabetes diagnosis, are risk factors for the development of type 2 diabetes. Prior to the development of type 2 diabetes, it has been established that the physiological metabolic environment is often associated with or subjected to insulin resistance, hyperinsulinemia,

abnormal glucose tolerance, and/or dyslipidemia (ADA, 2003.) Insulin resistance is directly involved in the pathogenesis of many cases of type 2 diabetes (ADA, 2003.) Findings of the pathogenic role of insulin resistance have recently been demonstrated in both pre-pubertal and pubertal overweight youth in single clinic studies conducted in the United States (Weiss *et al.*, 2003; Sinha *et al.*, 2002.) In addition, overweight European children had abnormal glucose tolerance, high concentrations of triglycerides, low high-density lipoprotein levels, and high blood pressure values, when compared to their normal weight counterparts (Invitti *et al.*, 2003.) Those with abnormal glucose tolerance were also found to be insulin resistant with hypersinulinemia (Invitti *et al*, 2003.)

Overweight and insulin resistance in youth are therefore key associative factors for the development of type 2 diabetes. Recent data shows a similar pattern between overweight and the development of a condition now known as prediabetes, formerly referred to as impaired glucose tolerance (IGT) and/or fasting glucose intolerance (FGT) (Weiss *et al.*, 2003; Invitti *et al.*, 2002; Sinha *et al.*, 2002.) A recent single clinic study showed that insulin resistance in overweight youth was the best predictor of prediabetes following a 2-hour glucose tolerance test (Sinha *et al.,* 2002.) While the progression from normal glucose tolerance to overt type 2 diabetes in adults has been studied extensively, studies investigating prediabetes in youth are rare.

An elevated plasma glucose that does not meet the criteria for diagnosis of type 2 diabetes, whether in the fasting state or following an oral glucose tolerance test is referred to as prediabetes. At risk adult individuals often develop prediabetes prior to the development of frank type 2 diabetes (Benjamin *et al.*, 2003.) Currently it is estimated that 40% of adults in the United States over the age of 45 have prediabetes (Health and

Human Services [HHS], 2004; Benjamin *et al.*, 2003.) Approximately 1,533,000 million Michigan adults are estimated to have prediabetes (Michigan Department of Community Health [MCDH], 2004.) Of those with identified prediabetes, it is estimated that 1/4 to 3/4 will go on to develop type 2 diabetes within a decade of its initial detection (HHS, 2002). The full extent to which prediabetes exists in overweight youth is unknown at this time.

There is concern that the rising trends of overweight in youth will exacerbate the already increasing rates of type 2 diabetes in youth. Of specific concern, is the fact that an earlier onset of type 2 diabetes in a child or adolescent increases the risk for the debilitating complications of diabetes to develop at a much younger age than those typically seen in adults. In addition, risk factors for metabolic syndrome often are present in youth at risk for type 2 diabetes and prediabetes. Complications of diabetes developing during an individual's twenties or thirties leave more years for chronic disease and debilitation, as well as a potentially decreased quality of life and the possibility of early mortality.

Successful prevention or delay of type 2 diabetes in adults has been demonstrated through both lifestyle and pharmacologic interventions (Diabetes Prevention Program [DPP], 2002; Toumilehto *et al.*, 2001.) Studies designed to assess lifestyle and pharmacological interventions in youth are few but growing. A number of lifestyle intervention projects for children and adolescents are currently underway in the Native American Indian and Canadian Native populations (Cook *et al.*, 1998; Teufel *et al*, 1998; Macaulay *et al.*, 1997.) Longitudinal data on the efficacy of diabetes preventative interventions currently do not exist for youth.

Screening at risk groups for prediabetes may be advantageous by making early interventions possible. Since the costs and health risks to those with type 2 diabetes is considerable, prevention is preferred. Currently, there are no established screening criteria for prediabetes in youth (ADA, 2002.) The ADA concedes that there are insufficient data currently available to make definite clinical recommendations for screening. However, the ADA Consensus Panel recommends screening at-risk youth for type 2 diabetes starting at 10 years of age (ADA, 2000; ADA, 2003.) By screening children and adolescents for the risk factors established for type 2 diabetes detection, prediabetes may be inadvertently recognized.

Research is needed to enhance our current understanding of the associations between overweight in children and adolescents and prediabetes. It is hoped that with earlier detection of prediabetes and appropriate lifestyle or pharmacologic interventions, when necessary and appropriate, the path to type 2 diabetes may be averted. Examination of the existence of prediabetes in youth and its associative factors will further research, knowledge, improve medical care, and increase public health awareness of this growing and preventable epidemic. Pediatric endocrinology clinics are ideal sites for conducting this research. Children who are overweight or have type 2 diabetes are commonly referred to endocrinologists due to their expertise in evaluating and treating these metabolic conditions. Pediatric endocrinology practices also are often staffed with registered dietitians and certified diabetes educators, who may be registered nurses, registered dietitians, or clinical psychologists. The expertise of an endocrinologist coupled with an interdisciplinary team of experts in lifestyle and medical care is necessary for treating the complex issue of overweight in youth. Through the

observations of care in clinics such as these, assessment and evaluation of the condition of prediabetes in overweight youth may be carried out. Given that this study will provide preliminary data for which to base the foundation for further research in this area, only three endocrinology clinics in Michigan's lower-peninsula were selected for data collection.

Due to the paucity of data on prediabetes in youth, nationally and in the state of Michigan, this study was formulated to provide preliminary data on the extent to which prediabetes and risk factors for diabetes, including metabolic syndrome, exists in a sample of overweight and at-risk for overweight youth. Michigan youth are the 3rd most overweight in the country (Cotton *et al.*, 2005.) Treatments for prediabetes in youth, including lifestyle (nutrition and physical activity) and pharmacological (metformin prescription), will also be reviewed. The purpose for assessing treatment administration is to determine the extent to which treatment recommendations shown to be effective for adults, are also being applied to youth. Currently, there are no specific treatment recommendations for youth diagnosed with prediabetes.

RESEARCH QUESTIONS

1. a. What proportion of youth with a BMI-for-age ≥85th percentile are being appropriately screened for prediabetes?

   b. What proportion of youth with a BMI-for-age ≥85th percentile meet ≥ 1 criteria for prediabetes set by the American Diabetes Association?

   c. Are there differences in youth who are likely to be screened for prediabetes based on gender, race/ethnicity, age, medical practitioner, number of risk factors present for metabolic syndrome and type 2 diabetes?

   d. Are there differences in youth who are diagnosed with prediabetes based on gender, race/ethnicity, age, pubertal stage, or number of risk factors present for metabolic syndrome and type 2 diabetes?

2. a. What recommendations are being made by health care professionals (MD, RN, RD, CDE) for lifestyle (diet, exercise, weight management) and metformin interventions?

HYPOTHESES

H_1: Health care providers are screening youth for prediabetes in concordance with recommended screening for type 2 diabetes in youth as recommended by the American Diabetes Association.

H_2: The proportion of youth aged 6 to19 years diagnosed with prediabetes will be similar to rates of diagnosis of type 2 diabetes in the same age group.

H_3: Lifestyle and medical interventions provided for the treatment of prediabetes will be comparable to those recommended for the prevention or delay of type 2 diabetes in adults.

CHAPTER 2
Literature Review

The comprehensive review to follow examines the most up-to-date findings related to the condition of prediabetes in youth and its associated risk factors, including metabolic syndrome, overweight status and family history of diabetes. An assessment of the current recommendations, occurrence rates, risk factors, and interventions for prediabetes (in both adults and youth) are discussed. Type 2 diabetes occurring in children and adolescents is also reviewed in full detail, due to the similar risk factors found between the condition of prediabetes and type 2 diabetes, as well as their distinct differences. Causes of and treatments for overweight in youth are evaluated because of the strong correlation between overweight status, insulin resistance, and the risk for type 2 diabetes.

Prediabetes

Prediabetes is a metabolic condition during which an individual's blood glucose values are elevated above those considered normal, but less than that of established levels for diagnosing diabetes mellitus. A diagnosis of prediabetes places a patient at "high-risk" for developing type 2 diabetes, one of the fastest growing and most costly chronic diseases of modern times (King *et al.*, 1998). It is estimated that 41 million Americans have prediabetes, with many unaware that they have the condition (HHS, 2004). The state of Michigan has an estimated 575,000 adults with prediabetes, representing 15.6% of those aged 40 to 74 years of age (MDCH, 2002). This rate is similar Michigan's rate of obesity in adults, with 20 to 24% of the population meeting the criteria for obesity, defined as a body mass index (BMI; kg/m2) of $\geq$ 30 (CDC, 2003; BRFS, 2001).

Research supported by the Department of Health and Human Services (HHS) concludes that prediabetes raises the risk for developing type 2 diabetes, with many of those with pre-diabetes going on to develop type 2 diabetes within ten years if lifestyle changes are not incorporated and maintained (HHS, 2003). Effective interventions for those with pre-diabetes have been labeled as critical for three primary reasons: 1) risk of heart attack or stroke is 50% more likely when carrying prediabetes as a risk-factor,
2) development of type 2 diabetes can be prevented or delayed through modest lifestyle modifications, and 3) a state of euglycemia can be reached with modest lifestyle changes (HHS, 2003).

The condition now known as "prediabetes" has combined the former terminology of two similar conditions known as impaired glucose tolerance (IGT) and impaired fasting glucose (IFG). The actual condition of prediabetes is therefore not new. The revised terminology is thought to provide more a understandable and concise means of communicating the risks of abnormal blood glucose values (either fasting or following oral glucose testing) and its' association with the likelihood of the development of type 2 diabetes to both the medical community and the public (American Diabetes Association [ADA], 2003). IGT is defined as a blood glucose value $\geq$140 mg/dl (7.8 mmol/L) and $<$ 200 mg/dl (11.1 mmol/L) following a 2-hour oral glucose tolerance test (OGTT). IFG is determined by a fasting plasma glucose test, with values $\geq$100 mg/dl (6.1 mmol/L) and $<$126 mg/dl (7.0 mmol/L) considered to be in the abnormal range (ADA, 2003). An individual may have either IGT or IFG, or both, and be considered to have prediabetes. Individuals with IGT and IFG may be euglycemic the majority of the time, with normal

glycated hemoglobin values in their daily lives, often demonstrating hyperglycemia only after an OGTT challenge (ADA, 2001.)

The prevalence of prediabetes in the adult population of the United States is estimated to be 40% of those aged 45 to 74 years of age (HHS, 2004; Benjamin *et al.*, 2003.) This number could potentially be expanded should those aged > 75 years, and those between the ages of 25 and 44 years be included in the estimates. Recently, a panel of physicians and diabetes experts represented by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), and the Centers for Disease Control and Prevention (CDC) announced recommendations for the screening of prediabetes in overweight adults aged 45 years and older (HHS, 2003.) Recommendations include administering screening as a component of regular medical visits using one of two standard tests for abnormal glycemia, the fasting blood glucose test or a 2-hour oral glucose tolerance test. Screening recommendations for adults younger than age 45 are depicted in table 2.1 (HHS, 2003):

Table 2.1 - Screening Criteria for Prediabetes in Adults <45 Years of Age

Overweight (BMI >25) **Plus one or more risk factor:** • Family history of diabetes • Low HDL cholesterol and high triglyerides • High blood pressure • History of gestational diabetes or gave birth to a baby weighing more than 9 pounds • Belong to a minority group (African-American, American Indian, Hispanic American/Latino, and Asian American/Pacific Islander)

Prediabetes, or abnormal glucose tolerance, is also associated with insulin resistance syndrome, characterized by a progressive failure in beta-cell (of the pancreas) secretory function, which over time typically progresses to type 2 diabetes (Expert Committee on Diagnosis of Diabetes Mellitus, 2001; Haffner, 1996; Weyer, 2001; Invitti, 2003). Type 2 diabetes is known to be a condition of progressive beta-cell failure, preceded by and often in concordance with hyperinsulinemia and low-insulin sensitivity. The condition of insulin resistance is characterized not only by the over-compensation in insulin secretion (hyperinsulinemia) necessitated by the body's need to maintain euglycemia, but obesity (namely abdominal and visceral), dyslipidemia of low-HDL and/or hypertriglyceridemia, and hypertension (ACE, 2003). Beta-cell function may be assessed using the "insulinogenic index", calculated as the ratio of the increment of change between fasting plasma insulin to plasma glucose level during the first 30 minutes of a glucose load. A low insulinogenic index is a predictor for the development of type 2 diabetes in adolescents (Sinha *et al.*, 2003). Insulin resistance can be assessed using the "homeostatic model", or the insulin-resistance index: the mathematical product of plasma insulin and plasma glucose, divided by 22.3. A high value obtained via the homeostatic model indicates a high level of insulin resistance (Matthew *et al.*, 2001).

In a recent study assessing overweight children, adolescents, and their predisposition towards prediabetes, it was found that beta-cell response was partially preserved in those with prediabetes. Slightly lower insulinogenic index values, though not significantly different from age-matched overweight peers with euglycemia, were observed (Sinha *et al.*, 2002). However, adolescents with frank type 2 diabetes did have significantly lower insulinogenic indexes, mirroring the same progression of beta-cell

demise found in adults. Children and adolescents with prediabetes have been found to have significantly higher levels of insulin resistance, compared to their overweight counterparts without prediabetes. It is postulated that in overweight youth with pre-diabetes, the beta-cells are able to produce adequate insulin, despite increased demand resulting from high levels of insulin resistance (Sinha *et al.*, 2002.)

Pubertal development and relative insulin resistance are related to elevated levels of growth hormone that are characteristic of puberty (Savage *et al.*, 1992.) Growth hormone and sex steroids were at one time both thought to contribute to insulin resistance during puberty (of which is compensated for when pancreatic beta-cell function is normal). Sex steroids have been ruled out as a facilitator of insulin resistance, due to levels remaining persistently high, even after puberty. Conversely, elevations in growth hormone have been shown to coincide with decreased insulin sensitivity (ADA, 2000.) Therefore, it can be postulated that degree of obesity during adolescence and the processes of sexual maturation may have direct additive effects on insulin sensitivity and subsequent risk for and eventual development of type 2 diabetes in youth.

The rising trends of overweight and obesity in youth, together with the newly recognized and rising conditions of type 2 diabetes, metabolic syndrome, hyperinsulinemia, and hypertension are of great relevance to public health status. These trends are appearing not only in the United States, but in many nations with a "westernized" lifestyle, encompassing a hypercaloric food environment coupled with a sedentary physical activity level. The progression from prediabetes to type 2 diabetes at an early age may result in serious health consequences. With the development of type 2 diabetes at documented ages as young as 5 years (Glaser *et al.*, 1998), there is a longer

time period (in comparison to cases of adult diagnosis) during which to develop diabetes related health complications, with potential for decades of compromised quality of life and decreased productivity. It is possible for the complications of diabetes to fully develop by ages 20 to 30 years in those diagnosed with diabetes in late childhood or adolescence (CDC, 1999; Glaser *et al.*, 1998.)

There are currently no formal estimates for prevalence of prediabetes in youth. At present time, the American Diabetes Association does not cite sufficient evidence to confirm treatment modalities effective for the prevention of type 2 diabetes in children and adolescents (ADA, 2000). While there are now screening criteria by the American Diabetes Association for type 2 diabetes in youth, there are no established guidelines for prediabetes. In a study recently published in the *New England Journal of Medicine,* 21% of obese children (4 to 10 years), and 25% of very obese adolescents (11 to 18 years) previously seen at the Yale University Pediatric Obesity clinic, were found to have prediabetes (Sinha *et al.*, 2002.) This research provides age sensitive data confirming the need for further exploration of the physiological state of overweight youth and risk for diabetes, as there is paucity in the literature of data examining abnormal glucose tolerance in overweight youth. Critics of the previously mentioned study argue against establishing any kind of prevalence using the data from this particular project. The study population in question consisted of a convenience sample of obese youth seeking prior treatment in one clinic, thereby not representative of all children and adolescents and not generalizable to the entire population (Goran *et al*,. 2003.)

The goal of the this project was also to provide new insight into the condition of prediabetes and associative factors in youth, even though data obtained will consist of only a sub-sample of the population.

Metabolic Syndrome in Youth

In addition to the metabolic phenomenon of insulin resistance, the "metabolic syndrome", a cluster of cardiovascular risk factors including hypertension, dyslipidemia, and abdominal obesity, often in combination with abnormal glucose tolerance, may be seen in those with prediabetes. The Adult Treatment Panel (ATP) III guidelines of the National Cholesterol Education Program (NCEP) have recently established the following guidelines for the diagnosis of metabolic syndrome for adults, as well as universal ICD-9 coding for medical reimbursement of the condition (NCEP, 2001) (table 2.2). The abnormalities listed in table 2.2 are increased in those with insulin resistance/hyperinsulinemia, predicting the development of type 2 diabetes and/or cardiovascular disease (ACE, 2003.) While metabolic syndrome includes known cardiovascular risk factors, its role in the pathogenesis of cardiovascular disease remains unknown. At present time the associative factors of metabolic syndrome and cardiovascular disease continue to serve as statistical correlations between the two conditions, rather than direct cause and effects of one another (Expert Committee on Diagnosis of Diabetes Mellitus, 2001). Factors may also be present in an individual independent of metabolic syndrome.

Prevalence of metabolic syndrome in adults ≥20 years of age is 23.7%, based on NHANES III data (Ford *et al.*, 2002.) A recent assessment of metabolic syndrome in a sample of adolescents derived from NHANES III data indicate that as many as 4% of all adolescents, and 30% of overweight adolescents meet ≥3 criteria for the metabolic syndrome (Cook *et al.*, 2003.) Metabolic syndrome was more common in males than in females, with Mexican-Americans and whites more likely to qualify for metabolic syndrome than blacks (Cook *et al.*, 2003.) In 2004, a study examining metabolic syndrome in 439 obese, 31 overweight, and 20 non-obese youth aged 4 to 20 years of age found that with each incremental increase in BMI, risk for metabolic syndrome and insulin resistance increased (Weiss *et al.*, 2004.)

Table 2.2 – Criteria for the Diagnosis of Metabolic Syndrome in Adults

The ATP III clinical definition of the metabolic syndrome requires the presence of 3 or more of the following:

1) Abdominal obesity	2) High triglyceride level	3) Low HDL cholesterol level	4) High blood pressure	5) High plasma fasting glucose concentration
waist circumference: ▪ >102 cm or 40" in men ▪ >88cm or 35" in women	▪ ≥ 150 mg/dl or ≥ 1.69 mmol/L	▪ <40 mg/dl or < 1.03 mmol/L in women ▪ <50 mg/dl or < 1.29 mmol/L in men	▪ systolic >130 mm Hg OR ▪ diastolic ≥ 85 mm Hg	▪ ≥ 110 mg/dl

Individuals with a previous physician diagnosis of hypertension or diabetes mellitus automatically meet criteria for high blood pressure and high plasma fasting blood glucose

The Bogalusa Heart Study found significant associations between excess abdominal adipose tissue and adverse clinical concentrations of lipids, including cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), triacyglycerol, and insulin in youth aged 5 to 17 years (Freedman *et al.*, 1999.) These results were consistent across both race and gender groups, including analysis of black and white children. Measurements of waist circumference and waist-to-hip ratios are indicative of a centralized adiposity, or a predominately abdominal fat distribution, which have been shown to be associated with insulin resistance in youth (Freedman *et al.*, 1999.)

Type 2 Diabetes and Implications

Type 2 diabetes has been referred to as an epidemic in the adult population, representing 90-95% of all newly diagnosed cases of diabetes (CDC, 2003). The prevalence of diabetes in the adult population (type 1 or 2) is 6.2% nationwide (National Institute of Digestive, Diabetes, and Kidney Disease [NIDDK], 2003). In 2002, 524,000 Michigan adults reported having been diagnosed with diabetes, with an overall population prevalence of 7.1% (CDC, 2003; Behavioral Risk Factor Surveillance [BRFS], 2000.) Michigan has the 7th highest prevalence rate of diabetes nationwide (CDC, 2003.) National statistics estimate that another 230,500 Michigan adults have diabetes and are unaware of it (CDC, 2003; National Centers for Health Statistics [NCHS], 1997). Complications arising from diabetes significantly affect morbidity and mortality through micro and macrovascular complications, which greatly increase the chances of developing cardiovascular disease, nephropathy, neuropathy, and retinopathy (CDC, 1999). Diabetes is one of the leading causes of blindness, renal failure, peripheral nerve damage, cardiovascular disease, stroke and non-traumatic amputation of lower limbs in the United States (ADA, 2003). When left untreated or poorly controlled, life threatening complications typically occur within 10-20 years from the time of disease onset (UKPDS, 2003.).

The direct per capita health care costs for a person with diabetes in 2002 was $13,243, compared with $2,560 for a person without diabetes (ADA, 2002). The total estimated costs the United States are $132 billion dollars per year, $92 billion in direct medical costs, $40 billion in indirect costs (CDC, 2003). National Health Objectives for Healthy People 2010 include 17 diabetes specific objectives (DHHS, 2000). Several

federal and state public health initiatives are addressing the rising number of individuals coping with the prevention, diagnosis, and management of diabetes, in order the prevent devastating complications often accompanying prolonged states of hypergylcemia (HHS, 2003; NDDK, 2002; MDCH, 2003).

The identification of risk factors and "pre-identifiers" for type 2 diabetes, which have been clearly defined from a clinical standpoint, are key in recognizing individual and family risk, screening, treatment, and outcomes. On the basis of expert opinion, screening for type 2 diabetes in asymptomatic individuals should be considered by health care providers at 3-year intervals beginning at age 45, particularly in those with BMI $\geq$25 kg/m^2 (ADA, 2003.) Testing should be considered at a younger age or be carried out more frequently in individuals who are overweight and have one or more of the other risk factors shown in table 2.3 (ADA, 2003.)

Table 2.3 -Risk factors for Type 2 Diabetes

- Family History of diabetes (i.e., parents or siblings with diabetes)
- Obesity (i.e., $\geq$20% over desired body weight or BMI $\geq$27 kg/m^2)
- Habitual physical inactivity
- Race/ethnicity (e.g., African American, Hispanic-Americans, Native Americans, Asian-Americans, and Pacific Islanders)
- Previously identified IGT or IFG
- Hypertension ($\geq$ 140/90 mmHg in adults)
- HDL cholesterol $\leq$ 35mg/dl (0.90 mmol/L) and/or a triglyceride levels $\geq$250 mg/dl (2.82 mmol/L)
- History of GDM or delivery of a baby weighing > 9 lbs
- Polycystic ovary syndrome

Type 2 Diabetes in Youth

Until recently, type 2 diabetes was considered rare in the pediatric population. However, in November 1998, Dr. David Satcher, former U.S. Surgeon General, declared the emergence of cases of type 2 diabetes in youth epidemic in the United States (CDC, 1998.) While type 2 diabetes in adolescence have been reported in the Pima Indians of Arizona since 1979, the condition was otherwise thought to be relatively non-existent in children and adolescents (Dabelea *et al.,* 1998, Savage *et al.*, 1979.). Recent reports of North American native groups and youth have been published indicating a rise in diagnosed cases of type 2 diabetes among those aged 19 years or younger in populations with high rates of type 2 diabetes in corresponding adult populations. (CDC, 2003; Pinhas *et al.*, 1998; Pinhoker *et al.*, 1998; Debeala *et al.*, 1998.) Harris *et al.* identified cases of "non-insulin dependent diabetes" (NIDDM), now referred to as type 2 diabetes, in First Nations (indigenous and aboriginal peoples of Canada and their descendents) children of northwestern Ontario in a published report in May, 1996. Subject characteristics of youth diagnosed with type 2 diabetes included a mean age of 11.7 years, with 71.4% being classified as overweight (having a BMI $\geq 95^{th}$ percentile.) 92.9% of those diagnosed had first or second degree relatives with type 2 diabetes, and the ratio of females to males was 6:1. Prevalence of type 2 diabetes in this population was estimated to be 2.5/1000, based on medical chart reviews of satellite clinics affiliated with the University of Toronto's Sioux Lookout Zone Program (Harris *et al.*, 1996.)

The *Journal of Pediatrics* also published a May, 1996 report on the emergence of type 2 diabetes among adolescents in the Children's Hospital Medical Center (CHMC) in the greater Cincinatti, Ohio area (Pinhas *et al.*, 1996.) Pinhas *et al.* hypothesized that

there was a correlation between the rise in the rates of childhood and adolescent obesity and diagnosis of type 2 diabetes in youth. Of the total sample of 1027 subjects aged birth through 19 years, 54 met the clinical criteria for type 2 diabetes, based on the National Diabetes Data Group (NDDG, 1979) diagnostic criteria. Prior to 1992, 2 to 3% of new cases of diabetes were classified as type 2 diabetes in those aged birth through 19 years (Arslanian, 1994.). In 1994, 16% of all new cases of type 2 were diagnosed in the same age group (Pinhas *et al.*, 1996.) Mean age of diagnosis in African American and Caucasian youth was 13.8 ± 1.9 years, all being in mid-puberty with a Tanner stage of III or greater. While the frequency of type 2 diabetes rose in both African American and Caucasian youth, 69% of those diagnosed from 1982 through1994 were African American (Pinhas *et al.*, 1996.) 85% of those diagnosed with type 2 diabetes also had a at least one first or second-degree relative with type 2 diabetes. 60% of subjects presented at diagnosis with acanthosis nigricans, a physical dermatological sign of insulin resistance. More females were diagnosed than males, with a ratio of 1.7:1. 17% were hypertensive, 6% had sleep apnea, and 8% had depression or eating disorders (Pinhas *et al.* , 1996.)

Mexican-American children and adolescents were assessed for type 2 diabetes and associative factors in two reports published in January, 1998. Neufeld *et al.* found that of Mexican-American youth diagnosed with type 2 diabetes by the Pediatric Endocrinology Service at the Pediatric Diagnostic Clinic in Ventura, CA, similar associative factors as those found by the work of Pinhas et al. existed. All were obese with elevated c-peptide levels, 62% presented with ketonuria, and family histories were positive for type 2 diabetes (Neufeld *et al.*, 1998). Similar findings were present in

another study of Mexican-American youth in southern California. A medical record review of 18 children and adolescents with type 2 diabetes produced common findings of obesity and acanthosis nigricans, as well as a strong family history. Mean age of diagnosis was 12.8 years, ranging from 5-17 years of age (Glaser *et al.*, 1998.)

Youth from Arkansas were studied in a report published in *Clinical Pediatrics* in February, 1998. Again, similar clinical characteristics were observed, including obesity, acanthosis nigricans, family history of diabetes, elevated blood pressure, and mean age of onset 14.0 years. While the majority of the sample studied included youth of African American and Caucasian descent, 74% of those diagnosed with type 2 diabetes were African American (Pinhoker *et al.*, 1998.) Of the remaining youth diagnosed with type 2 diabetes, 24% were Caucasian and 2% were Hispanic.

Children diagnosed with type 2 diabetes in Florida had many of the same clinical findings as those previously discussed. Of all youth diagnosed with diabetes from 1994 – 1998 in three university based diabetes centers in Florida, the proportion of those diagnosed with type 2 diabetes rose from 9.4% in 1994 to 20.0% in 1998 (Macaluso *et al.*, 2002). Factors associated with type 2 diabetes included a BMI $\geq 85^{th}$ percentile, Hispanic ethnicity, black race, female gender, and an older age (in one-year increments) compared to those with Type 1 diabetes. A full review of recent estimates of the magnitude of type 2 diabetes in North America is listed is table 2.4 (ADA, 2000).

Table 2. 4 – Estimates of Type 2 Diabetes in North American Youth

Study types	Year	Race/ethnicity	Age (years)	Estimates
				Prevalence per 1,000
Population-based				
	1992-1996	Pima Indians	10-14	22.3
Arizona			15-19	50.9
Mannitoba	1996-1997	First Nations	10-19	36.0 in girls
Clinic-based studies				
Manitoba	1998	First Nations	5-14	1.0
			15-19	2.3
				Incidence per 100,000/year
Clinic-based studies				
Cincinatti, OH	1994	Whites, African-Americans	10-19	7.2
				Percentage of type 2 diabetes among all newly diagnosed cases of diabetes
Case series				
Cincinatti, OH	1994	Whites, African-Americans	0-19	16
			10-19	33
San Diego, CA	1993-1994	Whites, African-Americans, Hispanics, Asian-Americans	0-16	8
San Antonio, TX	1990-1997	Hispanics, Whites		18
Ventura, CA	1990-1994	Hispanics	0-17	45
Florida	1994-1998	Hispanics, African-American, Whites	5-19	20

The burden of type 2 diabetes in youth has also surfaced globally. In Japan, 80% of diagnosed cases diabetes are type 2. A population-based study carried out over 20 years showed a 10-fold increase is the incidence of type 2 diabetes in 6-12 year olds, and a doubling in 13-15 year olds (Kitagawa *et al.*, 1998.) Taiwanese data shows similar findings in both male and female youth (Wei *et al.*, 2003.) Of all cases of diabetes

recorded in the those under the age of 18 in the United Arab Emirates, 12.5% have type 2 (Punnose *et a.l,* 2002.) Similar findings have been confirmed in Libya, Bangladesh, and aboriginal groups in Australia and Canada (ADA, 2000.)

There is undoubtedly great reason for concern given the obvious rise in diagnosed cases of type 2 diabetes in children and adolescents. The aforementioned data, which clearly identifies the growing trend in early-onset of type 2 diabetes in various North American racial and ethnic groups, likely underestimates the severity of the epidemic. At the time of publication, many of the above projects were using the National Diabetes Data Group's (NDDG) criteria for diagnosis of diabetes based on guidelines developed in 1979 (NDDG, 1979.) These former criteria classified diabetes according to pharmacological treatment modality, likelihood of ketosis, and plasma glucose values with more generous blood glucose cut-offs than what is now considered to be hyperglycemic. Should the 1997 revisions of the diagnostic criteria for diabetes from the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus be applied to existing data, it is likely that prevalence and incidence rates reported would be far greater than those listed. The continuing rising trend of overweight and obesity in youth is also likely to increase these existing estimates.

Research describing the pathophysiology of type 2 diabetes in the young is rare. Single-gene mutations like those seen with MODY (maturity-onset diabetes of the youth) are responsible for only a small portion of existing cases. Major and minor predisposing genes have been identified in some ethnic groups, still the bulk of existing data suggests that the progression of the disease mirrors a course similar to that in adults. Type 2 diabetes is a complex, multi-factorial metabolic disorder, with a heterogeneous genetic

component compounded by environmental, social, and behavioral factors (ADA, 2000.) Being overweight or obese, having a sedentary lifestyle, a family history of diabetes, belonging to a high-risk ethnic group, and having glucose levels above normal, yet below the diagnostic level for true diabetes diagnosis are risk factors for the development of type 2 diabetes.

As recommended in adult populations, screening for type 2 diabetes in youth is suggested only when increased risk is evident. Overweight children with a strong family history of diabetes or physical signs of insulin resistance are considered to be at substantial risk for type 2 diabetes (ADA, 2000). Given the prolonged latency of undiagnosed diabetes and risk for the development of early stages of micro and macrovasucalar complications, screening for type 2 diabetes in those at risk appears justified. The American Diabetes Association Consensus Panel currently does not have definitive data to make absolute recommendations for the screening of children and adolescents for type 2 diabetes. It does, however list criteria for screening youth, to be used in combination with professional medical judgement (ADA, 2000) (table 2.5). Screening should begin at age 10 and every two years following, or beginning at the onset of puberty (ADA, 2000.)

Table 2. 5 – Recommended Screening for Type 2 Diabetes in Youth

Overweight (BMI≥85th %tile for age and sex, weight for height ≥85th %tile, or weight >120% of ideal for height)
Plus **TWO** of the following:
-Family history of type 2 DM in first or second-degree relative
-Race/ethnicity (American Indian, African-American, Hispanic, Asian/Pacific Islander)
-Signs of insulin resistance (Acanthosis nigricans, polycystic ovary syndrome, hypertension, dyslipidemia)
Additional screening components
-Puberty status (Tanner stages III-V)
-Physical inactivity

ADA, 2000

Once diagnosed, treatment of type 2 diabetes in youth focuses on the normalization of blood glucose levels and glycosylated hemoglobin (ADA, 2003). Treatments are similar to those initiated in adults, including nutrition, exercise, and pharmacological interventions. The National Standards for Diabetes Self-Management Education (ADA, 2003) defines quality care and education as that which is designed to facilitate optimal healthcare outcomes. The course of treatment for children and adolescents with type 2 diabetes, like adults, depends upon the clinical presentation at time of diagnosis (ADA, 2001). Medical nutrition therapy is the cornerstone of diabetes treatment. The goals of treatment for youth with type 2 diabetes are to facilitate changes in eating and physical activity habits that reduce insulin resistance and improve metabolic status (ADA, 2003.)

Successful therapy with nutrition and physical activity may be defined as weight stabilization (or cessation of excessive gain) during linear growth with the achievement of blood glucose goals (ADA, 2003.) Meal planning should be individualized to address hypertension and dysplipidemia as needed, as well as behavioral management of lifestyle related habits – including those of the child's family. Decreasing sedentary behaviors such as television viewing and video games has been shown to be an effective way to increase exercise. The American Academy of Pediatrics recommends no more than 2 hours of television/computer/video game viewing each day (American Academy of Pediatrics [AAP], 2005.) Overall, lifestyle therapy should provide an individualized plan to increase caloric intake while increasing caloric expenditure for the purpose of weight

management. Specific goals for glucose management and medication interactions with meal planning are also personalized.

Overweight in Youth

As previously discussed, the rising cases of type 2 diabetes have been strongly associated with the corresponding trend in increasing rates of overweight in youth. Pinhas *et al.* were able to show that as the prevalence of overweight (using former cut-points of a BMI of >27 and/or > 90th BMI percentile) increased between 1982 and 1994, the incidence of type 2 diabetes was estimated to have increased by nearly a factor of 10 (Pinhas *et al.*, 1996; Rocchini, 2003.) Childhood overweight is considered by some to be the most serious and prevalent nutritional disorder in the United States (Rocchini, 2003.) Overweight children and adolescents are at greater risk for cardiovascular disease, hypertension, pseudotumor cerebri, orthopedic problems, early onset of puberty, sleep apnea, steatohepatitis, cholelithiasis, and polycystic ovary disease (Sorof *et al.,* 2002.)

In addition to the physiological concerns of overweight, potentially affecting morbidity and mortality, children and adolescents have been found to suffer from an impaired health-related quality of life when compared to normal weight children. Findings suggest that overweight youth show quality-of-life scores similar to those diagnosed with cancer (Schwimmer *et al.*, 2003.) Social and psychological consequences related to obesity include eating disorders, social discrimination, reduced socioeconomic status and fewer years of education (Evanston *et al.*, 1998.)

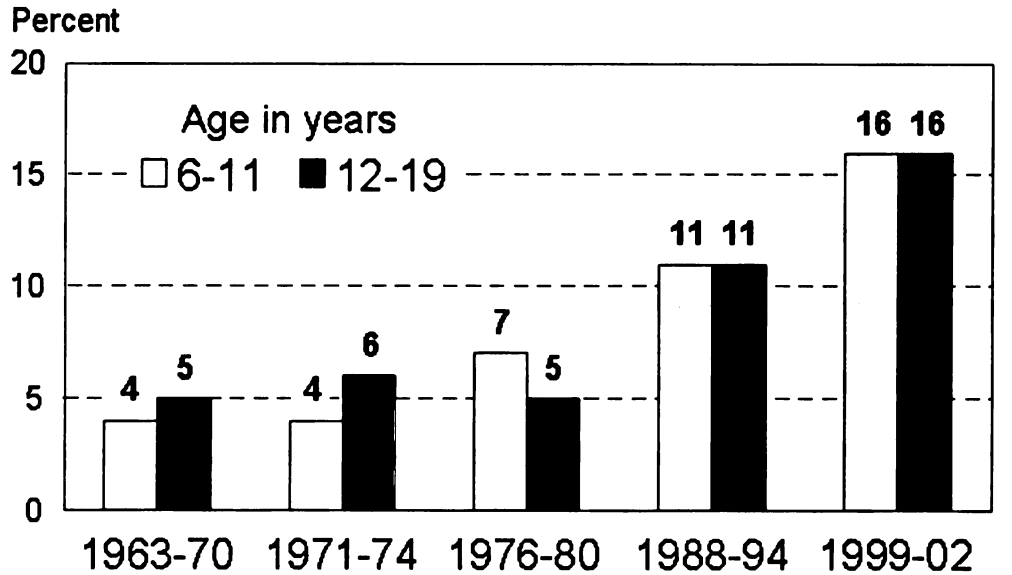
Overweight in children and adolescents is being referred to as epidemic in the health care community (Strauss *et al.,* 2001.) The latest published findings based on

analysis of NHANES III data from 1999-2002 show the overall prevalence of overweight in youth (BMI-for-age >95th percentile), stratified by age, is 16.1% in those ages 12–19 years of age, 15.8% in the 6–11 year age group, and 10.3% in children younger than six years of age (Hedley *et al.*, 2004.) 15% of those ages 6 to 19 years were considered to be at risk for overweight (BMI-for-age >85th percentile) (Hedley *et al.*, 2004.) Data analyzed by race and ethnic background show that non-Hispanic black and Mexican-American adolescents were more likely to be overweight than non-Hispanic white counterparts (HHS, 2003.) 24% of Mexican-American children were more likely to be overweight, compared to 20% of non-Hispanic black and 10% of white children. Non-Hispanic black preschoolers were the least likely to be overweight at 8%, with 11% of Mexican-American and 10% of non-Hispanic white preschool aged children being overweight (HHS, 2003.) An inverse relationship between overweight or obesity and socioeconomic status is sometimes seen in adults. However in Mexican-American and Non-Hispanic black youth, no significant correlation was found from the NHANES III data (Trioano, 1998.) Further analysis of the NHANES III data indicates some evidence showing a relationship between overweight in non-Hispanic white adolescents and income level (Trioano, 1998), though caution in the interpretation of this data is warranted due to large standard errors in the analysis. Support of a relationship between educational level and overweight is also limited, with the exception of a decreasing pattern of overweight with increasing educational level found in the parent(s) of Non-Hispanic white male children and adolescents (Trioano, 1998.)

The most resent results of NHANES show a 45% increase in overweight in youth 6-19 years from the 11% estimates of overweight obtained from NHANES III in 1988-

1994 (CDC, 2005). The following figure (figure 1) illustrates overall national trends for overweight in youth over the past four decades.

Figure 1. Prevalence of overweight among children and adolescents ages 6-19 years



NOTE: Excludes pregnant women starting with 1971-74. Pregnancy status not available for 1963-65 and 1966-70. Data for 1963-65 are for children 6-11 years of age; data for 1966-70 are for adolescents 12-17 years of age, not 12-19 years.
SOURCE: CDC/NCHS, NHES and NHANES

Assessment of Overweight

Currently, there is no working definition for obesity for children and adolescents, hence the repeated use of the term "overweight". Only measurements of adiposity, or "fatness" can be used to classify an individual as obese, or having excess adipose tissue. Anthropometric assessment of adiposity in youth is difficult to evaluate. Any criteria used to determine overweight or obesity for the measurement of prevalence in the United States must specify measurements and corresponding cut-off values for the classification

of abnormal anthropometrics (Goran, 1998.) While weight has been a long-time indicator of fatness in children, varying stages of height cause wide-ranging levels of adiposity, making it an unreliable measurement when used alone (Bellizzi & Dietz, 1999). Weight-based measures can only indirectly measure adiposity. Body mass index, or BMI; kg/m^2, is now the chosen anthropometric measurement used to assess adults and youth. In 2000, the Centers for Disease Control and Prevention (CDC) revised existing growth-charts for children and adolescents, utilizing BMI-for-age, rather than a comparison of weight-for-height and age for the assessment of growth (CDC, 2000.) BMI-for-age cut-offs for overweight are $\geq 95^{th}$ percentile, and values $\geq 85^{th}$ percentile but $<95^{th}$ are considered to be at risk for overweight (CDC, 2000.) Even though BMI is not the optimal measure of overweight in youth, because it co-varies with height, it has been validated against measurements of body density (Bellizzi & Dietz, 1999). Despite its high correlation with body density, until an individual reaches their peak height, BMI is not a reliable measure of fatness in children and adolescents, especially across different age and maturational stages (Troiano, 1998). The CDC recommends the following algorithm for screening youth for overweight (figure 2) (American Society for Clinical Nutritionists, 2004.)

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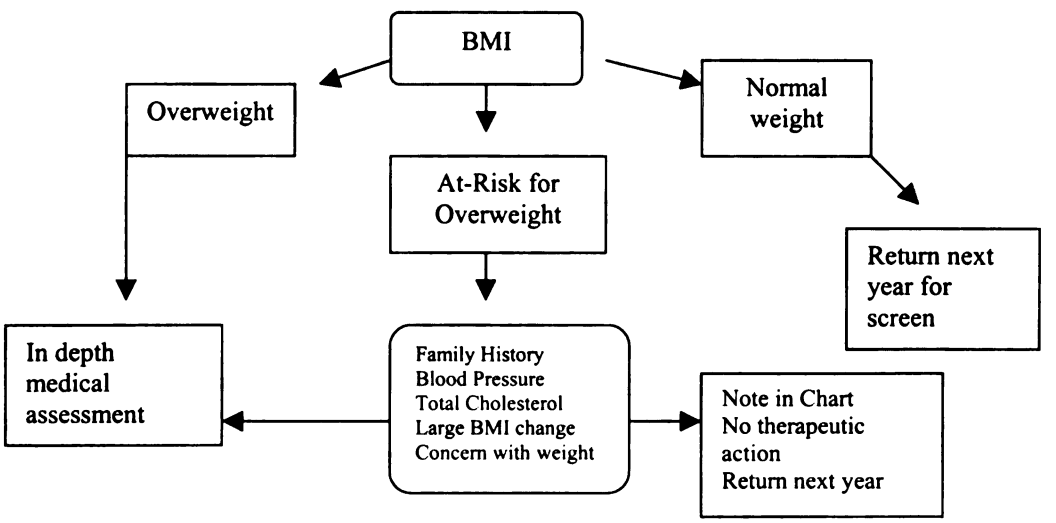
Figure 2.2 Recommended Overweight Screening Procedures



Familial Factors

Familial factors also appear to have a strong link to the development of overweight in youth. Children with two obese parents have an 80% greater chance of becoming overweight during their lifetime, with risk falling to 40% when only one parent is obese (Sothern *et al.*, 2003; Surgeon General, 2003.) Children of lean parents have only a 7% likelihood of becoming obese during their lifetime (Sothern *et al.*, 2003; Surgeon General, 2003.) Critical periods for the development of obesity in children include gestation, 5-7 years of age, and adolescence (Schonfeld *et al.*, 1997). Overweight adolescents have a 70% chance of becoming overweight or obese adults (Surgeon General, 2003.)

Dietary Factors

Birch and colleagues contend that early childhood experiences as they relate to self-regulation of energy intake are associated with parental feeding-practices and subsequent levels of adiposity (Birch *et al.*, 1998). By altering children's patterns of intake, stringent parental control of foods may necessitate the preference for high-fat energy-dense foods, limit acceptance to a variety of foods, and disrupt children's internal physiological signals of self-regulation by altering hunger and satiety mechanisms (Birch *et al.*, 1998). The Surgeon General has published healthy eating suggestions for parents for the prevention and decrease of overweight and obesity (Surgeon General, 2003) (table 2.6).

Table 2.6 - Healthy Eating Suggestions

- Follow the Dietary Guidelines for healthy eating (www.health.gov/dietaryguidelines)
- Guide your family's choices rather than dictate foods
- Encourage your child to eat when hungry and to eat slowly
- Eat meals together as a family as often as possible
- Don't place your child on a restrictive diet
- Carefully cut down on the amount of fat and calories in your family's diet
- Avoid the use of food as a reward
- Children should be encouraged to drink water and to limit intake of beverages with added sugars, such as soft drinks, fruit juice drinks, and sports drinks
- Plan for healthy snacks
- Stock the refrigerator with fat-free or low-fat milk, fresh fruits, and vegetables instead of soft drinks or snacks that are high in fat, calories, or added sugars and low in essential nutrients
- Discourage eating meals or snacks while watching T.V.
- Eating a healthy breakfast is a good way to start the day and may be important in achieving and maintaining a healthy weight

Physical Activity as a Risk Factor

A sedentary lifestyle with limited physical activity is a risk factor for overweight. The prevention of obesity is reliant on maintaining and/or increasing the physical activity of young children at risk for obesity (Sothern *et al.*, 1999.) Three methods for increasing physical activity in children include 1) increased opportunities, methods, and environments for unstructured physical activity or free play, 2) reductions in television viewing, and 3) parent training sessions and family behavioral counseling (Sothern *et al.*, 2003.) A randomized controlled study of television reduction as a means to prevent obesity in children was published in the *Journal of the American Medical Association* in 1999. Children in the intervention group had statistically significant reductions in BMI, triceps skinfold thickness, waist circumference, and waist-to-hip ratio (Robinson, 1999.) Reducing not only television viewing time, but also videogame and personal computer use time is suggested as a potential population approach to preventing childhood obesity (Robinson, 1999.) A review of published literature examining the relationship between television watching and food intake since 1970 indicates that the greater the hours spent viewing television, the more likely children are to consume high energy and sodium foods, and carbonated beverages accompanied by a lesser amount of fruit and vegetable intake (Coon, 2002.) The lifestyle accompanying excess television watching appears to not only predispose youth to obesity, but compromised nutritional intake (Coon, 2002.)

Treatment of Overweight in Youth

The treatment of overweight in children and adolescents has shown to be as great a challenge to health professionals as its prevention. While the application of a universal

intervention for the treatment of overweight in youth does not currently exist, the primary goal of treatment does seem to be consistent. Regulation of body fat and weight with adequate nutrition for normal growth and development are essential, while maintaining positive physiologic and psychological sequelae (Epstein *et al.*, 1998.) A brief review of the commonly utilized interventions for weight management in youth follows, including the examination of nutrition, physical activity, behavior-modification, surgical intervention, and pharmacotherapy interventions.

Diet and physical activity interventions focusing on weight management generally assume the equation associated with excess adiposity as a surplus of caloric intake combined with a deficit in caloric expenditure. The goals of nutrition therapy are often focused toward reducing or stabilizing caloric intake, reducing fat and/or sugar intake, and restructuring eating patterns to resemble those recommended by the current dietary recommendations for Americans (Epstein *et al.*, 1998.) The goals of calorie restriction or deficit when treating overweight youth include the maintenance of weight during linear growth (ADA, 03, Rosenbaum & Leibel, 1989), or losses of 0.5 to 1.0 kg every 2 to 4 weeks (Dietz & Hartrung, 1985.) Special considerations must be taken when prescribing calorie and macronutrient reduced diets in children and adolescents. Growth retardation, amenhorrea, binge eating, and the development of eating disorders are physiological and psychological consequences of calorie and nutrient restrictive diets in the young (French & Jeffrey, 1994; Gibbons *et al.*, 1995; Pugliese *et al.*, 1983).

Commonly utilized dietary approaches to caloric deficit and improved eating patterns in children and adolescents include individual counseling with and without exercise, utilization of the diabetic exchange lists (Becque *et al.*, 1988; Rocchini *et al.*,

1988; Rocchini *et al.*, 1987) with calorie deficits intended to induce a 1-pound per week weight loss, and the "traffic-light" diet, an approach using the concept of grouping foods according to nutrient content and an associated color; green (go) foods being consumed in unlimited quantities, yellow (caution) foods including those of average nutritional value, and red (stop) foods containing the least nutrient density and quality, usually those of high fat or simple carbohydrate content (Epstein *et al.*, 1998.)

Physical activity interventions are commonly applied in conjunction with dietary changes (Epstein *et al.*, 1998.) As with many of the treatment modalities for weight management, there is no one preferred prescription for exercise. Recent interest in "lifestyle exercise", or the attempt to increase caloric expenditure in everyday activities, has been shown to be a successful alternative to programmed exercise regimens. Epstein et al. was able to show lifestyle exercise to be an optimal choice in combination with the traffic-light diet both at 17 months and 2-year follow-ups with children (Epstein *et al.*,1982; Epstein *et al.*,1985.) Abstinence from sedentary activity has also shown favorable results for reducing weight gain and decreasing adiposity in youth (Robinson, 1999.) Physical activity should include aerobic fitness, muscle strength, and endurance . The Kid's Activity Pyramid is a teaching tool for health care professionals, educators, parents, and children themselves, to be used to encourage daily physical activity (Frary and Johnson, 2000.)

Behavioral modification has become a tenant of weight management in adults and children. Epstein and colleagues were able to show that the addition of behavioral treatment to nutrition education produced significantly greater weight reductions over a 5-month period in children (-17.5% compared to –6.4%) (Epstein *et al.*,1980.)

Techniques including contingency contracting, self-monitoring, praise, and stimulus control are well-accepted behavioral modification strategies. More recently, problem solving and non-food reward systems have been incorporated into treatments (Epstein *et al.*, 1998; Mellin *et al.*, 1987.) Family-based interventions show significantly more favorable results at 1-year follow-up, with greater differences in weight lost than controls at 2-years, though not significant (Epstein *et al.*, 1998.)

Pharmacological and surgical treatments are not generally the first line of medical treatment pursued for overweight children and adolescents. A 20-year review of obesity surgery in adolescents was published in the *Journal of Gastrointestinal Surgery* in January, 2003. Thirty-three adolescents undergoing bariatric procedures from 1981-2001 were reviewed. Gastroplasty, distal gastric bypass, long-limb gastric bypass, and laparoscopic gastric bypass were the procedures reviewed. Early complications included one case each of pulmonary embolism and major wound infection, four cases of minor wound infections and marginal ulcers, and three cases of stomal stenosis requiring endoscopic dilitation. Late complications included one incident of small bowel obstruction and incisional hernias in six patients (Sugerman *et al.*, 2003.) The March, 2003 issue of the *Journal of Pediatric Surgery* is the first to report on the roux-en-y gastric bypass procedure performed in adolescents. Medical record reviews of 4 patients less than age 20 indicated an average loss of 87% of excess body weight at 20-month follow-up, with no complications. Complete resolution of obesity co-morbidities including hypertriglyceridemia, hypercholesterolemia, asthma, and gastroesophageal reflux disease were observed (Stanford *et al.*, 2003.) Long-term psychological effects of surgical interventions were not reported in the above studies.

Two common anti-obesity pharmaceutical agents have been recently reviewed for safety and efficacy in children and adolescents. The results of a randomized clinical trial in adolescents using sibutramine, an anorexiant medication whose mechanism of action works to block the re-uptake of norepinephrine and serotonin, were recently reported in peer-reviewed literature (Berkowitz *et al.*, 2003). Eighty-two adolescents were assigned to receive intensive behavioral treatment and a placebo, or sibutramine for a 6-month period. Those treated with both sibutramine and behavioral therapy lost significantly more weight than the placebo group. However, Berkowitz found that differences in weight outcomes seen between treatment groups may be explained more by poor adherence to the behavioral modification group by the placebo treated adolescents than the sibutramine. Furthermore, 44% of those treated with subutramine experienced increases in systolic blood pressure, necessitating dose decreases or total discontinuation of the drug. Placebo controlled participants saw reductions in blood pressure. Other conditions associated with obesity, such as dyslipidemia and insulin resistance, were improved in both study groups, with no significant differences (Berkowitz *et al.*, 2003). This trial suggests that pharmacological interventions for the treatment of overweight in youth are still investigational.

Orlistat, trade-name "Xenical", a gastrointestinal lipase-inhibitor is used to reduce dietary fat absorption. Two studies were recently published reviewing findings of orlistat interventions in overweight prepubescent children and adolescents (Norgren *et al.*, 2003; Zhi *et al.*, 2003.) Overweight children aged 8 to 12 years were able to tolerate orlistat for 12-weeks with only mild gastrointestinal side-effects, and no reported negative psychological or physiological effects. Decreased fat intake, weight loss, and fat mass

loss were observed (Norgren *et al.*, 2003.) Overweight adolescents taking orlistat 21 days experienced mild to moderate gastrointestinal side-effects, while decreasing fat absorption by 27%. Macro and micromineral levels were not compromised by orlistat during the 21 day administration. Weight changes were not reported (Zhi *et al.*, 2003.)

Diabetes Prevention

Just as childhood overweight and resultant adulthood obesity prevention presents itself as a vast challenge, prediabetes and type 2 diabetes prevention also presents a challenge to the health-care professional. Established trends showing the rising numbers of cases of documented type 2 diabetes in children and adolescents necessitate the need for interventions geared toward prevention. During childhood, cognitive and physical development of patterns, that may predict or place an individual at greater risk for preventable chronic disease, are established. Therefore, risk factors that are not only genetic, but also environmental should be the focus when conceptualizing and developing intervention strategies (Mobely, 1999.) Because environmental modifiers of food selection and intake, and physical activity have been established as potential links to the development of prediabetes and type 2 diabetes, the roles of community, school, and family must be considered as modifying variables in diabetes risk for children (Mobely, 1999.) Recently, in a survey of the American public, 78% of respondents reported that their weight was not a serious health concern (Lee & Oliver, 2002.) Approximately two-thirds of those who responded were overweight, one-third obese, and 15% of their children were overweight. Whether this is an indication of indifference or ignorance, neither is appropriate (Weisburg, 2002.)

From a physiological standpoint, Buchanan theorizes that type 2 diabetes may be delayed or prevented through three types of interventions: 1) interventions that limit fat accumulation of the body (less obesity = less insulin resistance), 2) interventions that uncouple obesity from insulin resistance (less insulin resistance = β-cell less failure), and 3) interventions that directly preserve β-cell mass and/or function, despite high secretory demands imposed by insulin resistance (better β-cell function = less diabetes) (Buchanan, 2003.)

Adult Intervention Studies

Successful prevention or delay of type 2 diabetes in adults has been demonstrated through both lifestyle and pharmacologic interventions. Early work in Da Qing, China demonstrated a decrease in the development of type 2 diabetes in a large cohort of male and female subjects over the age of 25 with diagnosed IGT, followed over a 6-year period. Groups randomized to a diet or exercise intervention were able to effectively reduce over-all incidence of diabetes, with diet producing a risk reduction of 31%, and exercise 46%. Risk reduction for the combined effect of diet and exercise was 38% (Pan *et al.*, 1997.)

The 6-year Malmö feasibility study utilized a model similar to the Da Qing study in 47- 49 year-old Swedish males with early-stages of type 2 diabetes mellitus (n=41) or impaired glucose tolerance (n=181). A 5-year pilot study randomizing participants to a nutrition intervention and/or exercise intervention, or a control (no intervention) was completed by 90% of subjects, who were then followed annually (Eriksson & Lindgärde,

1991). Body weight decreased by 2.3 to3.7% in those in the intervention groups (compared to a 0.5 to 1.7% increase in controls), oxygen utilization during exercise increased 10 to 14% verses –5 to -9% in controls, and glycemia was normalized in 50% of those with IGT. The accumulated incidence of diabetes was 10.6%, with greater than 50% of those with diabetes maintaining euglycemia at a 6-year follow-up (Eriksson & Lindgärde, 1991). While the findings of these early studies are noteworthy, they have been criticized for weaknesses in their study designs, such as a lack of subject blinding between interviewers and intervention groups, making their generalizability of limited value (ADA & NIDDK, 2002.)

More recent lifestyle intervention trials have shown beneficial results in the prevention or delay of type 2 diabetes in adults (Diabetes Prevention Program [DPP], 2002; Tomilehto *et al.*, 2001.) The Finnish Diabetes Prevention Study was published in the May 3rd issue of the *New England Journal of Medicine* in 2001. Study subject recruiting involved the screening of first-degree relatives of existing patients with type 2 diabetes with an OGTT test using WHO criteria for the diagnosis of IGT (WHO, 2002.) Overweight (BMI >25) subjects with IGT between the ages of 40 and 65 years were also eligible for study participation. Participants were randomized to a control or lifestyle intervention group with partial blinding to health-professionals involved in the project. Both groups received a lifestyle intervention, with the control group modeling a more traditional medical approach involving the dissemination of oral and written information related to nutrition and physical activity with no individualization of the advice to the participant.

The intervention protocol included the following goals: 1) ≥5% reduction of weight, 2) total intake of fat to ≤30% and saturated fat intake ≤10% of total calories, 3) an increase in fiber intake to at least 15 grams per 1000 kilocalories, and 4) moderate exercise for at least 30 minutes each day. At an average follow-up of 3.2 years following the intervention, a 58% rate of reduction in the incidence of diabetes development was seen in the intervention group. Strong correlations were seen between diabetes prevention and the adoption of 1 or more of the treatment goals (Tomilehto *et al.*, 2001; ADA & NIDDK, 2001.)

The Diabetes Prevention Research Group conducted a multiple-site clinical trial in the United States to answer the following research questions among samples of overweight adults with prediabetes (DPP, 2002):

1) Does a lifestyle intervention or treatment with metformin, a biguanide antihyperglycemic agent, prevent or delay the onset of diabetes?

2) Do these two interventions differ in effectiveness?

3) Does effectiveness differ according to age, sex, or race or ethnic group?

Study subject inclusion criteria were as follows: age = ≥ 25 years, anthropometrics = BMI ≥24; ≥22 for Asians, and fasting and 2-hour post-OGTT testing (fasting = 95 to 125mg/dl [5.3 to 6.9 mmol/L, or ≤125 in American Indian clinics; 2-hour post OGTT load = 140 to 199 mg/dl [7.8 to 110 mmol/L]). Random assignments to one of three interventions included 1) a standard lifestyle plus metformin at 850 gm once a day, 2) a standard lifestyle intervention and drug placebo, and 3) an intensive lifestyle intervention. Instruction for the standard lifestyle intervention included diet recommendations from the Food Guide Pyramid (FGP) and a lowered total fat and

saturated fat intake, in concordance with the National Cholesterol Education Program guidelines. Directives to lose weight and increase physical activity were also given. Participants in the standard lifestyle intervention were provided recommendations in written form at a baseline visit, then seen at subsequent follow-up visits annually during 20-30 minute appointments. Treatment for the intensive lifestyle intervention were similar to those of the Finnish Study, including the achievement and maintenance of a ≥7% weight reduction through a lowered-calorie, low-fat diet and to engage in 150 minutes per week of moderate intensity exercise (DPP, 2002.)

The intensive lifestyle intervention included a curriculum addressing diet, exercise, and behavior modification delivered to participants on a one-to-one basis during the initial 24-weeks of the program, followed by either continued individual or group sessions for reinforcement of behavioral changes.

Findings of the intensive lifestyle intervention demonstrate that there were striking similarities to those found in the Finnish Diabetes Prevention Study. At 2.8 years follow-up, a 58% relative risk reduction for the development of diabetes was observed in the intensive lifestyle modification group. The group receiving metformin and standard lifestyle intervention also produced positive results, showing a 31% relative risk reduction for developing diabetes compared to the standard lifestyle with placebo group. On average, 50% of the those in the intensive lifestyle group achieved the goal of ≥7% weight loss and 74% maintained at least 150 minutes of moderate intensity exercise weekly (DPP, 2002; ADA & NIDDK, 2001).

Two pharmacological trials are noteworthy of mention for the prevention or delay of type 2 diabetes (Chiasson *et al.*, 2002; Buchanan *et al.*, 2002.). The STOP-NIDDM

trial published in *The Lancet* in June, 2002 involved a multi-clinic, international randomized trial taking place in Canada, Germany, Austria, Norway, Denmark, Sweden, Finland, Isreal, and Spain. Subject characteristics were similar to those of the lifestyle intervention studies discussed earlier with criteria including IGT, BMI, age, and family history of type 2 diabetes (DPP, 2002; Tomilehto *et al.*, 2001). Subjects were randomized to placebo-controlled or intervention group. Those receiving the intervention were given 100 mg of acarbose, an α-glucosidase inhibitor, three times daily taken with the first bite of food. The proposed mechanism whereby acarbose is thought to prevent or delay diabetes involves the reduction of post-prandial hyperglycemia, thereby improving insulin sensitivity and reducing stress on pancreatic β-cells (Chiasson *et al.*, 1996.). Results of the acarbose intervention at a mean follow-up of 3.3 years produced a 25% risk reduction in the delay of the development of type 2 diabetes (Chiasson *et al.*, 2002.).

The Troglitazone in the Prevention of Diabetes (TRIPOD) Study, Hispanic women with previous gestational diabetes were randomized to receive placebo or troglitazone, an insulin sensitizer now withdrawn from commercial sale in the United States due to questions related to its safety. Results were able to show a 56% relative risk reduction in progression to type 2 diabetes at 30 months (Buchanan *et al.*, 2002.)

Youth Intervention Studies

To date, longitudinal data documenting the effects of lifestyle and/or pharmacological interventions in youth are few. Initiatives in the Native American Indian population are underway to assess the efficacy of school and community-based

initiatives in elementary and high school-aged populations, for both the prevention of diabetes and obesity (Cook & Hurley, 1998; Macaulay *et al.*, 1997; Ritenbaugh *et al.*, 2003, Caballero *et al.*, 1998.) Early results of the "Quest" program, indicate that a school environment provides a stable environment for behavior change and educational interventions that may slow weight gain in early childhood (Cook & Hurley, 1998.) Pima Indian children in kindergarten and first and second grades continue to participate in an ongoing intervention encompassing education, physical activity, school-lunch modifications, and biochemical and anthropometric assessments (Cook & Hurley, 1998.)

A recently published study of Zuni Native American adolescents who were age-matched with an Anglo comparison group received an environmentally-based lifestyle intervention. Changes in plasma insulin levels (a marker for type 2 diabetes risk) were also assessed. (Ritenbaugh *et al.*, 2003.) The educational curriculum targeted consumption of sugared beverages, knowledge of diabetes risk factors, and physical activity. Fasting and 30-minutes plasma insulin levels (following a 75-gm glucose challenge) were collected at baseline, 1.5, and 3.0 years. At baseline, post-prandial insulin levels were significantly higher in Zuni youth. Throughout the study, insulin levels declined in both Zuni male and female subjects. At a three year follow-up, Zuni males' insulin levels were equal to those of their Anglo comparison groups; Zuni females had higher plasma insulin values than their age-matched Anglo peers, though had continued to show a progressive decline from baseline values (Ritenbaugh, 2003.)

The use of metformin has been shown to be safe and effective in children and adolescents for the treatment of type 2 diabetes (Jones *et al.*, 2002). Research on a small mixed-sample of obese children with either IGT or type 2 diabetes with insulin resistance

and acanthosis nigricans found that insulin resistance was decreased by 36.3% after six months of treatment with metformin. Body weight was reduced by 4.7±1.9% and body fat mass by 8.95±3.7% (Tankova, 2002.) Freemark was able to show that overweight youth (without prediabetes) at high-risk for diabetes with hyperinsulinemia and a family history of type 2 diabetes in first or second-degree relatives, responded positively to metformin administration. Fasting blood glucose and insulin concentrations, as well as well insulin sensivity improved after a 6-month trial of metformin (Freemark, 2003.)

Future Directions for the Challenge of Overweight and Prediabetes

The prevention of overweight and subsequent type 2 diabetes in youth presents an enormous challenge to public health and medical professionals. Findings of prediabetes in overweight youth from Sinha *et al.* in 2002 suggest future prospects of screening for prediabetes in those <20 years by physicians and healthcare staff (Sinha *et al.*, 2002; Ricchini, 2002.) Others suggest more rigorous efforts toward the identification of risk factors for overweight in youth with the hopes of preventing later obesity and co-morbidities, such as diabetes. Genetic, biological, socio-cultural and environmental influences are thought to work in concert, leading to the development of early childhood risk for overweight. Low levels of physical activity and a diet high in calories and fat are cited as associative factors in the development of obesity (Surgeon General, 2003.) The spread of a "Westernized" and industrialized lifestyle has been strongly indicated in the global spread of obesity (ADA, 2000.) However, the exact mechanism of these interactions is not clear. As seen with adult obesity, risk factors for childhood overweight have been identified. The American Academy of Pediatrics (AAP) recently released a

policy statement addressing the need for more aggressive prevention of overweight in children and adolescents through the identification of these risk factors and clinical management of at-risk youth throughout childhood and adolescence (AAP, 2003.)

The literature review provided concludes that the growing epidemic of overweight and type 2 diabetes in youth is a serious nutritional and environmental concern, often with serious outcomes if left unrecognized and untreated. Prediabetes represents an intermediate stage during which the development of a lifelong, debilitating chronic disease may be delayed or prevented. Examination of the existence, extent, associative factors, and current treatments for prediabetes in youth is warranted.

CHAPTER 3
Methods

Study Objectives

The aim of this study was to define the extent to which prediabetes can be detected in overweight and at-risk for overweight youth, through an assessment of screening practices performed by participating clinics. The objective of this specific aim was to determine the proportion of youth with a BMI-for-age ≥85th percentile who meet the criteria for prediabetes, and to further describe the biomedical and sociodemographic factors present in this population. The screening practices of clinics involved were also assessed based on recommendations given by the American Diabetes Association. The second specific aim was to review lifestyle and pharmacological recommendations provided to those with prediabetes. Lifestyle, including diet modifications and moderate physical activity, and pharmacological treatment utilizing the medication metformin have been shown to be effective in preventing or delaying the onset of diabetes in adults with detected prediabetes (Tomilehto *et al.*, 2001; DPP, 2002.) Based on the assumption that similar clinical recommendations are being provided to youth with prediabetes, a comparison of these recommendations and whether subsequent changes in biomedical risk factors associated with the development of diabetes (weight, blood glucose, blood lipids, blood pressure) occurs was the objective of the second study aim.

To accomplish the specific aims, two-phase retrospective medical record review was conducted in three urban Michigan pediatric endocrinology clinics. Overweight children and adolescents are commonly referred to pediatric endocrinologists for treatment of their overweight condition (Quattrin *et al.*, 2005.)

Study Population

Data on overweight and at-risk for overweight youth 6 to19 yr was collected from pediatric endocrinology subspecialty clinics located in lower-peninsula cities of Michigan including: Detroit, Flint, and Lansing. Pediatric endocrinology practitioners, to whom youth at risk for both obesity and diabetes are regularly referred for diagnosis and management, are thought to be exposed to or have a more likely pool of subjects with prediabetes parameters tested and monitored (Quattrin *et al.*, 2005.) Prior work conducted by Handu et al. in the same three clinics established the extent of type 2 diabetes in youth, calculated as a proportion of all of those diagnosed with diabetes, type 1 and type 2 (Handu *et al.*, 2004.)

Inclusion and Exclusion Criteria

Youth were selected based on the presence of overweight (≥95th percentile using the BMI-for-age) or at-risk for overweight (≥85th and <95th BMI-for-age percentiles) according to the CDC growth charts for children and adolescents (CDC, 2000). Presence of previously diagnosed type 1 or type 2 diabetes noted in the medical record prohibited study participation. Exclusion criteria included the presence of endocrinopathies associated with the development of insulin resistance as noted in the medical record. Conditions necessitating exclusion to participate: acromegaly, Cushing's syndrome, Glucagonoma, Pheochromocytoma, Somatostatinoma, and Aldosteronoma, or the use of medication known to induce hyperglycemia (ADA, 2004.)

Overweight or at-risk for overweight subjects identified as meeting the criteria for impaired fasting glucose (IFG), or impaired glucose tolerance (IGT) following a 2-hour

oral glucose tolerance test (ADA, 2003; Benjamin *et. al*, 2003) were classified as having prediabetes. IFG was defined as a blood glucose ≥100 mg/dl and <126 mg/dl; IGT was defined by a blood glucose ≥126 mg/dl and <140 mg/dl (ADA, 2004.)

Procedures

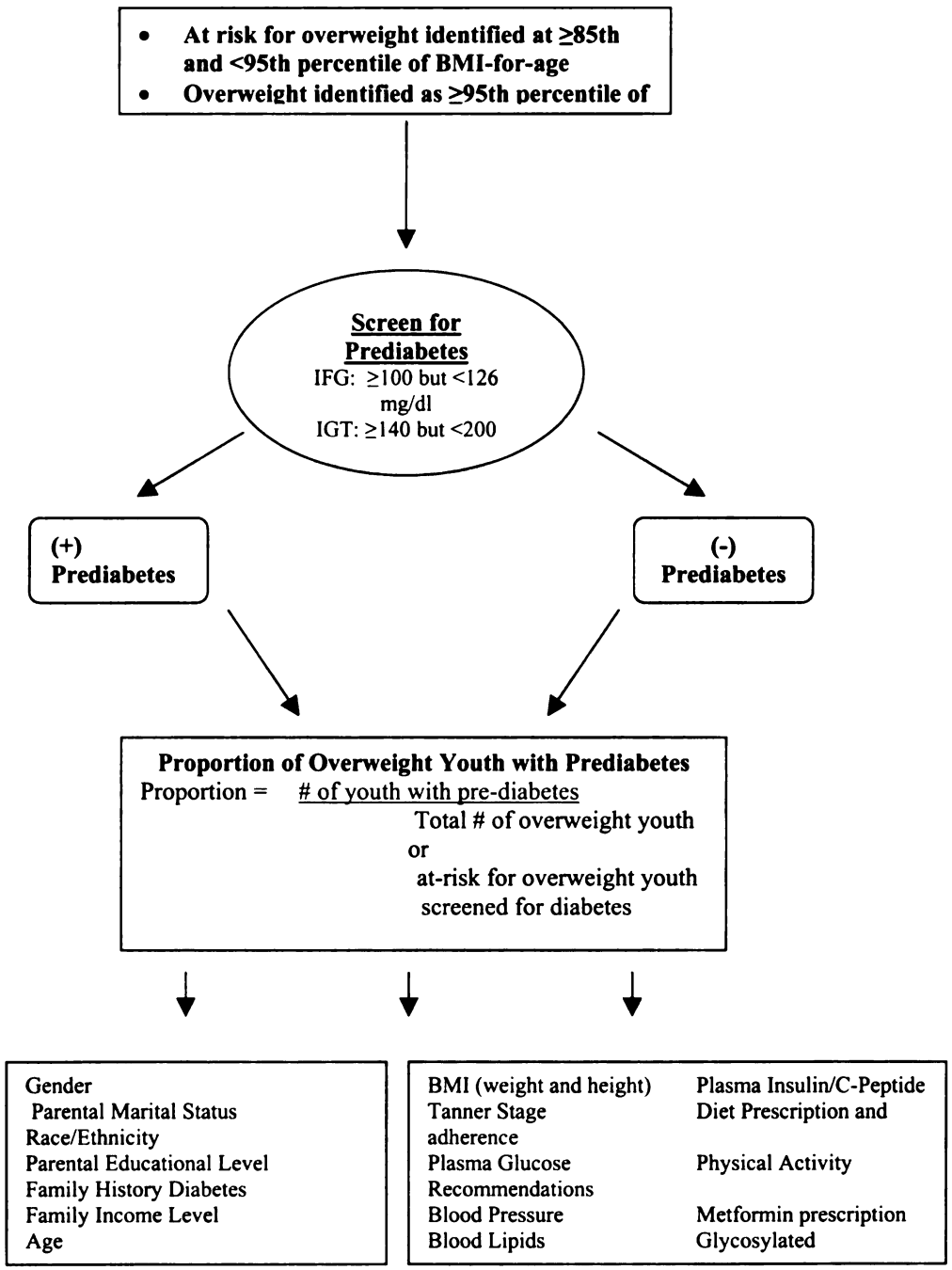
An application to the Michigan State University Committee on Research Involving Human Subjects (UCRIHS) was submitted and approved with permission to commence the project in December, 2003 (Appendix A.) In addition, applications to the Internal Review Boards (IRB) at each of the three study sites was submitted and approved prior to data collection (Appendices B,C, and D.) Health Insurance Portability and Accountability Act (HIPAA) regulations for healthcare organizations were followed and adhered to in both clinical and laboratory settings. Due to the nature of the acquisition of the data (retrospective medical record data analysis), HIPAA guidelines generally requiring the consent of all research participants as well as parents and/or guardians were waived. Due to the use of "no protected patient information", individual patient consent was not indicated for this study. Therefore, a "waiver of consent" was requested and granted when applying for the UCRIHS and IRB approvals.

The primary investigator(s) presented the study abstract to physicians and clinical administrators involved in patient care and treatment, for support and participation in the project. Ancillary staff (registered nurses, registered dietitians, certified diabetes educators, and medical assistants) involved in patient care and education were briefed on the study protocol prior to commencement of data collection. Supervision was provided by involved staff to assist in identifying study subjects. After IRB approval, appropriate scheduling and office procedures were confirmed and data collection was initiated.

Specific Aim 1

The first specific aim of the study encompassed medical record reviews of subjects meeting the study inclusion criteria. The aim was to defined the extent to which prediabetes is detected in overweight and at-risk for overweight young, through an assessment of screening practices performed by participating clinics. Overweight subjects' medical records were reviewed with limited demographic and biomedical information collected. Given that prediabetes was the focus of the study, more data was not abstracted from the overweight and at-risk for overweight youths' medical records. Demographic (race/ethnicity, gender, age) and biomedical (blood pressure, pubertal stage) data was collected to assess for differences, as well as associative factors in those classified as having prediabetes. Risk factors for diabetes and metabolic syndrome were also collected from the medical records of overweight and at-risk for overweight youth screened to assess and describe the study sample. A conceptual model of specific aim one is shown in figure 3.

Figure 3 – Conceptual Model of Specific Aim 1

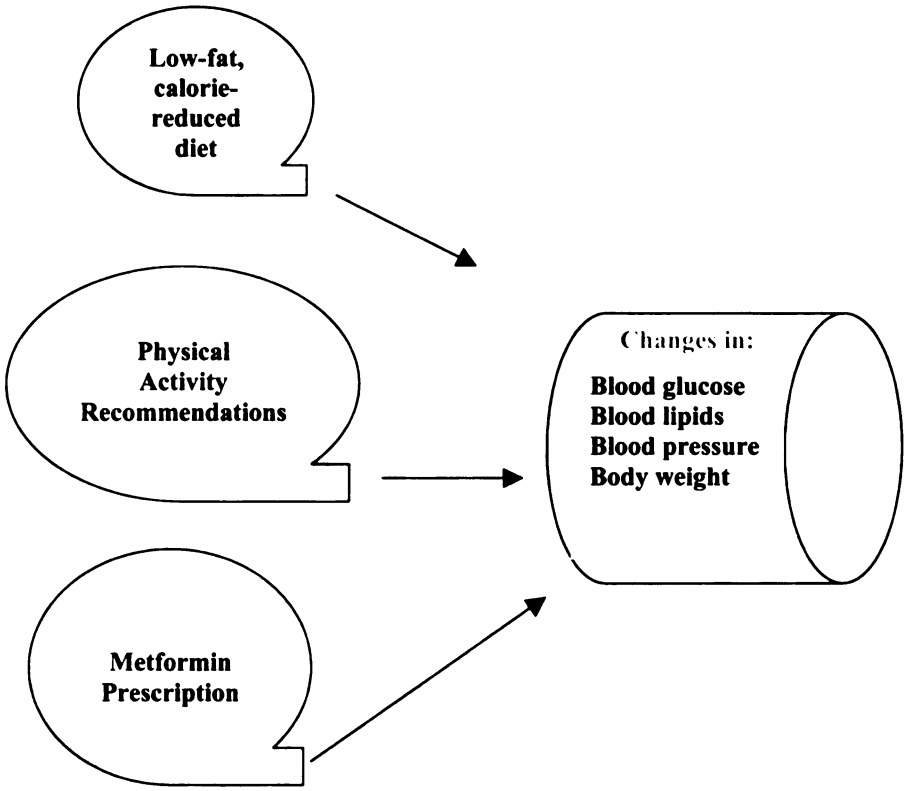


Specific Aim 2

To assess the second specific aim, the full chart review conducted on those meeting the criteria for prediabetes included: data related to treatment recommendations for prediabetes and the outcomes of those recommendations; an assessment of current interventions for the treatment of overweight and prediabetes, with the ultimate goal of preventing or delaying the development of type 2 diabetes; and assessment of changes in known risk factors associated with diabetes. These included weight, blood glucose (fasting, casual, and following a 2-hour OGTT), blood lipids, serum insulin, blood pressure, changes in physical activity and diet as noted in medical record (DPP, 2002; Tomilehto *et al.*, 2001.)

Only those subjects with two or more follow-up visits to their respective clinic were included for assessment of interventions and subsequent changes in risk factors. The intervention modalities intended to stabilize risk factors in youth, such as a prescription and adherence to a diet low in fat and lower in calories, increased physical activity, weight loss or stabilization, and in some cases the administration of metformin (Glucophage®), a biguanide class of pharmacological therapy, were recorded and assessed. A conceptual model of specific aim two is shown in figure 4.

Figure 4 – Specific Aim 2 Conceptual Model



A data abstraction sheet was used to collect data (Appendix E). Prior to conducting the formal chart review process, content validity of the data abstraction form was conducted by four professionals with expertise in the area of child and adolescent health, and diabetes and/or obesity in children, as well as two Michigan State University faculty involved in related research. Revisions based on the review of these professionals were incorporated prior to carrying out a pilot medical record review.

A pilot medical record review was conducted at the Sparrow Pediatric Endocrinology clinic to assess the effectiveness of the data abstraction tool in capturing the data needed for the research questions and hypotheses. Subsequent format and data collection changes were made as appropriate following the pilot review. Three student research assistants involved in data collections were trained by the lead investigator. For quality assurance, the lead investigator also cross-checked data collected periodically to affirm that the correct procedures were being followed. Hard copies of coded data, without personal identifiers of any kind, were kept in a locked, secured area with access given only to those directly involved in the research process to ensure that confidentiality was maintained.

Variable Definitions

Variables of interest in this study included: classification of prediabetes and weight maintenance and weight classification. Demographic information included gender, race/ethnicity, family history of diabetes, age, parental marital status, and educational level. Quantitative biomedical variables included body mass index, weight,

height, pubertal stage, diet, physical activity level, prescribed medications, lipid profile, blood pressure, insulin and/or c-peptide levels, and glycosylated hemoglobin level.

Prediabetes:

Prediabetes, the dependent variable of the first phase of the study, is a condition newly renamed and categorized by the American Diabetes Association (ADA, 2003). Subjects having either or both impaired fasting glucose (IFG) (plasma glucose level $\geq$100 mg/dl and < 126 mg/dl) or impaired glucose tolerance (IGT) following a 1 or 2 oral glucose tolerance test (plasma glucose levels of $\geq$140 mg/dl and < 200 mg/dl) are regarded as having prediabetes. The importance of capturing the extent of prediabetes occurring in a sample of youth seen in subspecialty clinics was intended to demonstrate the extent of the condition in overweight children and adolescents. The diagnosis of pre-diabetes would be a coded as a dichotomous variable (0 = yes; 1 = no).

Age

Age was be collected for all subjects. The age of the subject at the time of referral was used, as birth-date is considered to be protected information. The variable will serve as a descriptive identifier, as well as dichotomized to one of two groups (children aged 6-11 = 0; adolescents aged 12-19 years = 1.) Age groupings are in concordance with those used by the CDC for assessment of at-risk for overweight and overweight prevalence in youth (CDC, 2002.) Utilizing the same age grouping was considered necessary to in concordance with established guidelines for distinguishing between stages of development.

Gender

Literature exploring type 2 diabetes shows female youth having a greater predisposition towards its development than males (Pinhas *et al.*, 1996; Harris *et al.*, 1996). It is postulated that similar differences exist between gender and the diagnosis of prediabetes. Gender is a dichotomous variable (male = 0; female = 1).

Race/Ethnicity

Previous published literature has shown disparities between race/ethnicity and the diagnosis of type 2 diabetes in youth (Pinhas *et al.*, 1996; Dabelea *et al.*, 1999; Neufeld *et al.*, 1998). Whether there are associations with prediabetes and race/ethnicity in youth with prediabetes is unknown at this time. Race/ethnicity was categorized as; African American, Caucasian/European American, Asian, Pacific Islander, Native American, Hispanic, and "other".

Family history of diabetes

Type 2 diabetes in youth and adults is strongly associated with family history of the same condition in both first and second-degree relatives. The extent to which family history of type 2 diabetes is present in the sample will be recorded as a dichotomous variable (0 = yes; 1 = no.)

Body Mass Index

Body mass index, or BMI, is the metric ratio of weight in kilograms to height in meters squared. BMI is used to classify children and adolescents as overweight >95th tile for age as overweight = 0), at-risk for overweight (85th to 95th percentile at-risk for overweight = 1), or of normal weight for age (<85th percentile = 2.)

Pubertal stage

During puberty, there is an approximate 30% reduction in insulin sensitivity (Amiel *et al.*, 1986; Arslanian *et al.*, 1994). Insulin resistance and its association with hyperinsulinemia are well established as factors in the development of type 2 diabetes. Pubertal stages were categorized based on the system of Tanner staging (Tanner, 1984), with a total of five stages; I = prepubertal and V = full attainment of sexual maturation. Tanner stages II – IV are most associated with insulin resistance and the diagnosis of type 2 diabetes. Data for this variable were collected based on availability in the medical records, and were used categorically to show potential associations between sexual maturational stage and prediabetes.

Weight stabilization and weight loss

The Diabetes Prevention Program (DPP) and the Finnish Diabetes Prevention studies were able to show that modest weight losses of only 5 to 7% of total body weight in adults in combination with diet and exercise, were able to reduce the onset of type 2 diabetes with IGT by 58% (DPP, 2002; Tomilehto *et al.*, 2001). Prior review of treatment recommendations and goals for overweight youth emphasize the need to preserve normal growth and physiological development during treatment. Weight maintenance (±2.3 kg) during linear growth and/or weight losses limited to 0.5 to 1kg (1.1 to 2.2 lb) every 2 weeks are recommended (ADA, 2000; Rosenbloom, 1989; Dietz *et al.*, 1985). Therefore, weight will be assessed and categorized as a dichotomous variable (0 = weight stabilization or weight loss over 3 to 6-months or at follow-up from diagnosis visit; 1 = weight gain).

Diet

The Diabetes Prevention Program (DPP) was able to show desirable changes in weight and the delay or prevention of diabetes through both dietary and physical activity modification. Full assessment of nutritional intake will not be undertaken in this study. However, a comparison of the recommendations provided to youth with those found effective in the DPP study will be assessed. Recommendations to lower total fat intake and reduce caloric intake will be assessed as available in the medical records. While advice may be more individualized rather than regimented, the investigator will assess whether the focus is on fat and/or caloric intake versus other specific macrontrient recommendations. Narrative notes during chart reviews will be used to assess this variable. Diet will serve as a dichotomous variable (0 = a low-fat and/or lowered calorie recommendation; 1 = no diet recommendations or recommendations differing from those in the DPP) and (0 follows diet recommendations =; 1 = does not adhere to recommendations).

Physical Activity

The inclusion of physical activity is essential for weight stabilization or weight loss, as well as improving insulin sensitivity for the prevention or control of type 2 diabetes (ADA, 2003). Physical activity is correlated with lower fasting insulin and greater insulin sensitivity in childhood (Sohmitz *et al.*, 2002). Medical record review of narrative written notes will provide data related to physical activity recommendations and adherence. Physical activity will be a dichotomous variable (0 = no physical activity recommendations; 1 = physical activity recommendations provided) and (0 = sedentary; 1 = physically active).

Metformin

Metformin is a pharmaceutical agent of the biguanide class. It functions by decreasing hepatic glucose output and enhances (primarily) hepatic and muscle insulin sensitivity. It has no direct effect on pancreatic β-cells. Metformin has been shown in at least two randomized controlled studies to be clinically effective (and safe) in increasing insulin sensitivity in hyperinsulinemic, non-diabetic adolescents (Desci *et al.*, 2003; Jones *et al.*, 2002.) Metformin treatment is a catagorical variable (0 = currently is not prescribed; 1= currently is prescribed and takes (compliant); 3 = currently is prescribed and does not take (non-compliant); 4 = prescribed metformin in the past, has been medically discontinued; 5 = has never had a prescription for metformin).

Lipid Profile

Youth with type 2 diabetes and/or overweight may be hyperlipidemic. Hyperlipidemia is often seen in combination with insulin resistance in the metabolic syndrome. Lipid measurements that will be collected as available, ideally at diagnosis and follow-up visits. Values include: total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides. All lipid profile variables will be collected as continuous data, with later analysis categorizing values following the guidelines established by the National Cholesterol Education Program for children and adolescents age 2-19 years of age (NCEP, 1993):

- *Total Cholesterol (mg/dl):* <170 acceptable = 1, 170-199 borderline high = 2, ≥200 high = 3
- *LDL Cholesterol (mg/dl):* <110 acceptable = 1, 110-129 borderline high = 2, ≥130 high = 3
- *HDL Cholesterol (mg/dl):* ≥35 acceptable = 1, < 35 low = 2
- *Triglycerides (mg/dl*): ≤150 acceptable = 1, >150 high = 2

Blood Pressure

Hypertension is factor in metabolic syndrome, and correlated with overweight and insulin resistance in youth (Chien et.al, 1999; Young-Hyman et.al, 2001). A series of blood pressure values will be collected and percentiles for blood pressure will by plotted according to height-for-age growth charts based on gender (NIH, 1996). Values for both systolic and diastolic blood pressure will be categorized as follows: 0 = >90th percentile for age and gender; 1 = <90th percentile.

Insulin and C-Peptide Levels

Hyperinsulemia is a compensatory condition accompanying insulin resistance and often seen in the early stages of type 2 diabetes, prior to pancreatic beta-cell demise. Levels of insulin, or c-peptide, a substance released in amounts equal to insulin by the pancreas, will be collected. Normal serum insulin values are 6 to 27 microunits/milliliter and normal c-peptide levels range from 1.1 to 5.0 nanograms/milliliter. Values will be recorded as a series of continuous variables as available in the chart.

Glycosylated hemoglobin

Glycolsylated hemoglobin is used as a 3-month measurement of glycemic control in those diagnosed with diabetes. It is unknown whether glycolyated hemoglobin values are affected by the glycemic environment of prediabetes. This measurement will be collected as available and classified as a continuous variable.

Metabolic Syndrome

Metabolic syndrome is a clustering of risk factors associated with the development of type 2 diabetes and cardiovascular disease. No formal diagnostic criteria exist for classifying metabolic syndrome in youth. The adaptation of the adult criteria to children

and adolescents has been published in works by Weiss et al. and Cook et al. Those with ≥3 of the following criteria were said to have metabolic syndrome (Weiss *et al.*, 2004; Cook *et al.*, 2003.):

- *Systolic and/or Diastolic Blood Pressure >90th percentile*
- *High density lipoprotein <35 mg/dl*
- *Triglycerides >150 mg/dl*
- *BMI-for-age z-score ≥2.0*
- *Prediabetes – impaired glucose tolerance or impaired fasting tolerance*

Fasting Insulin-to-Glucose Ratio

A surrogate measure of insulin resistance obtained by computing the ratio of fasting insulin μU/ml/glucose mg/dl, and expressed as a percentage. The fasting insulin/glucose (FIT) ratio has correlated highly with the euglycemic clamp derived model of insulin resistance and the homeostatic model (HOMA) for measuring insulin resistance. FIT is expressed as a percentage, with ≥33% considered to be elevated (Sullivan et al., 2004; Guerrero-Romero & Rodriguez-Moran, 2001; Legro et al., 1998.)

Statistical Analysis

SPSS software version 11.0 was used for data analysis. Means and standard deviations were run on all continuous variables. Chi-square tests of association using 2x2 contingency tables were run to analyze proportion of those with prediabetes by gender, age, pubertal stage, and race/ethnicity, as well as associations between screening for diabetes/prediabetes and recommendations for screening set by the American Diabetes Association. Differences in biomedical values associated with metabolic syndrome and risk of developing diabetes were compared in overweight and youth with prediabetes using independent t-testing. Differences in screening and outcomes were evaluated in aggregate and individually by clinic. Current lifestyle and pharmacologic interventions were evaluated with descriptive statistics. Associations between treatment (diet, physical activity, or metformin) and outcome (weight changes) were assessed with chi-square analsyis.

CHAPTER 4

Results

Descriptive statistics

Three clinics in the lower-peninsula of Michigan participated in the study. All clinics involved were pediatric endocrinology sub-specialty practices located in urban areas, with a staff of one to three physicians per clinic and an ancillary staff of registered nurses, registered dietitians, and mental health professionals. Many of the registered nurses and registered dietitians were certified diabetes educators. Daily clinic case-load ranged from approximately 8 to 25 patients seen per day. The total number of patients with existing files in each clinic was no less than 300 and no more than 2000. Medical record reviews were conducted on 291 subjects who were identified by investigator(s), physicians, and office staff from the year 2000 until data collection commenced during the months of June and July of 2004. Clinic databases and ICD-9 coding were used to target patients seen for overweight, and rule out type 2 diabetes and diagnoses meeting exclusion criteria. Basic sociodemographic (table 4.1) and biomedical (table 4.2) descriptive information for the sample of overweight youth reviewed are listed in the following tables. The sample was sub-catagorized according to 1) those screened for prediabetes, 2) those who were not screened for prediabetes, and 3) those screened for prediabetes who subsequently met the criteria for the condition.

Table 4.1 – Sociodemographic Characteristics of At-Risk for Overweight (AR) and Overweight (OW) Youth with and without Prediabetes			N=291
	AR and OW and Screened n=134	**AR and OW and not screened n=136**	**Prediabetes n=21**
Age	11.7±3.8	11.3±3.2	12.8±2.6
Gender			
Male	48.5%	39.3%	33.3%
Female	51.5%	60.7%	66.7%
Ethnicity			
African American	26.9%	43.2%	42.9%
Caucasian	54.5%	32.4%	42.9%
Hispanic	3.0%	0%	4.8%
Native American	0.7%	0.7%	4.8%
Asian	0%	0%	0%
Other	3.7%	2.2%	0%
Not Available	11.2%	21.3%	4.8%

Table 4.2 - Sociodemographic Characteristics Specific to Prediabetes Sub-sample n=21	
Parental Marital Status	Single or divorced 42.9% Married 28.6% Separated 4.8% Not Available 23.8%
Living Status	Both parents with/without siblings 23.8% Mother only 9.5% One parent and siblings 33.3% One parent, step-parent and sibs 14.3% Not available 19%
Income (as determined by insurance provider)	Medicaid 28.6% Private Payer 66.7% Not available 4.8%

Table 4. 3 – Biomedical Characteristics of of At-Risk for Overweight (AR) and Overweight (OW) Youth with and without Predabetes			N=291
	Overweight and Screened n=134	**Overweight and not screened n=136**	**Prediabetes n=21**
BMI	36.1±8.0 n=132	35.6±9.2 n=135	36.6±7.3
At-Risk or Overweight	2.3%	2.2%	9.5%
Overweight	97.7%	97.8%	90.5%
BMI z-score	2.6±0.4 n=123	2.4±0.4 n=131	2.4±0.45
Fasting Blood glucose mg/dl	85.3±9.3 n=132	Not available	105.4±8.5
Triglycerides mg/dl	143.2±126.5 n=108	151.4±93.3 n=54	153.0±84.2
HDL cholesterol mg/dl	41.0±9.9 n=107	40.8±11.8 n=47	36.8±9.8
Insulin µu/ml	35.3±33.2 n=67	59.3±63.5 n=49	148.7±181.6
Systolic blood pressure mmHg	123.7±14.8 n=126	124.3±14.2 n=129	133.3±16.1
Diastolic blood pressure mmHg	68.2±8.8 n=126	67.7±11.6 n=129	68.2±9.2
Metabolic Syndrome	67.9% n=132	66.9% n=136	61.9%

Table 4.4 - Biomedical Parameters Specific to Prediabetes Sub- Sample	n=21
Hemoglobic a1c	5.8±0.98
Total Cholesterol mg/dl	187.8±38.6
LDL Cholesterol mg/dl	124.2±32.3
acanthosis nigricans	
yes	65%
no	10%
not available	25%
Tanner stage	
I	4.8%
II	4.8%
III	19%
IV	9.5%
V	19%
Not available	42.9%
Family history of diabetes	
yes	76.2%
no	4.8%
not available	19%

The study population was primarily overweight with mean BMI values of 35.0 kg/m^2 or greater. Caucasian and African American patients constituted the majority of the ethnic backgrounds represented. Greater than 60% of the sample can be described as having metabolic syndrome.

Parameters used to evaluate metabolic syndrome were 1) a z-score of ≥2.0 for BMI, 2) blood pressure percentile >90th tile, 3) HDL cholesterol <35mg/dl, 4) triglyceride levels >150 mg/dl and 5) prediabetes (Cook *et al.*, 2003; Weiss *et al.*, 2004.) Three or more of the metabolic syndrome parameters were present for the classification of metabolic syndrome. The majority of the sample had ≥3 risk factors present (65.6%.) Rates of abnormal (elevated) cardiovascular and diabetes risk factors in the study population constituting the metabolic syndrome are shown in table 4.3. Values are also shown for serum insulin levels.

Table 4.5 – Percentage of subjects with Risk Factors Above Recommended Cut-points for the Classification of Metabolic Syndrome

Risk factors	Prediabetes N=21	Overweight and Screened for Prediabetes N=134	Overweight and not screened for Prediabetes N=136
HDL-cholesterol <35mg/dl	24% n=5	28.3% n=106	36.2% n=47
Triglycerides >150	29% n=6	31.5% n=108	42.6% n=54
BMI z-score ≥2.0	100% n=21	100% n=113	100% n=120
Prediabetes	100% n=21	0% n=132	0% n=136
Systolic or Diastolic Blood Pressure >90th percentile	76% n=16	65.5% n=122	70.9% n=127
Serum Insulin >27 µU/mL	76% n=16	50.7% n=67	69.4% n=49
Metabolic Syndrome	61.9% n=13	67.9% n=132	66.9% n=136

Of 291 medical records reviewed, 21 subjects met the criteria for prediabetes. Two subjects had abnormal values following 2-hour oral glucose tolerance tests, signifying impaired glucose tolerance, and 19 subjects had abnormal fasting glucose levels, or impaired fasting tolerance. However, only 53% received screening for diabetes (and prediabetes). Demographic characteristics of youth with prediabetes are depicted in tables 4.1 and 4.2.

The male to female ratio of those with prediabetes was 1:2, with a mean age of 12.8 years. An equal number of Caucasian and African American youth were classified as having prediabetes. The majority of youth (42.9%) with prediabetes had parents who were single or divorced, with 33.3% living in single parent homes. Most subjects had insurance through private third-party reimbursement agencies, while 28.6% received federally funded healthcare. Biomedical indices in those with prediabetes are shown in tables 4.3 and 4.4.

Values for fasting blood glucose, serum total cholesterol, LDL-cholesterol, triglycerides, and insulin were above recommended levels for age. The biomedical values of overweight youth and at-risk overweight youth who did not have prediabetes were compared to those with prediabetes using independent t-tests (table 4.6 and figures 5-8.) Overweight youth without prediabetes were not subgrouped into those screened and those not screened for this analysis. Those with prediabetes had significantly higher levels of fasting blood glucose (107.7 vs. 85.1mg/dl; $p<0.001$), systolic blood pressure (137.7 vs. 124.0mmHg; $p<0.001$), serum insulin levels (149.7 vs. 45.4μU/ml; $p<0.001$), and a fasting insulin-to-glucose ratio (141.1 vs.50.0 μU/ml $p<0.01$) indicating metabolic

abnormalities beyond that of abnormal glycemia alone. Differences in BMI, HDL-cholesterol, triglyceride levels, diastolic blood pressure, bmi z-score, and numbers of risk factors for metabolic syndrome were assessed and not found to be significantly different.

Table 4.6 – Comparison of Biomedical Indices Between Youth with and without Prediabetes

Mean values (±SD*)	All N=291	Prediabetes N=21	Overweight N=270
BMI	36.0 (8.5)	36.6 (7.3) n=21	35.9 (8.6) n=267
BMI z-score	2.5(0.4)	2.4 (0.5)	2.6 (0.4) n=254
Serum Insulin µu/ml	58.8 (85.7)	***149.7 (181.3) n=17	**45.4 (49.5)** n=116
Fasting glucose mg/dl	88.2 (12.2)	***107.7 (8.8) n=21	**85.1 (9.6)** n=133
Insulin-glucose ratio	68.4 (107.9)	**141.1 (167.9)	**50.0 (78.1)**
Triglycerides mg/dl	148.1 (115.0)	178.2 (95.6) n=12	145.9 (116.3) n=162
HDL-cholesterol mg/dl	40.6 (10.5)	35.9 (9.5) n=12	41.0 (10.6) n=154
Systolic blood pressure mmHg	125.0 (14.9)	***137.7 (14.9) n=12	**124.0 (14.4)** n=255
Diastolic blood pressure mmHg	68.3 (10.4)	72.3 (11.3) n=12	67.9 (10.3) n=255
Metabolic Syndrome – number of risk factors present	2.9 (0.92)	2.9 (1.0)	2.9 (0.92)

a, SD=standard deviation
*p<0.05, **p<0.01, ***p<0.001

Figure 5 – Comparison of Serum Insulin Values in Youth with and without Prediabetes

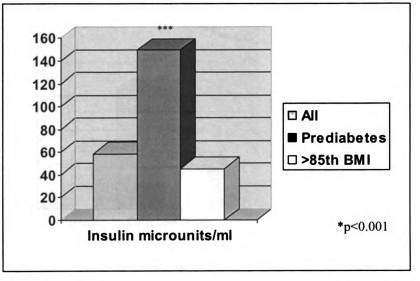


Figure 6 – Comparison of Blood Glucose Values in Youth with and without Prediabetes

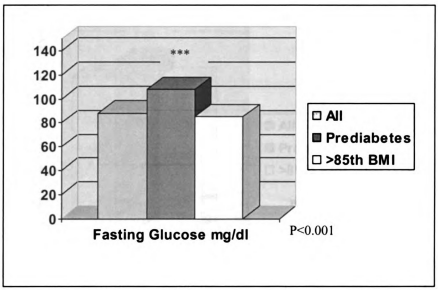


Figure 7 – Comparison of Insulin-to-Glucose Ratios in Youth with and without Prediabetes

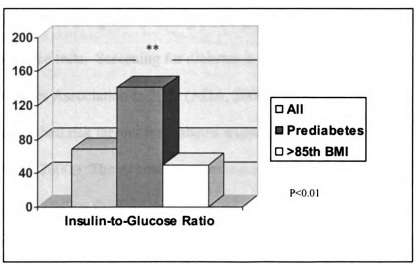
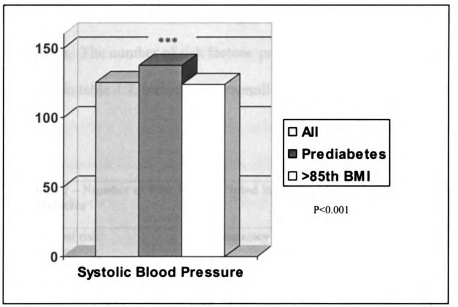


Figure 8 – Comparison of Systolic Blood Pressure Values in Youth with and without Prediabetes



Screening for Diabetes and Prediabetes

As mentioned previously, only 53% of all overweight youth seen by pediatric endocrinologists for their overweight or at-risk for overweight condition were screened for diabetes using either fasting blood glucose levels or standard 2-hour oral glucose tolerance tests. Screening for diabetes in youth was established by the American Diabetes Association in 2000 (ADA, 2000.) Being at-risk for overweight and having ≥2 established risk factors for diabetes warrants screening using a fasting blood glucose level (ADA, 2000.) The risk factors for screening for diabetes were evaluated in overweight youth based on their availability in the medical records. Overweight was a risk factors present in all youth (as defined by study inclusion criteria), therefore risk factors in addition to overweight were counted. Race/ethnicity, BMI, lipid levels, and blood

pressure were variables commonly noted in the medical records and included in the analysis. Family history of diabetes, pubertal stage, presence of pcos, and physical activity levels were not consistently recorded and therefore were not included in the analysis. The number of risk factors present in study subjects' medical records are shown in table 4.7, including an overall assessment and results reported by individual clinic.

Table 4.7 – Number of Risk Factors Noted in Medical Records for Screening for Diabetes

Number of risk factors	Frequency of Risk Factors			
	All clinic combined N=291	Clinic 1 n=82	Clinic 2 N=138	Clinic 3 n=71
0	16.6%	22%	18.1%	7.1%
1	38.6%	40.2%	29.7%	54.3%
2	33.3%	24.4%	37.7%	35.7%
3	10.3%	13.4%	12.3%	2.9%
4	1.0%	0%	2.2%	0%
≥2	45.2%	37.8%	52.2%	38.6%

Screening varied by clinic in overall frequency as well as method used (table 4.8.) Clinic 2 screened the majority of subjects, while clinic 3 screened <30%. The most common method of screening was a fasting glucose test, with only clinic 2 employing the 2-hour glucose tolerance test on a regular basis.

Table 4.8 – Proportion of Youth Screened for Prediabetes by Method and Clinic

Screening by method and clinic	**Using either fasting glucose or 2-hr OGTT**	**Fasting**	**2-hr OGTT**
All clinics combined N=291	53.3% n=155	52.6% n=153	10.7% n=31
Clinic 1 n=82	80.5%	76.8%	36.6%
Clinic 2 n=138	49.3%	49.3%	0.7%
Clinic 3 n=71	29.6%	29.6%	1.4%

Further analysis using chi-square testing (table 4.9) demonstrated a significant association when comparing clinic site with the likelihood of screening ($p<0.001$). Associations were assessed between subjects screened for diabetes and gender, clinic, age, ethnic background, and the presence of ≥2 ADA risk factors for screening (table 15.) Ethnic background was found to be a significant cause for screening ($p<0.01$), though from the data it appeared that those belonging to a low-risk ethnic group were more likely to be screened than those from high-risk ethnic groups. Significant associations were not seen between the remaining variables and screening.

Table 4.9 - Factors Associated with Screening for Diabetes in At-Risk for Overweight and Overweight Youth

	Screening for diabetes	
	Yes %	**No%**
Gender		
Female	53.1%	60.7%
Male	46.9%	39.3%
****Belongs to high-risk ethnic group**		
Yes	35.2%	56.6%
No	64.8%	43.4%
Age ≥ 10 years		
Yes	73.9%	69.6%
No	26.1%	30.4%
*****Study site**		
Clinic 1	46.2%	11.8%
Clinic 2	43.9%	51.5%
Clinic 3	13.5%	46.7%
≥2 DM risk factors for screening		
Yes	45.8%	43.4%
No	54.2%	47.8%

***p<0.05, **p<0.01, ***p<0.001**

Prediabetes

Of all the medical records reviewed, 7.2% (21/291) of youth assessed met the criteria for prediabetes. When adjustments for the number of youth screened for diabetes are factored into the proportion, 13.5% (21/155) of youth could be classified with prediabetes. Prior work done by Handu et al. assessed the proportion of youth with Type 2 diabetes (of all diagnosed cases of diabetes; type 1 and type 2) in the same three clinics participating in the present study. Comparisons of overall diagnosed cases of type 2 diabetes as noted in medical records and prediabetes are shown in aggregate and individually by clinic (table 4.10.)

Table 4.10 - Comparison of Diagnosed Type 2 Diabetes and Prediabetes by Clinic

	Prediabetes N=21	**Type 2 Diabetes N=103**
All clinics combined	13.5%	15.7%
Clinic 1	10.3%	10%
Clinic 2	12.1%	6.5%
Clinic 3	28.6%	20%

Associative factors for prediabetes were assessed. Due to a small sample size, chi-square statistics could not be computed. Cross-tabulations were run on data, with frequencies shown in table 4.11.

Table 4.11 – Prediabetes and Associative Factors in Youth	Prediabetes	
	Yes %	**No%**
Gender[a]		
Female	72.7%	56.2%
Male	27.3%	43.8%
Belongs to high-risk ethnic group[a]		
Yes	44.4%	44.9%
No	55.6%	55.1%
Age ≥ 10 years[a]		
Yes	90.0%	71.2%
No	10.0%	28.8%
≥2 DM risk factors for screening		
Yes		
No	42.9%	44.4%
	57.1%	55.6%

a; cell size <5

More females and youth ≥10 years of age were classified with prediabetes. While statistical differences could not be computed, high-risk ethnicity did not appear to be an associative factor with this subgroup. More "low-risk" ethnicities were screend compared with high-risk ethnicities. As previously mentioned, an equal number of Caucasian and African American youth were seen with prediabetes.

Lifestyle and Pharmacological Treatment for Prediabetes

Treatment recommendations provided to youth with prediabetes by healthcare professionals are compiled in table 4.12. Lifestyle recommendations and metformin prescription shown to be effective in the DPP (Diabetes Prevention Program) for adults with prediabetes were assessed. The majority (90%) of youth with prediabetes had received nutritional counseling. Registered dietitians provided nutrition

recommendations to 94.8% of the subjects (in one instance in conjunction with a physician). There were no notations of registered nurses providing medical nutrition therapy. Diet recommendations were similar to those of the DPP (a low total fat, low saturated fat, and calorie reduced diet) in 85.7% of the cases, though recommendations were individualized to include basic suggestions based on the subjects' usual dietary patterns and intake. Common recommendations included eating fewer fried foods, most notably from fast food restaurants, drinking fewer sweetened beverages, and reducing portion sizes of foods dense in calories from fat and simple carbohydrate sources. Fruits, vegetables, whole grains, and low calorie beverages were commonly encouraged. Other noted methods used for nutritional management of prediabetes were carbohydrate counting (1/21), a method of medical nutrition therapy education based on calculating an individual's daily caloric and carbohydrate needs and evenly distributing the total carbohydrate amount at meals and snacks. The intent of carbohydrate counting is to lessen the glycemic load of carbohydrate eaten at a given meal/snack with the ultimate goal of avoiding large fluctuations in blood glucose levels (Gillepsie *et al.,* 1998.) This method of nutrition education is commonly accepted practice for the nutritional management of type 1 and type 2 diabetes, however to date recommendations for its use in managing prediabetes have not been issued (ADA, 2003.) A calorie controlled diet utilizing the exchange lists for meal planning was observed in 3 cases. The Exchange Lists for Meal Planning are an established system utilizing common food groupings (fruits, grains, milk, vegetables, etc.) with standardized macronutrient amounts for individual foods based on portion sizes. For the purpose of diabetes and weight management, the Exchange Lists are provided based on individual calorie and

macronutrient needs (Wheeler *et al.*, 1996.) In one instance the Step 1 American Heart Association diet for the management of hyperlipidemia was observed. This includes a diet prescription containing ≤30% of total calories from fat, ≤10% of total calories from saturated fat and ≤300 milligrams of cholesterol each day (American Academy of Pediatrics, 1998.) No observations of recommendations for reduced/low carbohydrate diets were noted. Thirty and eight-tenths percent (4/21) of the sample declined (either subject or parent) a meeting with a registered dietitian.

Physical activity recommendations were given to 66.7% of the participants, primarily by registered dietitians. Physical activity assessment indicated that 71.4% of subjects were sedentary (15/21), 19% were physically active (4/21), and 9.5% (2/21) of the subjects had no data describing physical activity behavior. Metformin prescription was noted in the charts of 3 subjects (14.3%).

Subjects met with registered dietitians for lifestyle management counseling an average of 1.24 times. Thirty-eight and one-tenth percent of subjects were lost to follow-up. Those meeting with registered dietitians for medical nutrition therapy set personalized management goals in 42.9% of the encounters. Adherence to goals set were noted as "yes" at charted follow-up visits 35% of the time (with 30% "no" and 35% not documented in medical records.) Results on noted on follow-up visits may be described as 1) weight loss, 2) weight stabilization, 3) weight gain, and 4) not available in medical record. Weight loss and stabilization both considered desirable goals of therapy and were merged for further analysis, representing 33.4% of the sample. Weight gain was merged with missing data to represent negative outcomes of therapy, constituting 66.6%

of the sample. Outcomes were combined to represent desirable and undesirable categories for testing associations with treatment modality.

Table 4.12 – Clinical Recommendations Provided to Youth with Prediabetes

Nutrition Recommendations		
Provided:	Yes	90% (19/21)
	No	10% (2/21)
Provided by:	Registered Dietitian (RD)	89.5% (17/19)
	Medical Doctor (MD)	5.3% (1/19)
	Registered Nurse (RN)	0% (0/19)
	RD and MD	5.3% (1/19)
Diet recommendations: Low-fat, low-kcal		85.7% (18/21)
Physical Activity Recommendations		
Provided:	Yes	66.7% (14/21)
	No	28.6% (6/21)
	Not available	4.8% (1/21)
Provided by:		
	RD	80% (12/21)
	MD	13.3% (2/21)
	RN	0% (0/21)
	Not available	4.8% (1/21)
Metformin Prescriptions		
Provided:	Yes	14.3% (3/21)
	No	85.7% (18/21/)

Treatment outcomes were measured using weight as an outcome variable. Significant associations were seen between subjects following nutrition and physical activity recommendations and weight changes on follow-up (table 4.13.)

Table 4.13 - Impact of Clinical Interventions on Weight in Youth with Prediabetes N=21		
TREATMENT INTERVENTION	**POSITIVE OUTCOME**	**NEGATIVE OUTCOME**
Nutrition**	**Weight loss/stabilization**	**Weight Gain/No Follow-up**
Followed recommendations	71.4%	28.6%
Did not follow recommendations	7.7%	92.3
Physical Activity*		
Followed recommendations	75%	25%
Did not follow recommendations	17.6%	82.4%
Metformin prescribed		
Yes	33.3%	66.7%
No	27.8%	72.2%

*p<0.05, **p<0.01, ***p<0.001

CHAPTER 5
Discussion

This study described the screening practices, associative factors, anthropometric and clinical variables, and treatment recommendations in a sample of overweight and at-risk for overweight youth with or without prediabetes. Basic demographic and clinical data was also included for the entire sample of overweight and at-risk for overweight subjects whose medical records were reviewed. Key findings from this study include 1) of those overweight and at-risk for overweight youth seeking medical care from a pediatric endocrinologist, only 53.3% were screened for diabetes, and hence prediabetes, 2) Metabolic syndrome was observed in 61.9% of youth with prediabetes, and 65.6% of those without prediabetes, 3) serum insulin, fasting blood glucose, fasting insulin-to-glucose ratio (a surrogate for measuring insulin resistance), and systolic blood pressure values were significantly higher in those with prediabetes, and 4) prediabetes was not significantly different between Caucasian and African American youth. The high percentages of metabolic syndrome and lack of screening were particularly disturbing, given the age of the sample and possibility of detrimental health outcomes in this vulnerable group.

The subject pool for this study was obtained from a cross-sectional sample of children and adolescents receiving care for their overweight condition in pediatric endocrinology subspecialty clinics in three urban Michigan cities. The three offices involved in the study assumed similar practice arrangements involving the participation of one or more pediatric endocrinologists, a registered nurse or medical assistant, and a

registered dietitian. Clinical practice guidelines for prediabetes in youth currently do not exist. However, those for the detection and treatment overweight, and screening for diabetes in youth have been established and therefore, are the basis for the assumptions of clinical care recommendations made in this study.

Prediabetes was detected in 13.5% of subjects screened for diabetes. The large variations observed in the number of youth screened when comparing clinics was an important finding. Overall, approximately half of the overall sample was screened for diabetes, yet the percentage of those screened by clinic ranged from 29.5% to 80.5% when assessed individually. This indicates that differing practice approaches are being followed in the respective clinics. This finding is particularly troubling. Type 2 diabetes in children and adolescents is a growing problem with potentially serious ramifications if left undetected. The onset of type 2 diabetes in childhood or adolescence is disturbing given the medical complications which may arise when the disease is left untreated or poorly controlled. The reality of nephropathy, neuropathy, retinopathy, and cardiovascular complications developing at a much younger age (for example, as young as one's twenties and thirties) must be considered more seriously by those providing care to patients who are overweight and at-risk for overweight.

When screening for diabetes and risk factors for screening were assessed for associations, there were few relationships observed beyond those differences seen between individual clinic screening rates. Race and ethnicity had a significant association with screening, though it appears that those belonging to the high-risk ethnic groups were less likely to be screened. This is contrary to the screening recommendations outlined by the American Diabetes Association, where African

American, Asian and Pacific Islander, Hispanic and Latino, and Native American ethnicities are considered at highest risk for developing diabetes(ADA, 2000.) The findings suggest that in many cases screening may have been carried out in a random fashion. Missing data in the medical records, as well as data unable to be analyzed due to study design (presence of PCOS, physical activity level, family history of diabetes, and tanner stage) limited these assessments. If full medical record reviews had been completed on all overweight and at-risk for overweight subjects, a more complete analysis of risk factors for diabetes could have been completed. An additional factor to note is that our sample from pediatric endocrinology clinics most likely underestimates the magnitude of the problem. Extrapolation of these findings is unlikely and therefore this study serves as a preliminary work, justifying the need for further, large-scales studies.

Screening is recommended to start at age 10 (or at the first sign of puberty) and continue every 2 years when a child overweight (specified below) and exhibits ≥2 of the following risk factors (ADA, 2000.):

- *≥85th BMI percentile for age and gender, or weight-for-height or >120% of ideal weight-for-height*
- *Family history of type 2 diabetes in first or second-degree relatives, race/ethnicity (American Indian, African-American, Hispanic, Asian/Pacific Islander)*
- *Signs of insulin resistance (acanthosis nigricans, PCOS, HTN, dyslipidemia)*
- *Additional screening components*
    - *puberty level of tanner stage III-IV*
    - *physical inactivity*

Clinical judgment of the practitioner may also supercede the current recommendations for screening

Reports of inconsistently applied recommendations for overweight detection and treatment, and diabetes screening and have been published. The extent to which pediatric clinicians identified overweight in youth was reviewed in a large, primary care practice in an urban academic, tertiary care practice. Medical record reviews indicated that of all children meeting the definition for overweight, care for the condition was documented in only 53% of the cases, with obesity noted on physical examination in only 39% of cases (O'Brien *et al.*, 2004.) Only 13% of providers ordered laboratory testing exploring metabolic assessment of premature cardiovascular disease (lipid profile) and diabetes screening (plasma glucose). Interestingly, the majority of those requesting laboratory data evaluated thyroid function, despite the low occurrence (0.1%) of hypothyroidism in overweight children, despite the absence of the American Academy of Pediatrics specific recommendations to do so on a routine basis (O'Brien *et al.*, 2004.) Similarly, a survey of pediatricians, nurse practitioners, and registered dietitians found that unnecessary laboratory tests, primarily thyroid function tests, are performed on overweight youth (Barlow *et al.*, 2002.) The survey also revealed that a minority of pediatricians and nurse practitioners routinely utilized medical history and physical examination to assess type 2 diabetes and insulin resistance (39% and 42%) (Barlow *et al.*, 2002.) A medical record review in a clinic with a population of youth at high-risk for diabetes in Chicago, IL also described inconsistent screening for diabetes in youth, despite a clinic-initiated protocol based on the ADA's 2000 recommendations for screening of diabetes in children and adolescents (Drobac *et al.*, 2004.) In addition to the ADA's screening recommendations, the Obesity Consensus Working Group reports that all children with a BMI-for-age percentile $\geq 95^{th}$ should have fasting glucose, insulin, and lipid profiles examined. Those

at risk for metabolic syndrome and greater than the age of 10 should have a 2-hour OGTT administered (Obesity Consensus Working Group, 2004.) The screening and assessment inadequacies observed in the current study warrant the need for widespread dialogue to take place in the pediatric medical community regarding this issue and its potentially devastating long-term effects. Larger-scaled surveys and studies are needed to explore the reasons for these findings. Lack of knowledge regarding the current recommendations for screening and care, reimbursement and cost issues, and long-term efficacy of treatment are critical elements for consideration. This implies that medical follow-up and continuing care is a key issue for public health education and public policy priority. Prediabetes and metabolic syndrome are appropriate for inculusion into the national diabetes education program.

Controversy exists surrounding the most effective method for screening for diabetes. The fasting plasma glucose level is the preferred screening modality, yet both the fasting glucose and the 2-hour post-prandial tests (following an OGTT) are suitable for detecting abnormal glycemia (ADA, 2000.) The OGTT has been shown to be an invalid tool in research, with inferior reproducibility compared to the fasting plasma glucose test (ADA, 2003.) The OGTT is also more costly and less convenient for subjects undergoing it. However, of all methods used for detecting early diabetes, the OGTT is considered the most sensitive (Phillips *et al.,* 1993.) At least 30% of adults with undiagnosed diabetes have normal fasting glucose levels (ADA, 2003.) This reiterates the variability of the fasting glucose at detecting abnormal glycemia.

In a study of 112 adolescents, fasting hyperglycemia was present in those with diabetes, but with a very low prevalence (0.08%) observed in those with prediabetes,

suggesting that fasting hyperglycemia is indicative of an advanced stage of pancreatic beta-cell dysfunction (Sinha *et al.*, 2002.) In our sample, abnormal fasting glucose was the primary form of prediabetes observed, which may be in part due to the fact that fasting plasma glucose test being employed most often for screening (52.6% versus 10.7%). Nonetheless, one may consider that, in addition to the possibility of having advanced prediabetes and perhaps a greater likelihood of developing diabetes sooner, the number of those with prediabetes was under-represented due to both inadequate screening and testing modality employed for screening. The possibility of missed cases of overt type 2 diabetes also exists. Other concerns with the screening and diagnostic criteria are whether adult cut-points for abnormal glucose and glucose loads used for the OGTT (standard 75 grams or 1.75 grams per kilogram with a 75 gram maximum dose) are applicable to the young. Population-based studies are needed to further examine the ideal testing methods and screening protocols for type 2 diabetes in the young (ADA, 2000.)

The differences and similarities between IFT and IGT are still under investigation. It is generally accepted that both are intermediate stages of glucose intolerance, with a component of insulin resistance and varying degrees of pancreatic secretory insufficiency. However, there are conflicting opinions as to whether IFT or IGT presents a greater degree of impaired glycemia and/or insulin resistance. In a cross-over comparison study utilizing an OGTT with glucose, insulin, and c-peptide measurements every 30 minutes, Hanefeld et al. was able to show that those with IFT had a greater degree of insulin resistance, while those with IGT had greater first and second-phase insulin secretory defects. Both groups had equal and greater likelihoods of

cardiovascular disease when compared with controls of normal glucose tolerance (Hanefeld *et al.*, 2003.) In contrast, Festa et al., showed the opposite using the same methodology. In this multi-ethnic sample, subjects with IGT had a greater degree of insulin resistance than those with IFT (Festa *et al.*, 2004.) Both studies present relevant data needing further study utilizing the hyperinsulinemic, euglycemic clamp procedure, the gold standard for measuring insulin resistance. The invasiveness of this procedure is however a barrier for the researchers and study participants.

The proportion of youth with detected prediabetes in our sample mirrored that of diagnosed cases of type 2 diabetes in the same age group, when compared with data previously collected from the same clinics (13.5% vs. 15.7%) (Handu *et al.*, 2004.) Considering that many cases of prediabetes will most likely proceed to diabetes if left untreated, the potential magnitude of the disease in Michigan youth is of grave concern. Pathophysiology of disease progression from normal glucose tolerance to prediabetes, and ultimately prediabetes to diabetes involves defects in both insulin resistance and insulin secretory function as independent and additive predictors of disease (Weyer *et al.*, 2001.) A 13-year prospective study of Pima Indians compared physiological differences in adults progressing from normal glucose tolerance to prediabetes, with those remaining glucose tolerant. Insulin secretory capacity was lower in those with progressive glucose intolerance (though not significantly), and insulin-mediated glucose disposal rates were significantly lower due to insulin resistance. Once prediabetes was present, both insulin secretory capacity and insulin disposal rates were lower and appeared additive in the progression to diabetes (Weyer *et al.*, 2001.) Sinha et al. demonstrated the same progression in adolescents with prediabetes, where essentially beta-cell function (and

secretion) was able to compensate for insulin resistance until overt diabetes was established, despite profound insulin resistance (Sinha *et al.*, 2002.)

The understanding of the disease pathology of type 2 diabetes in youth may present a window of opportunity for aggressive preventative treatment for the delay or prevention of prediabetes and diabetes. The length of time elapsing between the different stages of glucose tolerance deterioration is unknown in the young, and therefore limits timing for effective interventions. Identifying early stages of the disease properly by screening, combined with effective treatment may be a successful strategy for achieving this goal.

Youth with prediabetes had similar associative factors as those reported in children and adolescents with type 2 diabetes (Pinhas *et al.*, 1998; Pinhoker *et al.*, 1998; Debelea *et al.*, 1998.) A female preponderance (2:1), a strong family history of diabetes in a first or second degree relative (76.2%), mid-puberty (47.5%), and acanthosis nigricans (65%) were common findings among our sample. Subjects were also hypertensive, hypercholesterolemic, hyperinsulinemic, and had elevated low-density lipoprotein levels. Sixty-one and nine-tenths percent met the definition for metabolic syndrome, placing them at high-risk for both diabetes and cardiovascular disease.

The number of African American and Caucasian youth with prediabetes was similar. As described earlier, having an African American ethnic background is considered a risk factor for diabetes, while being Caucasian is not. Some single-gene mutations predisposing individuals to diabetes, such as the calpain 10 gene in Mexican Americans and the HNF-1α G319S in the Cree-Ojibway have been identified and are specific to these ethnic groups (Bloomgarden, 2004.) Similar genes have not been named

in the African American population. Rather, epidemiological findings suggest an increased risk for type 2 diabetes in African American youth (Dabelea *et al.*, 1998; Pinhas *et al.*, 1998.) Therefore, the findings of this study are in contrast to the ethnic and racial risk factors previously described for type 2 diabetes. A study of 710 obese Italian children of Anglo-European origin indicated a low prevalence (4.5%) of prediabetes (Invitti *et al.*, 2003.) In an American multi-ethnic cohort of youth with prediabetes, 25% of children age 4 to 10 years and 21% of adolescents had prediabetes, specifically IGT following a 2-hour OGTT (Sinha *et al.*, 2002.) Of the total sample of each respective ethnic group participating in the study, 26% of Caucasian, 33% of African American, and 11% of Hispanic children had prediabetes. Of the adolescent subjects involved, 16% of the Caucasian, 29% of African American, and 29% of Hispanics had prediabetes. The majority of children and adolescents with prediabetes in this sample were African American or Hispanic (Sinha *et al.*, 2002.) The Bogalusa Heart Study showed African American adolescents, especially females, to have a greater amount of insulin resistance and secretory abnormalities than Caucasians (Svec *et al.*, 1992; Jiang *et al.*, 1996.) When our sample was compared by race, no significant differences were seen between age, tanner stage, or fasting insulin levels, although Caucasian youth did have higher levels of plasma fasting insulin (191.0±293.5 versus 125.4±91.7 μU/ml). When adults (both male and female) participating in NHANES were analyzed for metabolic aberrations, Hispanic/Latinos had the highest prevalence of metabolic syndrome (Yong-Woo *et al.*, 2003.) Our findings suggest despite reports of some ethnic and racial youth groups having prevalences of type 2 diabetes, that all overweight youth be screened for diabetes (and prediabets), despite ethnic background.

Also noteworthy is the lack of racial and ethnic diversity in our sample. Few Hispanic/Latino (1.8%), Asian (0%), Native American (0.7%), or Middle Eastern (0.4%) subjects were seen in the clinics. Given that each clinic site was in an urban setting, it is likely that the sample may not be representative of the population. The metropolitan area of one of the participating clinics has an Arabic population of 0.87%, yet only one subject of Middle Eastern descent was seen (United States Census Bureau, 2000.) This raises the question of whether access to healthcare, including subspecialty services, is a barrier to detecting and treating prediabetes. The possibility may also be raised that healthcare services in some urban areas are confined to local neighborhood clinics, without subspecialty referrals. Investigation of local healthcare services to youth at high-risk for diabetes should be followed-up with appropriate education and screening initiatives targeted to those providing care.

Differences in metabolic biochemical parameters were observed between overweight youth with and without prediabetes. Fasting glucose, fasting insulin, insulin-to-glucose ratio, and systolic blood pressure values were significantly higher in those with prediabetes. Metabolic syndrome was prevalent in both groups, with greater than 60% of subjects overall (65.6 in overweight/61.9% in prediabetic) meeting the classification criteria. This exceeds previously published reports, in which 35.5% of those with BMI-for-age percentiles ≥85th in ages 12 to 19 years had the syndrome (Cook *et al.*, 2003.) In another report of metabolic syndrome in children and adolescents ages 4 to 20 years, metabolic syndrome was determined by degree of obesity using BMI-for-age z-scores. In moderately obese (z-score >2.0; mean age 12.8 years) youth, the prevalence of metabolic syndrome was 38.7%, and in severely obese youth (z-score >2.5; mean age

11.3 years) the prevalence was 49.7% (Weiss *et al.*, 2004.) While this supporting data exemplifies the issue of metabolic syndrome in youth, the results of our study show a much greater magnitude of the syndrome that has not yet been reported elsewhere. A barrier to reporting metabolic syndrome in youth includes the lack of a clear definition for this age group. All of the current published reports utilize age-appropriate adaptations of the Adult Treatment Panel's working definition of metabolic syndrome for adults. Until specific criteria are set for youth, the scope and significance of the problem may not be fully described.

Youth with prediabetes had lower rates of metabolic syndrome compared to overweight youth in this sample, but serum glucose, insulin, insulin-to-glucose ratio, and systolic blood pressure values were significantly higher. As mentioned previously, abnormal glycemia, elevated insulin, and a high insulin-to-glucose ratio are indicative of insulin resistance (Sinha *et al.*, 2002.). Hypertension has also been linked to insulin resistance. There is evidence to support and refute a postulated relationship between hyperinsulinemia and stimulation of the sympathetic nervous system, causing hypertension through changes in heart, renal, and blood vessel dynamics (Corry and Tuck, 1999.) Whether the degree of hypertension observed in youth with prediabetes is due to insulin resistance or essential hypertension is unknown and remains an area for further study. While not statistically significant, values for triglycerides, LDL-cholesterol, HDL-cholesterol, and diastolic blood pressure were more elevated in those with prediabetes as well. The precipitating factor(s) pushing the metabolic abnormalities seen in the overweight youth to the point of developing prediabetes is unknown. Further research is much needed to identify the progression more clearly.

Treatment for prediabetes focused largely on nutrition interventions, with a registered dietitian providing care in the majority of cases. Registered dietitians have the educational background and practical clinical experience required for the administration of medical nutrition therapy. The findings of this study suggest that the most qualified medical professionals are providing youth with nutrition education. Most children and adolescents were given information on reduced total fat and saturated fat food plans, with the aim of reducing caloric intake while increasing activity levels. Registered dietitians also gave recommendations to increase physical activity more than other health professionals. In no instances were exercise physiologists noted to be providing physical activity guidelines. Goal setting and follow-up visits were observed, yet weight loss and weight stabilization occurred in only 33.4% of the cases. Subjects met with dietitians on average less than 2 times, with some declining an initial visit. Regular follow-up would allow for the adequacy of nutrition therapy to be assessed, and for individual goals to be revised as needed. Further investigation into the hesitancy to seek medical nutrition therapy should be pursued. Perceived value by both overweight youth (when age appropriate) and their families, as well as readiness to change are potential areas for study.

The American Dietetic Association has no position statement on nutrition for the treatment of insulin resistance, prediabetes, or type 2 diabetes in youth. The American Diabetes Association's position statement for nutrition in diabetes does address type 2 diabetes in youth. A diet promoting a healthy lifestyle (as opposed to strict weight loss) and glycemic management is recommended. Maintaining weight during linear growth is advised with considerations for dyslipidemia and hypertension as needed.

Recommendations for diabetes prevention in all age groups (though not specific to youth) emphasize a diet lower in fat of all kinds (except omega-3 fatty acids), as dietary fats have been implicated in insulin resistance (American Diabetes Association, 2003.) Increasing intake of fiber and whole grains is also advised for the prevention of diabetes. Interestingly, recommendations for weight loss are not stated as outcomes of medical nutrition therapy in youth. While weight loss is advocated in adults for the prevention of diabetes, children and adolescents are advised differently for weight managment. Concerns related to the physiology of growth and eating behaviors are factors setting youth and adults apart in regard to weight recommendations (Epstein *et al.*, 1998). A recent consensus paper on childhood obesity describes any decrease in BMI z-score to be positive whether attained through weight stabilization with linear growth, or weight loss once one's adult height is reached. A mild caloric restriction is considered appropriate when the minor subject and family agree to commit to long-term lifestyle and behavioral changes (Obesity Consensus Working Group, 2004.) In the DPP, successful lifestyle interventions included both individualized consultation and behavioral support groups. Further research is needed to address whether such interventions are effective in youth.

The use of the drug metformin was observed in only 14.3% of the subjects (3/21). The use of thiazolideniones (to enhance insulin sensitivity), alpha-glucosidase inhibitors (slows carbohydrate digestion), orlistat (prohibits fat digestion), or sibutramine (appetite suppressant) were not observed. Three subjects (of 18) were on medications for hypertension.

This study documents cases of prediabetes in youth as young as 9 years of age. While medical record reviews have limitations in capturing consistent data among the

subjects assessed, it does present an unbiased observation of current screening and clinical care procedures. We showed that despite being under the care of medical practitioners specializing in metabolic abnormalities and diabetes, many of those at-risk for diabetes are not being screened properly. By missing the opportunity to capture insulin resistance and impaired glycemia in its early stages, the chances of overweight youth delaying follow-up with a healthcare provider until symptoms of diabetes (and underlying, silent cardiovascular risk factors) are present is a concern. Also, the number of those lost to follow-up is noteworthy, even for those screened and found to have normal glycemia. The ADA recommends screening youth beginning at age 10 (or at the first signs of puberty) with repeated screening every 2 years (ADA, 2000.) Whether screening is repeated and subjects are followed long-term for overweight remains unknown.

The question of a more aggressive screening policy for diabetes is under debate. Whether diabetes in the young is considered a public health concern, and whether screening would be cost effective are issues in need of clarification. Easy, cost-effective ways of identifying youth at risk, such as routine evaluation of acanthosis nigricans, need to be explored as possibilities. Another consideration is medical reimbursement issues related to the care of obesity. Medical testing and treatments, such as nutritional counseling and laboratory testing are traditionally not covered services by most third-party insurance providers (Hill and Bessesen, 2003.) Therefore, evaluation of these barriers remain to be areas for further examination.

The extent to which metabolic abnormalities were observed in this sample of youth was profound. The metabolic syndrome was present in over 60% of all cases

reviewed. Whether a young person was identified with prediabetes or not, hyperlipidemia and hypertension were common findings in this sample. The long-term impact of these metabolic disturbances may be devastating. Thirty-one percent of American youth have a BMI-for-age ≥85th percentile. Based on the findings of this study, the potential for approximately 1/3 of this generation of our population to develop type 2 diabetes and/or cardiovascular disease earlier in life is a consideration that must be taken into account. The medical field, public health arena, public education system, federal and state policy makers, and parents/families must be made aware of the potentially devastating health effects that the problem of overweight presents to the young.

Strengths and Limitations

As mentioned previously, the study design was a limitation in both the acquisition and analysis of data. Medical record reviews provide a broad range of information, however, in this study the content of the records varied by clinic and patient. The amount of missing data in the medical records was also a barrier to analysis. In many cases, information critical to the evaluation of a subject's predisposition (risk) for diabetes was absent from the medical record, including notations of family history of diabetes, presence or absence of ancanthosis nigricans, tanner stage, and physical activity status. Therefore, these limitations as well as the small sample of those with prediabetes allowed for only basic descriptives and comparisons to be run.

A larger, prospective study is needed to study the magnitude of the problem of prediabetes in youth. The results of this study as well as published small, single clinic

studies do show that prediabetes is present in overweight youth. Effective treatment specific to children and adolescents is needed. Screening initiatives among agencies involved with child and adolescent health and interest are also imperative. Formal recommendations for the nutritional treatment of insulin resistance and prediabetes are needed for the young, with physiological, psychological, and social needs considered as key considerations.

The strengths of this study include some of the first documented findings of prediabetes in overweight and at-risk for overweight youth detected primarily with fasting blood glucose testing. Sinha et al. found up to 25% of youth to have prediabetes after 2-hour oral glucose tolerance testing (Sinha *et al.*, 2002.) This study also reiterates that the American Diabetes Assocation recommendations for screening children and adolescents for type 2 diabetes are not being carried out on a consistent basis, even from endocrine specialists, who are often seen as diabetes specialists. Nutrition recommendations similar to those found to be effective for adults in the Diabetes Prevention Program are being given by registered dietitians. This is a strength considering that nutrition is an area often victim to misinformation, specifically when weight is a concern. While no position statements currently exist in terms of nutrition recommendations specifically for prediabetes in youth, those being applied have been researched in the adult population (DPP, 2002.)

As mentioned previously, the relatively small number of youth screened for prediabetes (N=153) and ultimately the small number of those detected with prediabetes (N=21) caused limitations in statistical analysis of the data collected. A larger sample

size with more data present may have provided more detailed information for which to draw further inferences.

Conclusion and Future Research Directions

Public health initiatives for the prevention of diabetes in adults are being pioneered nationally and statewide. The National Diabetes Education Program (NDEP) and the U.S. Department of Health and Human Services (HHS, 2003) have launched a campaign titled, "Small Step, Big Rewards! Prevent Type 2 Diabetes", targeting the 41 million Americans with prediabetes (NDEP/HHS, 2003.) The project provides those with prediabetes or at risk for prediabetes and healthcare practitioners with risk assessment, lifestyle change tools, and resources. The American Diabetes Association has more recently launched a health education campaign titled, "Weight Loss Matters". This is the ADA's first attempt at publicly linking overweight (and the need for weight reduction) with risk for type 2 diabetes (ADA, 2003.). Current estimates of overweight and obesity in US adults from the CDC are 64% (CDC, 2003.) A survey conducted in conjunction with the "Weight Loss Matters" initiative showed that while 59% of those surveyed did report that being overweight or obese was a risk factor for type 2 diabetes, 59% of those who responded maintained that they themselves were not at personal risk for the development of the disease (ADA, 2003.)

The Michigan Diabetes Prevention and Control Program (MDPCP) operates from a small grant from the CDC and Michigan legislature. This statewide program partners with the Michigan Diabetes Outreach Networks, the Michigan Diabetes Core Measures

Initiative, and national initiatives such as the NDEP to address state efforts for the prevention and control of diabetes in the public (MDCH, 2003.)

Public programming targeted toward youth and prediabetes awareness and type 2 diabetes is currently lacking. However, awareness at the federal and state levels to address the problem of overweight in youth and risk for diabetes in the United States and Michigan are currently underway. The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) is funding clinical trials for the prevention and treatment of type 2 diabetes in youth (NDEP, 2004.) The NIDDK has also partnered with the ADA and the Juvenile Diabetes Research Foundation to provide further training in pediatric endocrinology research and career development. And finally, the NIDDK and the CDC made a cooperative effort in 2000 to establish a national multi-center registry of diabetes in children. The aim of the registry is to study the incidence, prevalence, natural history, quality of care, and racial/ethnic disparity issues related to diabetes in the young (NDEP, 2004.)

Overall, the lack of specific guidelines and definitions for metabolic syndrome, nutrition and physical activity treatments, glycemic cut-off points, and glucose challenge in youth make much of this work preliminary. However, future implications of this work are that prospective, longitudinal studies to better assess the effectiveness of treatment recommendations in this population may be conducted over time. A clinical trial evaluating treatment with a control and experimental group, similar to the Diabetes Prevention Program in adults would provide more precise information as to whether adult lifestyle recommendations are effective in a younger population, with the physiology of growth and development remaining factors of consideration. Qualitative research

focusing on the child and their families may also provide useful insight into the challenges and development of lifestyle treatment programming, by identifying the barriers and facilitators to adhering to changes needed for the prevention.

APPENDICES

APPENDIX A

December 23, 2003

TO: Lorraine WEATHERSPOON
334 Trout FSHN Bldg
MSU

RE: **IRB# 03-942** CATEGORY: EXPEDITED 2-5

APPROVAL DATE: December 22, 2003
EXPIRATION DATE November 22, 2004

TITLE: ASSESSMENT OF PRE-DIABETES AND LIFESTYLE INTERVENTIONS IN A SAMPLE OF OVERWEIGHT MICHIGAN YOUTH

The University Committee on Research Involving Human Subjects' (UCRIHS) review of this project is complete and I am pleased to advise that the rights and welfare of the human subjects appear to be adequately protected and methods to obtain informed consent are appropriate. Therefore, the **UCRIHS approved this project.**

"UCRIHS has approved a waiver of authorization under expedited review procedures to use or disclose protected health information for this research that involves no more than minimal risk, and could not practicably be conducted without the waiver and without access to and use of existing medical records at Detroit Children's Hospital, Sparrow Health System, Mott Children's Hospital and Covenant Health Care for youths aged 5-19 years of age seen by pediatric endocrinology specialists who are or at-risk for overweight."

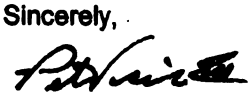
RENEWALS: UCRIHS approval is valid until the expiration date listed above. Projects continuing beyond this date must be renewed with the renewal form. A maximum of four such expedited renewals are possible. Investigators wishing to continue a project beyond that time need to submit a 5-year application for a complete review.

REVISIONS: UCRIHS must review any changes in procedures involving human subjects, prior to initiation of the change. If this is done at the time of renewal, please include a revision form with the renewal. To revise an approved protocol at any other time during the year, send your written request with an attached revision cover sheet to the UCRIHS Chair, requesting revised approval and referencing the project's IRB# and title. Include in your request a description of the change and any revised instruments, consent forms or advertisements that are applicable.

PROBLEMS/CHANGES: Should either of the following arise during the course of the work, notify UCRIHS promptly: 1) problems (unexpected side effects, complaints, etc.) involving human subjects or 2) changes in the research environment or new information indicating greater risk to the human subjects than existed when the protocol was previously reviewed and approved.

If we can be of further assistance, please contact us at (517) 355-2180 or via email: UCRIHS@msu.edu. Please note that all UCRIHS forms are located on the web: http://www.humanresearch.msu.edu

Sincerely,



Peter Vasilenko, Ph.D.
UCRIHS Chair

APPENDIX B

Code ID _____

Data Abstraction Form for Prediabetes in Youth Study

Study Site: _____ Date Abstracted: _____

Reviewer: _____ Physician: _____

BMI%tile _____

Demographic Data:

Gender M F

Age_____

Race/Ethnicity:
African American___
Latino/Hispanic ___
Asian/Pacific Islander___
Caucasian___
Native American____
Other (please explain)____

Parents' marital status:

Single Divorced Widowed/er Married

Living Status:

Father, Mother, and sibling(s)___
Father, Mother____
Father only ____
Mother only____
One parent and sibling(s)____
Other_____

Family Meals_____
_____

_____

_____

Other:_____

_____

_____

_____

_____

Family History:
Family members (1st or 2nd degree) with history of type 1,2, gestational diabetes or pre-diabetes:

1. Family member _____ Diabetes Type _____
2. _____ _____
3. _____ _____
4. _____ _____
5. _____ _____
6.

Total number of family members with type 2 diabetes _____
Total number of family members with pre-diabetes _____

Family Weight History:
First degree relatives overweight: _____
Second degree relatives overweight:_____

Parental Information:
Highest level of education:
Father _____ Mother_____

Parents' employment status:
Father_____ Mother_____

Home environment/Lives with: _____

Medical Insurance Provider:
None_____ Medicaid_____

Private Payer_____ PPO HMO

Clinical Information:

Ht_____cm/in Wt_____kg/lb

BMI _____ BMI-for-Age% tile _____

Waist Circumference _____cm (if available)

Tanner Stage: I II III IV V

Age of Onset of Puberty_____

If female, age of first menses: _____

Medications:_____

_____

Metformin Yes No if yes, dose: _____

Blood Pressure

Date:	Date:	Date:
Value:	Value:	Value:
Percentile:	Percentile:	Percentile:

Laboratory Analysis:

Blood Glucose Values	Date/Value	Date/Value	Date/Value
Hgb A1C	/	/	/
Fasting Glucose	/	/	/
Other Glucose	/	/	/
OGTT results	/	/	/

Blood Lipid Values	Date/Value	Date/Value	Date/Value
Total Cholesterol	/	/	/
HDL-cholesterol	/	/	/
LDL-cholesterol	/	/	/
Triglyceride	/	/	/
TC:HDLRatio	/	/	/

Insulin	Date/Value	Date/Value	Date/Value
Insulin	/	/	/
C-peptide	/	/	/

Vitamin D _____

Other significant lab values: _____

Lifestyle Factors (as noted in chart by health professionals):

Physical Activity: Sedentary: Yes No

Recommendations Yes No By whom?_____

Followed: Yes No

Comments on physical activity:

_____

_____

Diet

Low-fat, calorie reduced diet recommended? Yes No

By whom? _____

If other diet is recommended, explain:

_____

_____

Goals set: _____

Followed: Yes No Date of follow-up: _____

Comments on Diet:

_____

_____

_____

Multivitamin/Mineral supplements: Yes No

If yes, physician recommended? Yes No

Chapter 6
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