ANALYSIS OF FACTORS THAT INFLUENCE SHORT-TERM INCREASE IN BMI AMONG CHILDREN RECENTLY DIAGNOSED WITH DIABETES

by

Abidemi Kassim Adeniji

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This thesis was presented

by

Abidemi K. Adeniji

It was defended on

April 25, 2008

and approved by

Thesis Advisor:
Vincent C. Arena, PhD
Associate Professor
Department of Biostatistics
Graduate School of Public Health
University of Pittsburgh

Ingrid M. Libman, MD, PhD
Assistant Professor
Division of Pediatric Endocrinology, Metabolism and Diabetes Mellitus
Children's Hospital of Pittsburgh of UPMC Health System

Dorothy J. Becker, M.B.B.Ch.
Professor of Pediatrics, Director
Division of Endocrinology, Metabolism and Diabetes Mellitus
Children's Hospital of Pittsburgh of UPMC Health System

Maribel Cedillo, MS, RD, LDN.
Program Coordinator, Etiology and Epidemiology of T1D
Division of Endocrinology, Diabetes & Metabolism
Children's Hospital of Pittsburgh of UPMC Health System

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Abidemi K. Adeniji, M.S.

University of Pittsburgh, 2008

There is extensive literature on the etiology of Type 1 diabetes mellitus (T1DM). T1DM is a disease that has levied a substantial burden on the health of millions; as such a study into the factors associated with T1DM is of utmost importance in the field of public health. It is widely believed that a person's genetic predisposition is linked with the susceptibility of T1DM. Some genes are largely unknown, while some like the HLA gene class II molecules DQ has been greatly studied. It is believed that the haplotype Non-Asp/0602 is actually protective against T1DM. The risk of Type 1 diabetes in individuals with a genetic susceptibility- homozygous non-Asp/non-Asp are at higher risk whereas the individuals with Asp/Asp are at lower risk of Type 1 diabetes. Studies have suggested that those patients who are at greatest risk genetically tend to have a low body mass index (BMI), low pro-insulin, and a higher number of positive antibodies. In the past, children diagnosed with type 1 diabetes were not overweight and actually would present with considerable weight loss and underweight. This seems to be changing.

The purpose of this study is to investigate precipitating factors that are associated with short-term weight gain in children who were diagnosed with T1DM at Children's Hospital of Pittsburgh, from 2004 through 2006. We investigated the prevalence of increased BMI after 3

months of diagnosis in patients with Type 1 diabetes in relation to BMI at onset, gender, age at onset, HLA-DQ type, C-peptide, hemoglobin A1c (HbA1c) and race.

BMI percentile at diagnosis was significantly different from BMI percentile at 3months, which showed an average increase from baseline of 21.5 and a standard deviation of 24.6 (p-value<0.0001, paired t-test). Greater change in BMI percentile from onset to 3 months was significantly associated with younger age, higher HbA1c, male gender and being under the 25th percentile in BMI at onset. The subjects with the highest BMI percentile at 3 months were significantly associated with the independent predictors of younger age, higher HbA1c, male gender and being in the 85th percentile in BMI at onset.

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1.0 INTRODUCTION

1.1 PURPOSE OF THE STUDY

There is extensive literature on the etiology of Type 1 diabetes mellitus (T1DM). T1DM is a disease that has levied a substantial burden on the health of millions; as such a study into the factors associated with T1DM is of utmost importance in the field of public health. It is widely believed that a person's genetic predisposition is linked with the susceptibility of T1DM. Some genes are largely unknown, while some like the HLA gene class II molecules DQ has been greatly studied. It is believed that the haplotype Non-Asp/0602 is actually protective against T1DM. The risk of Type 1 diabetes in individuals with a genetic susceptibility- homozygous non-Asp/non-Asp were at the highest risk whereas as the individuals with Asp/Asp were at the lowest risk of Type 1 diabetes [20]. Studies have suggested that those patients who are at greatest risk genetically tend to have a low body mass index (BMI), low pro-insulin, and a higher number of positive antibodies. In the past, children diagnosed with type 1 diabetes were not overweight and actually would present with considerable weight loss and underweight. This seems to be changing. In fact, it has been proposed that excessive weight gain may be a contributing factor to the development of type 1 diabetes [24].

The origins of Type 1 are not fully understood. Ten percent of people diagnosed with diabetes have Type 1 and the majority of them are children or young adults when it strikes. Genetic factors are important; however scientists believe that environmental factors also play an

important role, among them viral infections. Several clinical trials of methods for the prevention of type 1 diabetes are currently in progress or are being planned.

There are no known preventative measures that prevent Type 1 diabetes. Most people affected by Type 1 diabetes are otherwise healthy and traditionally not overweight when onset occurs. Diet and exercise cannot reverse or prevent Type 1 diabetes. On the other hand, Type II diabetes seems to be prevented or delayed with modifications in diet and exercise. As such, I am interested in understanding and investigating ways to prevent obesity in children. According to the CDC, the percentage of young people who are overweight has more than tripled since 1980, and 16% of children aged 6-19 considered overweight. This increase has also been described in children diagnosed with type 1 diabetes at onset of the disease [25]

The purpose of this study is to investigate precipitating factors that are associated with short-term weight gain in children who were diagnosed with T1DM at Children's Hospital of Pittsburgh. We investigated the prevalence of increased BMI at 3 months after diagnosis in patients with Type 1 diabetes in relation to BMI at onset, gender, age at onset, HLA-DQ type, C-peptide, HbA1c and race.

1.2 BACKGROUND AND SIGNIFICANCE

DIABETES OVERVIEW

Type 1 diabetes accounts for between 5 and 10% of all diagnosed diabetes in the United States. Although Type 1 diabetes develops most often in children and young adults (one in every 400-600 children has Type 1 diabetes) [1], the disease can be diagnosed at any age throughout the lifespan, and is equally distributed among males and females. Unlike Type 2 diabetes, Type 1 diabetes is more common in Caucasians than in those of Latino, African-American, or other non-Caucasian backgrounds.

Type 1 diabetes is an autoimmune disease that occurs when the insulin-producing β cells within the pancreas are gradually destroyed and eventually fail to produce insulin. Insulin is a hormone that helps the body's cells use glucose for energy. Blood glucose (or blood sugar) is manufactured from the food we eat (primarily carbohydrates) and by the liver. If glucose cannot be absorbed by the cells, it builds up in the bloodstream, and eventually leads to high blood sugar. Over time, the high blood glucose levels of uncontrolled diabetes can be toxic to virtually every system of the body. As a result, individuals with T1D require daily exogenous insulin treatment as well as frequent surveillance of blood glucose levels.

After eating, the glucose level in blood rises, which leads to insulin being released from the pancreas. In a person with TIDM, beta cells of Langerhans are damaged by autoimmune inflammation, leading to an insufficiency of insulin. The glucose level in blood rises and cells do not have enough energy for metabolism [3].

1.3 THE PATHOLOGY OF IDDM

Type 1 diabetes is a chronic autoimmune disease resulting from the progressive destruction of the pancreatic β-cells, which in turn leads to an absolute insulin deficiency [9]. The timing of the clinical presentation is highly variable, with the youngest patients diagnosed in infancy and the oldest patients diagnosed at a senior age. It is believed that at least half of the inherited genetic predisposition to Type 1 diabetes is due to HLA-DQ genes [6].

People with type 1 diabetes develop an abnormal immune reaction which causes T-cells to destroy the insulin producing cells in the pancreas. Antibodies are markers of this process and the ones that are well described include are ICA (Islet cell antibodies), the insulin auto-antibodies (IAA), auto-antibodies to glutamic acid decarboxylase (GAD) and auto-antibodies against the protein tyrosine phosphatase (IA-2A).

The clinical onset of diabetes does not occur until 80% to 90% of these cells are destroyed. Prior to clinical onset, Type 1 diabetes is often characterized by circulating auto-antibodies against a variety of islet cell antigens, including glutamic acid decarboxylase (GAD), tyrosine phosphatase (IA_2), and insulin [10-15]. The autoimmune destruction of the insulin-producing pancreatic beta cells is thought to be the primary cause of Type 1 diabetes. Auto-antibodies are valuable markers that predict Type 1 diabetes and can be detected many months or years before the onset of diabetes [2]. The presence of these auto-antibodies provides early

evidence of autoimmune disease activity, and their measurement can be useful in assisting the physician with the prediction, and diagnosis, of patients with diabetes.

Glutamic acid decarboxylase-65 (GAD_{65}) is an enzyme that is produced primarily by pancreatic islet cells. A number of recent studies indicate that patients with insulin-dependent diabetes mellitus (IDDM) often have antibodies to GAD_{65} and several other islet cell antigens [7]. This is consistent with the hypothesis that IDDM is an autoimmune disease and that autoantibody production is an early step in the development of IDDM. Auto-antibodies can be detected in many cases prior to the onset of glucose intolerance. The presence of GAD_{65} auto-antibodies is shown to be a strong predictive marker for the eventual onset of IDDM. Measurement of GAD_{65} antibody can also be of use in distinguishing insulin-dependent from non-insulin-dependent diabetics when the clinical history is ambiguous [8].

Auto-antibodies to IA_2 (IA2A), a tyrosine phosphatase-like protein, are found in 50% to 75% of Type 1 diabetics at and prior to disease onset. These auto-antibodies are generally more prevalent in younger onset patients. Because the risk of diabetes increases with the presence of each additional autoantibody, the positive predictive value of the IA_2 antibody test is enhanced when measured in conjunction with antibodies to GAD and insulin.

Insulin auto-antibodies (IAA) are one of several markers for Type I (autoimmune) diabetes, but alone deserve special attention. Unlike the other markers, their ligand is unique to the beta cell. IAA are the first markers to appear during the symptomless period which precedes diabetes and they are present in the vast majority of young children destined to develop diabetes. The primary and tertiary structures of insulin have been known for decades [16].

C-peptide is a substance that the pancreas releases into the bloodstream in equimolar concentrations with insulin. A test of C-peptide levels will show just how much insulin the body

is making [23], and thus is a measure of insulin secretion. C-peptide has proven to be invaluable in the study of the natural history of IDDM.

Hemoglobin A1C ($HbA1_C$) is a substance of red blood cells that carries oxygen to the cells and sometimes joins with glucose (sugar). Because the glucose stays attached for the life of the cell (about 3 months), a test to measure hemoglobin A1C shows what the person's average blood glucose level during that time period. In the blood, glucose binds irreversibly to hemoglobin molecules within red blood cells. The amount of glucose that is bound to hemoglobin is directly tied to the concentration of glucose in the blood. Since red blood cells have a lifespan of approximately 90 days, measuring the amount of glucose bound to hemoglobin can provide an assessment of average blood sugar control during the 60 to 90 days prior to the test. This is the purpose of the glycated hemoglobin tests, most commonly the hemoglobin A1C (HbA1c) measurement. Since the test results give feedback on the previous two to three months, getting an HbA1c test done every three months will give a good estimate of a persons' average blood sugar [18].

1.3.1 HLA & DQ

The human leukocyte antigen (HLA) complex is located on chromosome 6. It is the primary region of susceptibility for Type 1 diabetes mellitus, as well as other autoimmune disorders. The DQ locus consists of two tightly linked genes (DQA1 and DQB1) that encode α and β glycoprotein, respectively [19].

Past studies have confirmed that subjects presenting with Type 1 diabetes during childhood have a stronger HLA-defined genetic susceptibility than those diagnosed during adulthood [4, 5]. This indicates that highly predisposing HLA genes not only increase the risk of

Type 1 diabetes, but also have an effect on the rate of progression to clinical disease. The weaker HLA-conferred genetic risk in adults raises the issue of whether adult patients carry stronger disease susceptibility as defined by non-HLA genes or whether they experience more exogenous factors, which predisposes them to Type 1 diabetes in the preclinical period [7].

The risk of Type 1 diabetes in individuals with the genetic susceptibility- homozygous non-Asp/non-Asp is the highest, whereas the individuals with Asp/Asp have the lowest risk of Type 1 diabetes [20].

2.0 MATERIALS AND METHODS

2.1 THE STUDY POPULATION

The population studied consists of individuals who were newly diagnosed with IDDM at the Children's Hospital of Pittsburgh. These clinically diagnosed IDDM patients were recruited and termed "new onsets". New onsets are defined as children less than 19 years of age diagnosed with insulin-requiring diabetes. This study was approved by the Institutional Review Board (IRB) of the University of Pittsburgh and parents provided informed written consent. The individuals in the study were recruited from January 2004 through December 2006. Exclusion was based on the presence of any severe illness, or other abnormality that could interfere with the assessment of T-cell function.

2.2 MEASUREMENTS AND HLA-DQ TYPING

The children had various testing and measurements done prior to discharge from the hospital. At the time of diagnosis, blood samples were obtained to determine HLA-DQ typing, HbA1C, lipids and C-peptide levels. Height and weight measurements were also obtained to calculate body mass index (BMI). The patients first study blood draw for autoantibody (GAD65,

IA2) analysis was done within 3 months of diagnosis; this is done to assess their autoantibody status at the onset of IDDM. Antibody analysis is believed to change over time as disease progresses. At the time of autoantibody analysis, HbA1C, lipids, C-peptide levels, waist/hip measurements, blood pressure, height and weight were also ascertained.

2.3 BLOOD PRESSURE PERCENTILES

Advances have been made in detection and evaluation of high blood pressure (BP), or hypertension, in children and adolescents. Because of the development of a large national database on normative BP levels throughout childhood, the ability to identify children who have abnormally elevated BP has improved. On the basis of developing evidence, it is now apparent that primary hypertension is detectable in the young and occurs commonly. The long-term health risks for hypertensive children and adolescents can be substantial; therefore, it is important that clinical measures be taken to reduce these risks and optimize health outcomes.

Hypertension in children and adolescents continues to be defined as systolic BP (SBP) and/or diastolic BP (DBP), that is, greater than the 95th percentile. BP between the 90th and 95th percentile in childhood had been designated "high normal." To be consistent with the Seventh Report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7), this level of BP is deemed "pre-hypertensive".

It is now recommended that adults, children and adolescents who have BP levels ≥120/80 mm Hg but <95th percentile be considered pre-hypertensive. The definition of

hypertension in children and adolescents is based on the normative distribution of BP in healthy children.

Normal BP is defined as SBP and DBP that are <90th percentile for gender, age, and height. Hypertension is defined as average SBP or DBP that is ≥95th percentile for gender, age, and height on at least 3 separate occasions. Average SBP or DBP levels that are ≥90th percentile but <95th percentile had been designated as "high normal" and were considered to be an indication of heightened risk for developing hypertension.

2.4 BP TABLES

The blood pressure standards are based on gender, age, and height, and it provides a precise classification of BP according to body size. BP standards that are based on gender, age, and height provide a more precise classification of BP according to body size. This approach avoids misclassifying children who are very tall or very short.

2.4.1 Blood Pressure Percentile Computation

To compute the SBP percentile of a boy who is age *y* years and height *h* inches with SBP =*x* mm Hg, we referred to the most recent Centers for Disease Control and Prevention growth charts [21], and converted the height of *h* inches to a height *Z* score relative to boys of the same age, this is denoted by *Zht*. We then computed the expected SBP (μ) for boys of age *y* years and height *h* inches which given by,

$$\mu = \alpha + \sum_{j=1}^{4} \beta_j (y-10)^j + \sum_{k=1}^{4} \gamma_k (Zht)^k$$

The boy's observed SBP is then converted to a *Z* score. The formula is as follows: (*Zbp*) given by $Zbp = (x-\mu)/\sigma$, where σ is given in the third column of Appendix Table 1A. Finally, we converted the blood pressure *Z* score to a percentile (*P*), compute $P=\Phi(Zbp)$ *100%, where Φ(*Z*) is the area under a standard normal distribution to the left of *Z*. Thus, if $Zbp = 1.28$, then $\Phi(Zbp)= 0.90$ and the BP percentile= 0.90*100%= 90% [21]. Appendix Table 1A shows regression coefficients from blood pressure regression models.

2.5 WAIST CIRCUMFERENCE

2.5.1 Waist Circumference Percentiles

Research has supported the notion that the trends in waist circumference in the US adult population and the waist circumference cutoff points which are used in identifying risk of co morbidity in adults, differ according to race [22]. Thus, waist percentiles based on age, gender and ethnicity is a critical tool in the assessment of a child's adiposity. Although waist-to-hip ratio has been widely accepted in the past, more recently, there is a consensus that waist circumference alone may be a more useful index in both adults and children [22].

Due to the fact that the distribution of waist circumference according to age is not normally distributed, the 10th, 25th, 50th, 75th, and 90th percentiles of the waist circumference

distribution are examined for each race/ethnic gender classification. After consulting with the author Dr. Fernandez, we obtained an additional percentile category, the 85th.

A percentile regression approach was used to describe the changes in the percentile estimates as a function of age for every ethnic/gender group [22]. The following tables list the variables that were used in calculating the percentiles for each participant's waist. Appendix Table 1B through Table 1E gives the estimated value for percentile regression for European-American Boys, European-American Girls, African- American Boys and African-American girls.

2.6 CONSOLIDATING DATA

2.6.1 Waist and HIP

The date of the waist and hip measurements was matched with the three month height and weight date from the baseline cohort data. This initial match produced 205 subjects, we then matched within a span of 14 days of the height and weight date, this produced 207 subjects. Further exploration was done to measure just how much more subjects could be gained by relaxing the window around the height and weight date. The span was widened to a span of 120 days; this only produced one additional subject. The researchers agreed to consider those participants with a span of 14 days, which gave us a sample of 207 subjects.

2.6.2 Antibody GAD

The date of the GAD_{65} antibody blood draw was matched with the height and weight date of the baseline cohort data. This produced 149 GAD_{65} values.

2.6.3 Antibody IA2

The date of the IA-2 antibody blood draw was matched with the height and weight date of the baseline cohort data and produced 124 IA2 values. Antibodies were analyzed for those subjects who had values for both antibodies (GAD_{65}, IA2). However, due to sparse data, antibodies received no further consideration in the final analyses.

2.6.4 Lipids

The Heinz lab blood draw date of cholesterol, triglyceride, HDL and LDL were matched with the height and weight date of the baseline cohort data and 229 subjects matched for lipids.

2.6.5 C-peptide

The blood draw date of the C-peptide values from Dr. Becker's lab were matched with the height and weight date of the baseline cohort data at 3 months, this produced 228 subjects. C-peptide values that were less than detectable were set to 0.5.

2.6.6 Baseline Height

We had 268 subjects who had a BMI at baseline and at 3 months. However, height does not change significantly in 3 months, so we decided to use the 3 month height of subjects that were missing a baseline height, thereby increasing the number of subjects who had both BMI measurements to 295.

2.7 THE CREATION OF INDICATOR VARIABLES

2.7.1 Waist class

Waist percentiles were categorized '0' if the subjects waist fell under the 10^{th} percentile, '1' if the waist fell above the 10^{th} percentile but below the 25^{th} percentile, '2' if the waist fell above 25^{th} percentile but below the 50^{th} percentile, '3' if the waist fell above the 50^{th} percentile but below the 75^{th} percentile, '4' if the waist fell above the 75^{th} percentile but below the 85^{th} percentile '5' if the waist fell above the 85^{th} percentile but below the 90^{th} , and '6' if the waist fell above the 90^{th} percentile. Due to sparse data, the 7 categories stated above, were collapsed into two categories '0' if a subject's waist is less than the 75^{th} percentile and '1' for the 75^{th} percentile and upwards.

2.7.2 BMI class

Body Mass Index (BMI) is a number that reflects how a person's weight compares to the person's height, the general formula for calculating BMI is as follows: weight/height^2. Weight is expressed in kilograms and height in centimeters. However, this form of BMI is inaccurate due to the difference in the growth rate between boys and girls as well as the difference in growth rates among ages. Thus, BMI percentile is a better index since it adjusts for age, gender and height. BMI percentile is acquired by plotting the BMI number on the Center for Disease Control BMI-for-age growth charts (by gender) to obtain a percentile ranking.

This indicator variable was created by classifying baseline BMI percentile as 'less than the 25th percentile', 'between the 25th and the 85th percentile' and 'greater than the 85th percentile'. The BMI class variable took on values '0', '1' and '2' respectively. The same was done for BMI percentile at 3 months.

2.7.3 Antibodies

GAD_{65} antibody values that were greater than 0.069 were deemed as 'positive' and IA2 antibody values greater than 0.032 were deemed as 'positive'.

2.8 STATISTICAL METHODS

We summarized continuous data using basic descriptive statistics, such as the mean, standard deviation, minimum and maximum. Categorical data was analyzed using frequency counts. Two models were investigated; the first modeled the change in BMI percentile from onset to three months as the outcome, and the second modeled BMI percentile at 3 months as the outcome. Both models had the following baseline predictors: Gender, Age at onset, HLA-DQ type, C-peptide, HbA1c, Race and BMI percentile at onset.

Multiple linear regression was used to analyze the relationship between BMI and predictors at baseline. The data was analyzed using Statistical Analysis System (SAS) software using a Windows operating system. PROC GLM was used to fit the various regression models. This procedure allows for the automatic creation of indicator variables with the CLASS statement. We also used PROC GPLOT to analyze the residuals for variance homogeneity. The Kolmogorov-Smirnov test as well as the quantile-quantile (QQPLOT) plot of the residuals in PROC UNIVARIATE was used to assess normality.

3.0 RESULTS

3.1.1 Demographics

Table 1 shows the distribution of race and gender. Of the 19 black subjects, 32% are female. The number of Caucasian subjects (94%) greatly outnumbered the number of black subjects (6%), although the ratio of male to female is comparable.

Table 1. Cross tabulation depicting the relationship between gender and race among study participants.

	RACE		
	White	Black	**Total**
GENDER			
Male	163 55%	13 68%	176 56%
Female	133 45%	6 32%	139 44%
Total	296 94%	19 6%	315 100%

3.1.2 Distribution Continuous Predictors

Table 2 and Table 3 illustrate the distribution of the continuous predictors of interest. Of the predictors that we have at onset and at 3 months, all showed an average increase except HbA1c, which went from an average of 11.7% at onset to 7.36% at 3 months for an average change of -4.35%.

Table 2. Descriptive statistics for baseline variables used in the study of Type I diabetes in children.

Variable	N	Mean	Std Dev	Minimum	Maximum
Percentile for body mass index-for-age	303	52.2	34.27	0.02	100
Age at baseline in Years	315	9.37	4.24	0.58	18.92
C peptide: baseline (CHP) (ng/ml)	287	0.88	0.82	0.5	7.01
HbA1c (%)	306	11.7	2.4	5.3	17
Triglyceride (mg/dl)	265	113	78	28	718
HDL (mg/dl)	164	39	11	13	82
LDL (mg/dl)	161	91	36	10	280
Cholesterol (mg/dl)	268	148	36	51	319

Table 3. Descriptive statistics for variables at time 3-months used in the study of Type I diabetes in children.

Variable	N	Mean	Std Dev	Minimum	Maximum
Percentile for body mass index-for-age (3 months)	295	73.5	22.85	1.38	100
Age at 3 months in Years	315	9.62	4.24	0.83	19.17
C peptide (CHP) (ng/ml)	226	1.85	1.81	0.01	17.3
HbA1c (%)	306	7.36	0.92	4.5	11.8
Diastolic BP: 3 months	270	63.97	6.99	44	89
Systolic BP: 3 months	271	110.19	12.75	81	180
Average BP	270	87.06	8.59	69	125
HDL	222	48	11	20.8	78.5
Triglyceride	225	124	67	38	640
cholesterol	225	154	28	80	293

Table 4. Descriptive Statistics for Average Three Month Change.

Label	N	Mean	Std Dev	Minimum	Maximum
Difference in BMI	295	21.52	24.58	-41.89	88.53
Difference in age	315	0.25	0	0.25	0.25
Difference in C-peptide (ng/ml)	213	1.04	1.6	-1.98	13.94
Difference in HbA1C (%)	299	-4.35	2.52	-10.9	4.2
Difference in HDL	117	9.42	10.7	-21.2	31.9
Difference in Triglyceride	188	14.68	81.84	-423	259
Difference in Cholesterol	190	8.17	30.25	-96	107

3.1.3 Distribution Categorical Predictors

We found no evidence of an effect of genes on BMI percentile, an explanation may be due to the under-representation of ASP and Non-ASP/0602, these genes only accounted for 3.6% and 1.8% of the total gene frequency respectively.

Waist circumference was found to be significantly associated with BMI. Putting aside the '75^{th} and 85^{th} percentile' categories, the frequency of subjects were more or less evenly distributed. As mentioned earlier, we obtained an additional category (85^{th}) from Dr. Fernandez; if we were to consolidate these two categories, the frequency of the waist circumference is interestingly almost evenly distributed. Of the two hundred and one subjects who had a waist measurement, sixty-six percent were under the 75^{th} percentile. The majority of subjects (43%) fell between the 25^{th} and the 85^{th} percentile in BMI. Table 5 shows their distributions and Figure 1 through Figure 3 give a pictorial representation.

Table 5. Frequency distribution of HLA/DQ, waist percentiles, waist class and BMI class.

Variable	Frequency
HLA (n = 276)	
ASP	10 3.6%
Non-ASP	266 95%
Non-ASP/0602	5 1.8%
Waist Percentiles (n=201)	
0th	22 11%
10th	30 15%
25th	36 18%
50th	44 22%
75th	20 10%
85th	10 5%
90th	39 19%
Waist Class (n =201)	
< 75th	132 66%
>= 75th	69 34%
BMI class (n = 315)	
< 25th	102 32%
25th - 85th	135 43%
> 85th	78 25%

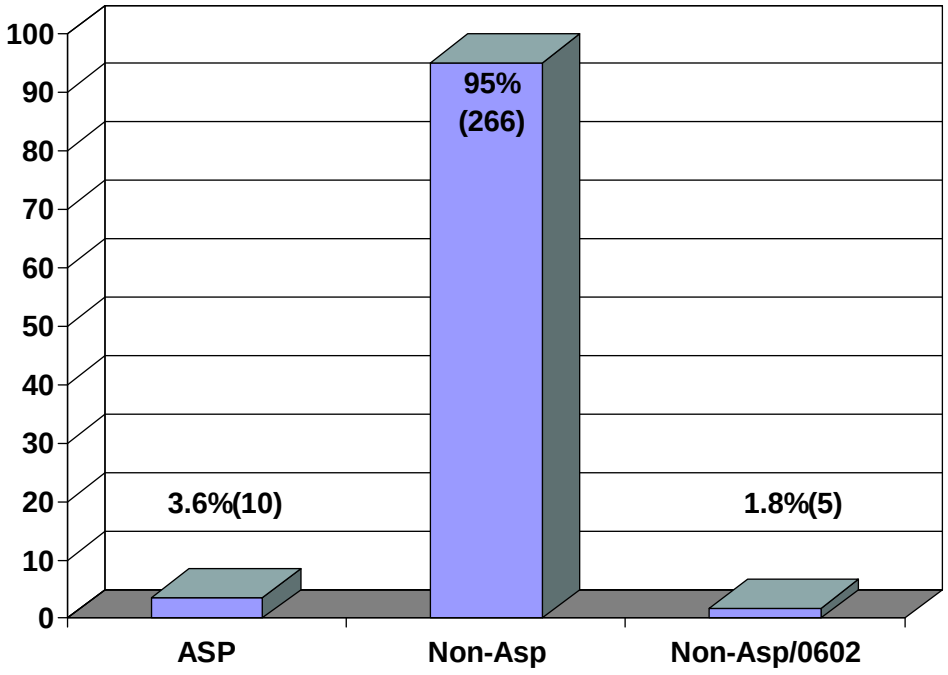

Figure 1: Percent Distribution of HLA/DQ

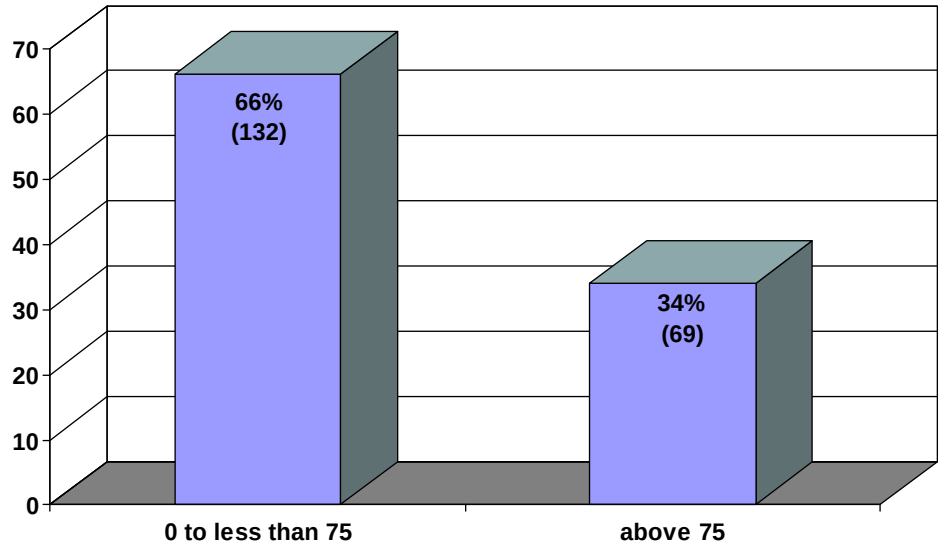

Figure 2: Percent Distribution of Waist Class

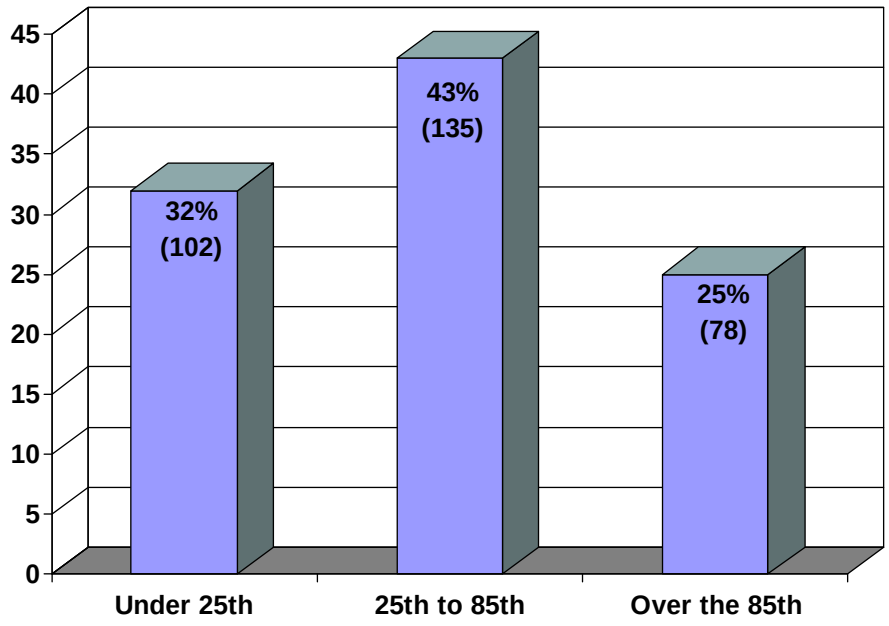

Figure 3: Percent Distribution of BMI Class

3.1.4 Interpretation of the Regression Models

BMI percentile at diagnosis was significantly different from BMI percentile at 3months, a paired t-test showed an average increase from baseline of 21.52 and a standard deviation of 24.58 (p-value<0.0001). Even though Caucasian subjects (n=276) vastly outnumbered the African American subjects (n=19), both races showed a significant increase in BMI percentile at 3 months (with mean, standard deviation and p-value of [21.753, 24.14, p<0.0001]; [18.1, 30.9, p=0.02]). Table 6 and 7 show the regression outputs.

Table 6. Regression coefficients for BMI change as outcome.

Parameter	Estimate	P-value
Age at onset	-0.67	0.0195
C-peptide	-1.22	0.4379
A1C	1.83	0.0001
Race		0.7744
Black	-1.13	
White	*	
Gender		0.0011
Female	-6.83	
Male	*	
HLA		
ASP	-3.24	0.7247
Non-Asp	2.13	0.7824
Non-Asp/0602	*	
BMI at Onset		
25^{th} to 85^{th} percentile	-25.27	<.0001
Over the 85^{th} percentile	-41.69	<.0001
Under the 25^{th} percentile	*	

* : Reflects the reference group

Table 7. Regression coefficients for BMI at 3-months as outcome.

Parameter	Estimate	P-value
Age at onset	-0.58	0.0451
C-peptide	0.02	0.9883
A1C	1.95	<.0001
Race		0.3017
Black	4.14	
White	*	
Gender		0.0048
Female	-6.00	
Male	*	
HLA		
ASP	-5.01	0.5939
Non-Asp	1.81	0.8185
Non-Asp/0602	*	
BMI at Onset		
25^{th} to 85^{th} percentile	19.18	<.0001
Over the 85^{th} percentile	42.36	<.0001
Under the 25^{th} percentile	*	

*: Reflects the reference group

Greater change in BMI percentile from onset to 3 months was significantly associated with younger age, higher HbA1c, male gender and being under the 25^{th} percentile in BMI at onset. The subjects with the highest BMI percentile at 3 months were significantly associated with the independent predictors of younger age, higher HbA1c, male gender and being in the 85^{th} percentile in BMI at onset.

One of the current theories is that individuals with the lowest risk HLA haplotypes (ASP) should have the lowest frequency of antibodies and highest BMI. Table 8 shows the frequency

of positive antibodies versus HLA, and even with a high amount of missing data of these predictors, the results shows some sign of concurrence with this theory. They are 4 individuals in this cross-tabulation of which 3 have the lowest risk haplotype. Table 9 depicts the cross-tabulation of HLA versus BMI percentile, here also, our data shows some accordance with the theoretical belief. There are 4 individuals with the lowest risk haplotypes, and none of the 4 are under the 25th percentile at onset.

Table 8. Cross tabulation depicting the relationship between positive antibodies and HLA.

	HLA			
	ASP	Non-ASP	Non-ASP/0602	**Total**
Positive Antibodies				
0	3	32	1	36
1	1	40	1	42
2	0	35	3	35
Total	4	107	2	113

Table 9. Cross tabulation depicting the relationship between HLA and BMI.

BMI				
	Under 25th percentile	25th - 85th percentile	Over 85th percentile	**Total**
HLA				
ASP	0	2	2	4
Non-ASP	32	47	28	107
Non-ASP/0602	1	1	0	2
Total	33	50	30	113

4.0 DISCUSSION

We started the analysis with a larger range of predictors; these predictors were lipids, systolic and diastolic blood pressure, C-peptide, age, race, HLA-DQ, gender, waist circumference, antibodies and HbA1c. Lipids and blood pressures showed no evidence of an association with BMI percentile; this is true in the univariate and in the multivariate models. As stated earlier, no evidence was found of an association between antibodies and BMI; however an explanation might be the fact that we had only 120 subjects (38%) who had an antibody measurement. Waist circumference was quite interesting, in the fact that we found an association with BMI percentile. The addition of waist circumference did not change the effects of other predictors in the model as described in section (3.1.3), the subjects that are at least in the 75th percentile had the greatest change in BMI and the highest BMI percentile at 3 months. However, due to sparse waist circumference data, only 53% had a value for waist, the waist predictor was not included in the final model. Similarly, there was no association with the HLA haplotype (only 10 had ASP haplotypes) with BMI.

Although age at onset is positively correlated with BMI at 3 months, after adjusting for BMI at onset or C-peptide along with the other covariates in the model, the effect of age is negative. Hence younger subjects are associated with a higher BMI at 3 months. This was verified by fitting all of the models on the subgroup with non-missing data for all the predictors.

5.0 CONCLUSION

No definitive statement could be made about the relationship of positive antibodies and BMI. Our data set only had two of the four antibodies that are suspected to be related to diabetes, and of the two antibodies, we had 120 out of 315 (38%) subjects who had antibody analysis. One of the current beliefs is that individuals with the lower risk HLA haplotypes (ASP) should have the lowest frequency of antibodies and highest BMI. However inconclusive; our data is consistent with this belief.

We have seen that a younger age, male gender, higher HbA1c is associated with the highest BMI percentile at 3 months and also with the highest degree of change in BMI percentile from onset to 3 months. Future research should provide a more definitive statement about the relationship of antibodies, BMI and diabetes.

APPENDIX: TABLES

Table 1A. Regression Coefficients from study of blood pressure.

Variable	Regression Equation Symbol	Systolic BP		Diastolic BP	
		Male	Female	Male	Female
Intercept	α	102.20	102.01	61.01	60.51
Age					
Age-10	β_1	1.82	1.94	0.68	1.01
$(Age-10)^2$	β_2	0.13	0.01	-0.10	0.01
$(Age-10)^3$	β_3	0.00	-0.01	0.02	0.00
$(Age-10)^4$	β_4	0.00	0.00	0.00	0.00
Normalized Height					
Zht	γ_1	2.73	2.04	1.47	1.17
Zht^2	γ_2	-0.20	0.03	-0.08	0.13
Zht^3	γ_3	-0.05	-0.02	-0.03	-0.04
Zht^4	γ_4	0.01	0.00	0.01	0.00
Standard Deviation	σ	10.71	10.49	11.60	10.96
ρ^*		0.41	0.38	0.24	0.26
n(persons)		32161.00	31066.00	24057.00	23443.00
n(visits)		42074.00	41017.00	29182.00	28794.00

Table 1B. Waist Percentiles for European American Boys

	10th	25th	50th	75th	85th	90th
Intercept	39.3	43.18	42.94	43.3	43.3727	43.83
Slope	1.8	1.86	2.08	2.63	3.1091	3.39
Age	10th	25th	50th	75th	85th	90th
2	42.9	46.9	47.1	48.56	49.5909	50.61
3	44.7	48.76	49.18	51.19	52.7	54
4	46.5	50.62	51.26	53.82	55.8091	57.39
5	48.3	52.48	53.34	56.45	58.9182	60.78
6	50.1	54.34	55.42	59.08	62.0273	64.17
7	51.9	56.2	57.5	61.71	65.1364	67.56
8	53.7	58.06	59.58	64.34	68.2455	70.95
9	55.5	59.92	61.66	66.97	71.3546	74.34
10	57.3	61.78	63.74	69.6	74.4637	77.73
11	59.1	63.64	65.82	72.23	77.5728	81.12
12	60.9	65.5	67.9	74.86	80.6819	84.51
13	62.7	67.36	69.98	77.49	83.791	87.9
14	64.5	69.22	72.06	80.12	86.9001	91.29
15	66.3	71.08	74.14	82.75	90.0092	94.68
16	68.1	72.94	76.22	85.38	93.1183	98.07
17	69.9	74.8	78.3	88.01	96.2274	101.46
18	71.7	76.66	80.38	90.64	99.3365	104.85

Table 1C. Waist Percentiles European American Girls

	10th	25th	50th	75th	85th	90th
Intercept	39.88	41.76	43.64	45	45.4201	46.75
Slope	1.6	1.68	1.89	2.3	2.69	2.87
Age	10th	25th	50th	75th	85th	90th
2	43.08	45.12	47.42	49.6	50.8001	52.49
3	44.68	46.8	49.31	51.9	53.4901	55.36
4	46.28	48.48	51.2	54.2	56.1801	58.23
5	47.88	50.16	53.09	56.5	58.8701	61.1
6	49.48	51.84	54.98	58.8	61.5601	63.97
7	51.08	53.52	56.87	61.1	64.2501	66.84
8	52.68	55.2	58.76	63.4	66.9401	69.71
9	54.28	56.88	60.65	65.7	69.6301	72.58
10	55.88	58.56	62.54	68	72.3201	75.45
11	57.48	60.24	64.43	70.3	75.0101	78.32
12	59.08	61.92	66.32	72.6	77.7001	81.19
13	60.68	63.6	68.21	74.9	80.3901	84.06
14	62.28	65.28	70.1	77.2	83.0801	86.93
15	63.88	66.96	71.99	79.5	85.7701	89.8
16	65.48	68.64	73.88	81.8	88.4601	92.67
17	67.08	70.32	75.77	84.1	91.1501	95.54
18	68.68	72	77.66	86.4	93.8401	98.41

Table 1D. Waist Percentiles African American Boys

	10th	25th	50th	75th	85th	90th
Intercept	40.1	41.23	42.69	44.1	44.4782	43.58
Slope	1.55	1.69	1.86	2.2	2.5719	3.21

Age	10th	25th	50th	75th	85th	90th
2	43.2	44.61	46.41	48.5	49.622	50
3	44.75	46.3	48.27	50.7	52.1939	53.21
4	46.3	47.99	50.13	52.9	54.7658	56.42
5	47.85	49.68	51.99	55.1	57.3377	59.63
6	49.4	51.37	53.85	57.3	59.9096	62.84
7	50.95	53.06	55.71	59.5	62.4815	66.05
8	52.5	54.75	57.57	61.7	65.0534	69.26
9	54.05	56.44	59.43	63.9	67.6253	72.47
10	55.6	58.13	61.29	66.1	70.1972	75.68
11	57.15	59.82	63.15	68.3	72.7691	78.89
12	58.7	61.51	65.01	70.5	75.341	82.1
13	60.25	63.2	66.87	72.7	77.9129	85.31
14	61.8	64.89	68.73	74.9	80.4848	88.52
15	63.35	66.58	70.59	77.1	83.0567	91.73
16	64.9	68.27	72.45	79.3	85.6286	94.94
17	66.45	69.96	74.31	81.5	88.2005	98.15
18	68	71.65	76.17	83.7	90.7724	101.36

Table 1E. Waist Percentiles African American Girls

	10th	25th	50th	75th	85th	90th
Intercept	39.87	41.18	41.69	42.1	42.54	42.75
Slope	1.56	1.71	2.13	2.82	3.33	3.675

Age	10th	25th	50th	75th	85th	90th
2	42.99	44.6	45.95	47.74	49.2	50.1
3	44.55	46.31	48.08	50.56	52.53	53.775
4	46.11	48.02	50.21	53.38	55.86	57.45
5	47.67	49.73	52.34	56.2	59.19	61.125
6	49.23	51.44	54.47	59.02	62.52	64.8
7	50.79	53.15	56.6	61.84	65.85	68.475
8	52.35	54.86	58.73	64.66	69.18	72.15
9	53.91	56.57	60.86	67.48	72.51	75.825
10	55.47	58.28	62.99	70.3	75.84	79.5
11	57.03	59.99	65.12	73.12	79.17	83.175
12	58.59	61.7	67.25	75.94	82.5	86.85
13	60.15	63.41	69.38	78.76	85.83	90.525
14	61.71	65.12	71.51	81.58	89.16	94.2
15	63.27	66.83	73.64	84.4	92.49	97.875
16	64.83	68.54	75.77	87.22	95.82	101.55
17	66.39	70.25	77.9	90.04	99.15	105.225
18	67.95	71.96	80.03	92.86	102.48	108.9

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