South American Journal of Medicine
Volume 3, Issue 2, 2015

Trisomy 21 and Diabetes: Assessing the Risk of Diabetes in Persons with Down's Syndrome < 20 Years in Special Schools in Guyana

Article by [1]Boston C, [1]Cummings E, [1]McKenzie M, [1]Aaron R, [2]Singh J, and [3]Adeghate E
School of Medicine, Faculty of Health Sciences, University of Guyana[1], School of Forensic and Investigative Sciences and School of Pharmacy and Biomedical Sciences, University of Central Lancashire, Preston, Lancashire, UK[2] and United Arab Emirates University, Al Ain, UAE[3]
Email:- emanuelcummings98@yahoo.com

Abstract

There is correlation between Down syndrome and Type 1 Diabetes (T1DM). Many researchers have fuelled this concept by chromosomal analysis, anatomical and physiological analysis aand has provided support by assessing the prevalence of diabetes mellitus (DM) in persons with Down Syndrome. The objective of this study was to provide information of the risk of DM in persons under the age of 20 years with Down Syndrome and the awareness of caregivers (parents/guardians and teachers) of Down syndrome children on the potential development of T1DM in those children. The study was conducted with the use of two groups involving children with Down Syndrome and their caregivers. Questionnaires were distributed to the caregivers and a rrandom blood glucose analysis was performed on the children using the glucose oxidase method. The results show that 38% of Down syndrome children were at risk of becoming diabetic having blood glucose levels above 140mg/dl. The mean blood glucose in this study was 141.2mg/dl. Children 6-10 years had the highest mean blood glucose levels (143 mg/dl). Males had greater proportion (14%) of very high blood glucose as compared to females (4%). Children whose parents/guardians answered yes to monitoring their diet had a high blood glucose level mirroring those that were not monitored. Caregivers were also not aware of the predisposition to diabetes. The results have indicated that the situation requires attention from parents, the schools and the Ministry of Health and Education in Guyana and in turn they have to address this problem as soon as a child is born and diagnosed with Down syndrome so as to combat the potential situation from the inception.

Word for index: *Trisomy- 21, Down syndrome, Glucose, Children, Guyana, Type 1 diabetes mellitus.*

Introduction

There is correlation between Down syndrome and Type 1 Diabetes (T1DM). Many researchers have fuelled this concept by chromosomal analysis [1, 2] and provided support by assessing the prevalence of Type I diabetes Mellitus (DM) in persons with Down syndrome. Research on this phenomenon in the population in Guyana is yet to be done. This research aims to provide information on the risk of DM in persons with Down syndrome, less than 20 years old and also provide information about awareness of caregivers (parents/guardians and teachers) of Down syndrome children on the potential development of T1DM in those children.

The Down syndrome phenotype is expressed if there is a Trisomy at chromosome 21[3-5], with 95% of Trisomy's 21 traced to non-disjunction during meiosis in the mother [3]. Research implicating men in the development of Trisomy 21 is insufficient. The chances of a woman producing a child with Down syndrome increases with age. The likelihood of women of Tanner stage V producing a child with Down Syndrome is 0.05% and this increases gradually with maturation to 3% by the age of 45 [3]. Some geneticists hypothesize that the probability of

Trisomy 21 occurrence is directly proportionate to the time an oocyte remains in the ovary and this may explain why older women are at higher risk [3]

The health complications associated with Down Syndrome are numerous including heart defects, leukemia, infectious diseases, dementia, sleep apnea, obesity and diabetes [6]. In 1929, children with Down syndrome rarely lived 10 years or more compared to today when the life expectance of persons with Down syndrome has increased to age 50 years with modern medicine.

Information on the Down Syndrome population in Guyana is lacking. There is no published data on the percentage of the Down Syndrome persons in the population. The prevalence of diseases within the Down Syndrome population, including rate of co-existence of DM and Down Syndrome is also lacking. This leads to a lack of awareness and corrective practices by persons with Downs Syndrome and their caregivers. Evidence of ill-practice is demonstrated in public schools that facilitate Down Syndrome children. The national school feeding programme provides cookies and fruit juice for the pupils every day. It is noteworthy that this snack which is served daily to the pupils consist of 5 cookies which consist of 10 grams of carbohydrate and a 200 ml box of juice contains 23 grams of carbohydrates , equivalent to 25% of carbohydrate a diabetic persons are allowed daily. Considering the three larger meals to be consumed in a day, the sugar intake of diabetic children is not being monitored. This can be attributed to the lack of information made available to caregivers of Down syndrome children.

Research on Down Syndrome has already commenced in many parts of the world, mostly in the United Kingdom. Many authors have presented constructs to be patterned to further the range of information on this topic. Down Syndrome is associated with many autoimmune and metabolic defects [7, 8]. Hozyasz and colleagues reported a triad of defects in Down's syndrome. This triad comprises of coeliac disease, Insulin Dependent Diabetes Mellitus (IDDM) and hhypothyroidism. This notion is supported by Hoorn, Vogel and Zietse's case study of an 18 year old girl with Down syndrome who was diagnosed with hypothyroidism as well as Insulin Resistant Diabetes (IRD). Anwar and colleagues in their article *Type 1 Diabetes Mellitus and Down 's syndrome: Prevalence, Management and Diabetic Complications* suggested that 38% of persons with Down's syndrome may have hypothyroidism. Badiu further adds in *Autoimmunity puzzle in Down Syndrome* that Coeliac disease may even contribute to Diabetes, if undetected and untreated, due to the exposure to gluten and the inability to metabolize it. Hypothyroidism may also lead to obesity which may then lead to IRD. Fonseca and colleagues explain in their article *Insulin resistance in adolescents with Down Syndrome: a cross sectional study* that Down's syndrome persons are prone to hypotonacity; this creates a domino effect by leading to accumulation of fat as a compensatory mechanism which increases the risk of developing IRD.

Confirmative research is yet to be done on Trisomy 21's involvement in the existence of multiple health complication; it is only speculated based on the high prevalence in persons with Down's syndrome who are plagued with diseases.

Several studies have unanimously suggested that the age of onset of Diabetes is younger in persons with Down's syndrome than in the normal population. Most researchers conducted their studies on subjects under 20 years old. In Fonseca's found the average of persons with Down syndrome was 13 years;. Bergholdt's, reported, the age of onset for diabetes was 6 years. Other researchers such as Hozyasz suggests an age range of 2-19 years of age while Chistiakov suggested 7-8 years, and he further states that 22% of Down syndrome children with diabetes are diagnosed at this age compared to 7% of normal children. Additionally, Rohrer's suggested that 19% of persons with Down's syndrome and diabetes were diagnosed before age 4, while only 6.4% of the normal population was diagnosed at this age. Shields reported that 22% Type 1 Diabetes mellitus in children with Down syndrome of with are diagnosed before age 2. Jeremiah's found 2 % of glycosuria in children 0-15 years old with Down's syndrome to be 2% meaning that the diabetic condition may have occurred earlier.es

Many Studies have indicated varied national prevalence of Type 1 diabetes among children with Down syndrome, these figures varies between 0.05% (Van Goor et al) and 10.6% (Chistiakov). Chistiakov further reported that in these findings 0.1% of the normal population were diabetic. Van Goor's small prevalence may be attributed to the narrowed age range sample population; his study included only children within 0-14 years of age. This prevalence may be obsolete for other age groups; however, Van Goor stated that premature aging and deaths in Down syndrome may be a contributing factor to the low prevalence. Chistiakov's indicated that the prevalence may be higher than various because it encompasses a range from other research. Anwar, Bergholdt and Shield reported a prevalence of 0.18, 0.38 and 5.5 respectively. As different as these figures may be they all are significant in comparison to the prevalence of Diabetes in the normal population which is 4 to 8 times less [9], Shield indicated that it is 10 times greater in children with Down's syndrome. It is extremely clear that persons with Down' syndrome are more prone to Diabetes based on prevalence.

The most common signs and symptoms associated with diabetes are polydipsia and polyuria. These symptoms are caused by the effect of diabetes on the body. If the level of glucose in the blood becomes too high, excess glucose is removed from the blood by the kidneys and excreted via the urine (glycosuria). This results in greater urine production and causes the patient to urinate frequently. Water held in the cells is required to replace lost blood volume, and thus causes dehydration and thirst [10]. Ketoacidosis occurs when the body cannot use glucose as a fuel source because there is no insulin or not enough insulin. Fat is used for fuel instead. Byproducts of fat breakdown, called ketones, build up in the body. [11] These symptoms are frequently used in the assessment of Diabetes. Rohrer's analysis of metabolic status and glycaemic control has revealed that ketoacidosis accompanied persons with biomarkers for Diabetes. Van Goor indicated that more attention must be paid to the symptoms of polydipsia and polyuria in order to promptly detect diabetes and prevent implications such as hyperosmolar coma. This notion is supported in Hoorn's presentation of an 18 year old with Down's syndrome and Diabetes who was experiencing with polyuria and polydipsia; this patient was in a diabetic coma at the time of the case study. Hozyasz and colleagues suspected Diabetes in the subject of their case study for he presented with the previous symptoms, strengthening its importance in diabetes analysis. It is suggested by Chistiakov that polyuria, polydipsia and ketoacidosis be closely monitored in diabetic patients.

After detecting the signs and symptoms of Diabetes, clinical confirmation is done by assessing glucose levels in serum and urine, HbA1c, autoantibody presence and other biomarkers (glucose and HbA1c being the most common). Jeremiah conducted research on this topic using clinitest and bililabstix to detect glucosuria. He and his colleagues divided subjects into age groups to determine the prevalence of glucosuria in these groups. Their findings indicated that 0.75% of children below 4, 2% of 5-14 and 2% above 25, who had Down syndrome, also had glucosuria. It was noted that in the age group 0-15 years the mean level of glucosuria was 1.4%, only 0.6% less than the adult category further indicating early onset. In the case study of Badiu and colleagues a 21 year old had serum glucose of 221.7 mg/dl. Not mentioning the subjects fed state, this level is beyond the border for established diabetes. [12] HbA1c is considered the most accurate way of diabetes measurement and control. Badiu's subject also had an HbA1c level of 10.3%, indicative of poorly controlled diabetes. After treatment the patient's HbA1c level was still poorly controlled at 9.3% indicating insulin resistance (reference ranges from Med India's Diabetes control chart). Anwar's reported that HbA1c for both Down's syndrome and non Down's syndrome persons were well controlled, however, persons with Down's syndrome had 0.3% higher than the normal group (HbA1c level: Down's syndrome 7.8%, normal persons 7.5%.).

Detection of biomarkers such as GAD, 1A and 2A are more advanced for the diagnosis of Diabetes. Rohrer and colleagues found 43 of 56 Down syndrome persons with diabetes to have at

least 1 autoantibody to beta islets, indicative of autoimmune diabetes. These subjects had no family history of diabetes. In Gillespies study on islet autoimmunity it was found that 15% of children with Down's syndrome and diabetes were positive for biomarkers to diabetes; the normal population only had 6%. Fonseca introduces a method to assessing diabetes, this involves the use of the homeostatic model assessment (HOMA), it is a method of measuring insulin resistance using the formula [glucose (mg/dl) X insulin (μU/ml)] / 405]. HOMA increases with BMI, persons in the study who were of normal weight had an average measurement of 1.3, obese persons were 3.3. BMI influences the development of diabetes in both Down's syndrome as well as normal people. Studies of Rohrer and Van Goor reveal that persons with Down syndrome have a higher mean BMI than normal citizens.

The prevalence of Guyana Down syndrome population is unknown, making it difficult to assess and compare the prevalence of diabetes in this population to the normal population.

This research was aimed at determining if there is a risk of Diabetes in children with Down syndrome in special schools in Guyana. Its secondary aim was to assess the knowledge of care-givers on the potential risks of diabetes developing in children with Down syndrome.

In a nation where information on the clinical dispositions of Down syndrome is lacking this research was extremely necessary. It provides data on the risk of Diabetes occurring in persons under 20 years old with Down syndrome who are currently enrolled in public special schools in Guyana. Further, it assessed the knowledge of care-givers on the health risks and dietary needs of these children. This research provides information that may influence a change in the procedures of the Ministry of Education on mandatory medical examinations (which currently does not include blood glucose analysis) and school feeding programs by highlighting the special needs of children in schools for the intellectually impaired.

Methodology

Description of the Subjects: This study encompassed two groups of persons; persons with Down syndrome who are < 20 years old and their care givers (teachers and parents/guardians). The setting used for obtaining data was special schools in Guyana that facilitated intellectually impaired students; it was selected because of the policy by the Ministry of Education that allows persons with mental disabilities to access public education until age 21. Blood glucose of all Down syndrome students enrolled in the schools were assessed as well as the knowledge of their caregivers. There are approximately three public schools that facilitate intellectually impaired students in Guyana and these schools each have approximately 15 students with Down syndrome. Obtaining information from these subjects was done after consent was granted from caregivers and the governing bodies of those schools.

Inclusion Criteria: Individuals who have been identified as having Down syndrome in special schools. Caregivers (Parents/guardians and teachers) who care for Down syndrome children

Exclusion Criteria: Individuals who do not have Down syndrome and who are not caregivers (parents/guardians and teacher) of children with Down syndrome.

Research Design: This research encompassed both quantitative and qualitative methods of analysis. In this cross-sectional study, the random blood glucose levels in persons with Down syndrome and the knowledge of their care-givers (parents/guardians and teachers) were simultaneously assessed. With the use of questionnaires, this research ascertained the level of knowledge possessed by caregivers (teachers and parent/guardians) about the health risks involved with Down syndrome and the dietary requirements of children with Down syndrome to prevent the development of diabetes.

Variables: *Students with Down syndrome*: Independent variable was Down syndrome children enrolled in the public special schools--- children who were diagnosed as having Down syndrome

Dependent variable was blood glucose levels—whether the random blood glucose level of these children are high, borderline or low

Both variables will provide quantifiable information about the predisposition that Down syndrome gives to Diabetes.

Care givers of children with Down's syndrome: Independent variable was the parent's knowledge about the predisposition Down syndrome has to diabetes

Dependent variable was the dietary constituents given to the child/children with Down syndrome in their care. These variables were both qualitative, aimed at unraveling the practices of both parents/guardians and teachers and children that may influence the development of Diabetes.

Method of Measuring Each Variable: A random blood sugar test was performed on children with Down syndrome using the Glucose Oxidase method. The collection of the intravenous blood samples was done by a certified phlebotomist, under strict international regulation, using a 22 gauge needle. The left hand was used to obtain the blood sample. Sample was coded for traceability and no names were assigned, analysis was done at the Georgetown Public Hospital Cooperation (GPHC).

Simultaneously, caregivers (teachers and parents/guardians) were issued questionnaires to assess their level of knowledge and practices in regard to Diabetes and Down's syndrome. Level of knowledge was categorized as good, fair and poor based on responses.

Data Analysis: The Data was analyzed using SPSS statistical package and Epi info and was tabulated to obtain information on the risk factors of diabetes existing among children with Down syndrome and identify trends and variables. The findings will be analyzed using WHO's standard for measuring blood glucose. See Table 1 below

Table 1 Reference ranges for Random Blood Glucose Test

Normal	70-140 mg/dl
Prediabetes	140 -180 mg/dl
Diabetes	>180 mg/dl

Charts and grafts displayed correlations of dietary practices and blood glucose levels.

Research Ethics: Permission to conduct this research was requested by the governing bodies of the schools, the Ministry of Health, Ethical Review Board and the Ministry of Education. Once granted they were assured confidentiality and privacy of the children and caregivers involved. In addition, caregiver (parent/guardian and teacher) had to read and sign a consent form prior to their participation and were made aware of the voluntary nature of the study and their right to discontinue participation at any point of the study. No names were published in this paper. A parent or teacher was asked to be present to witness the sample collection and was enlightened on the procedure before it was conducted.

Results and Discussion

Demographics and Distribution

Currently, in Guyana, there is no information available on the prevalence of Diabetes co-existing with Down syndrome. This research encompassed 2 of 3 public special schools in Guyana located in the county of Berbice and Demerara which give a total of 45 students participating in this study. From this research it was observed that 38% of Children with Down syndrome in public special schools are at risk of becoming Diabetic by having a random blood glucose level that exceeds 140mg/dl. The mean blood sugar of the sample was 141.2mg/dl, this exceeds the maximum value in the normal range of blood glucose for normal persons. The

distribution of blood glucose levels suggests that persons with Down syndrome are prone to higher levels of blood glucose as seen in figure 1 and figure 2

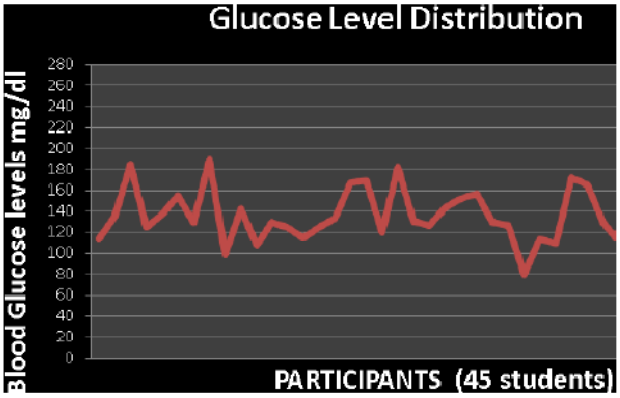

Figure 1: Glucose level Distribution of all participants in the study

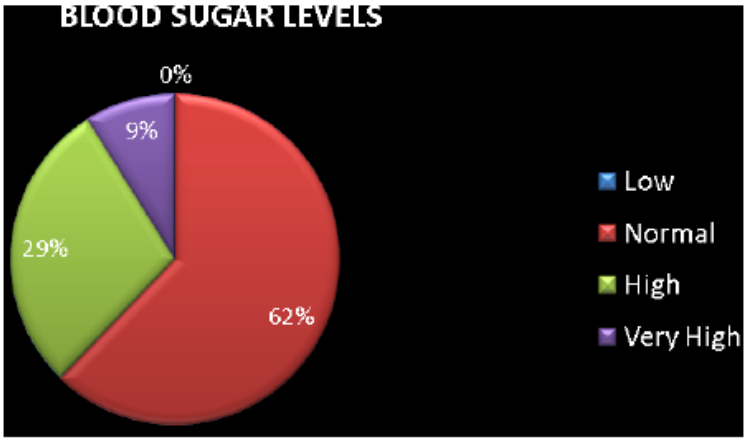

Figure2: Pie chart of Ratios of Blood Glucose Levels in Categories of low to very high

Early Onset

The data collected during this research shows an early onset of 6-10 years for the development of high blood glucose. The mean blood sugar in the 6-10 years age range is 143mg/dl this supersedes the mean blood glucose of the entire sample population. In the 11-15 age range the mean blood glucose was approximately 140mg/dl. Another peak was observed in the >15 age range who's average blood glucose level was parallel to the 6-10 age group as seen in figure 6. Comparison of the blood glucose level on the different age ranges does not suggest that any age group is less prone to developing high blood glucose levels for they all exist with ± 2mg/dl of the mean.

Early onset of Diabetes in persons with Down syndrome was described by many authors. The age range (6-10) in this study which has high blood sugar levels coincides with a study done by Bergholdt and Chistiakov which collectively suggested 6-8 years as the onset of diabetes in children with Down syndrome. Anwar 1998 stated that the life expectancy of persons with Down syndrome is increasing allowing more time for the manifestation of Diabetes. Data collected during this research suggest the possibility of early manifestation of this disease within this population. See figure 3

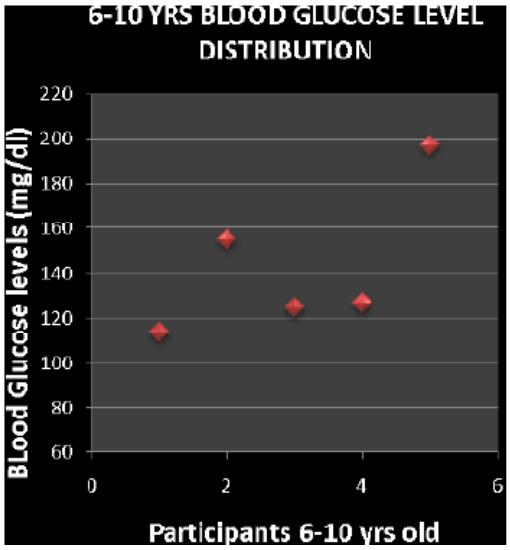

Figure 3: Chart showing participants 6-10 years blood glucose distribution

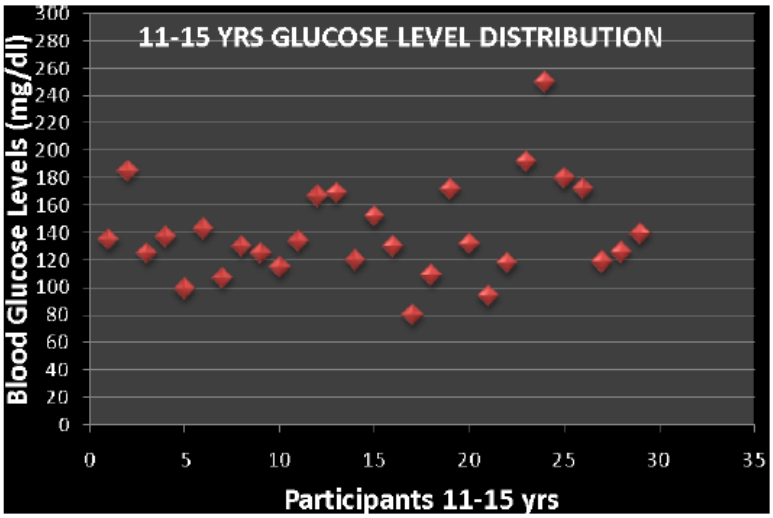

Figure 4: Chart showing blood glucose levels in children 11-15 years

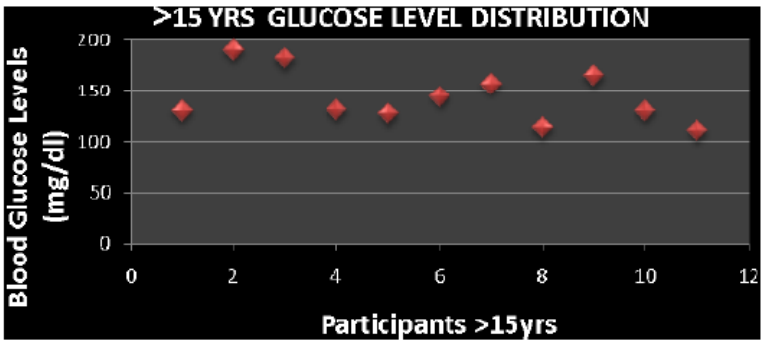

Figure 5: Chart showing blood glucose levels in children >15 years

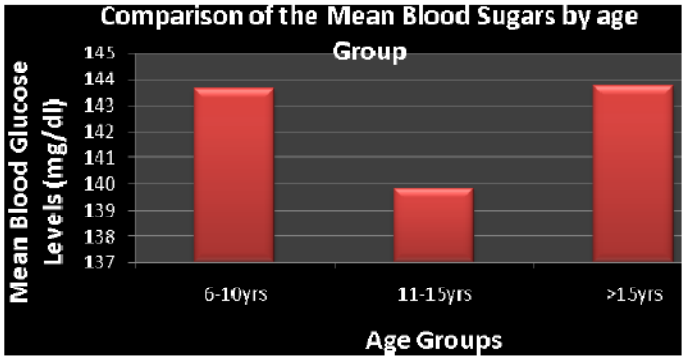

Figure 6: Chart showing comparison among the mean blood glucose levels among the three age groups

Involuntary Influencing Factors

Gender was an influential factor in the level of blood glucose during this research as it was seen that males had greater proportion (14%) of very high blood glucose. Lifestyle differences could not be determined in this research that may justify the difference between male and female blood glucose levels. No published information suggests a correlation between trisomy 21 and Y chromosome leading to increased prevalence of Diabetes.

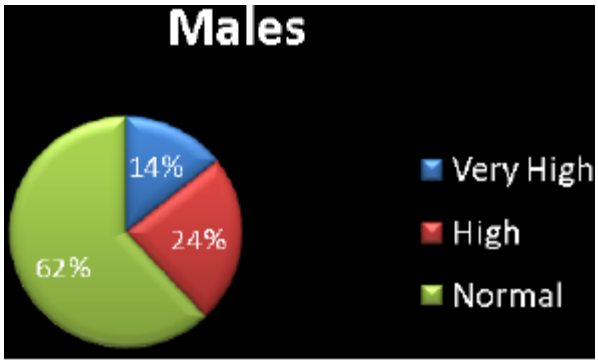

Figure 6

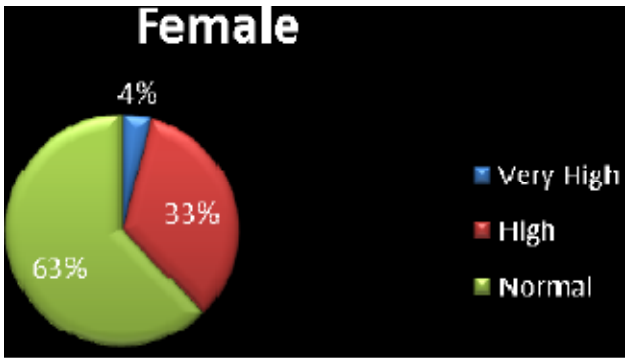

Figure 7

Categories of Blood Glucose levels for Males Categories of Blood Glucose level for Females

Voluntary Influencing Factors

A major contributing factor in the manifestation of Diabetes is diet. The care givers of Down syndrome children were not aware that this population was predisposed to diabetes. 100% responded no to the question “Are you aware that Down syndrome may be a predisposition to

Diabetes?" Most Care Givers answered "YES" to Healthy habits including, exercise and monitoring of diet, however the mean blood glucose of the children whose diets are supposedly monitored by care givers monitored were parallel to that of children whose parents responded no to monitoring their diets, 142mg/dl and 141mg/dl respectively. If the participant's answers were accurate, this may suggest that diet is not the determining factor in the blood glucose of Down syndrome children. This could be refuted however after examination of the components of the diet provided to the children by their caregivers. Of respondents that monitor their children diets 97% indicated that their children ate fried meats at least once a week, 85% indicated the consumption of soda at least once a week, 91% fed their children high carbohydrate foods at least once a week and government biscuits and beverages were consumed 5 days a week by 100% of the children in this study. 53% of care givers stated that diabetes was not a trend in their families. This information further fuels the theory that Trisomy 21 may be a predisposition to diabetes.

Implication of Research

The blood glucose levels of Down syndrome children in ppublic special schools in Guyana are high enough to indicate pre-diabetes in >33% of the population. It is high enough for community concern. Care givers of Down Syndrome children are not aware of the risks and predispositions that Trisomy 21 may have upon their children's metabolism especially as it relates to diabetes. Even though there was a high indication of diets being monitored by the care givers, the specifics about the diets contradicts this monitoring.

The probability of a Down syndrome child in Guyana developing Diabetes is 0.38. The risk is high and may be attributed to many factors including Genetic predisposition as well as the diet of children with Down syndrome which are not being modified enough to ensure good health and longevity.

Awareness about the health complication of Down syndrome children, including diabetes, should be promoted. A requirement for entry into public special schools is a diagnosis of an intellectual impairment and syndromes. During the diagnosis, blood glucose analysis should be performed and documented so that school may efficiently participate in the monitoring of diets during school hours. The Ministry of Health should employ effective health promotion and education of parents/guardians which should begin just after delivery and further continued at the clinics where the parents/guardians attend to get the child's check-ups. Likewise, in the special schools that these children attend a collaborative effort between the Ministry of Health and the Ministry of Education should be done to further strengthen the knowledge of parents/guardians and teachers who are caring for these children. A monitoring process should also be instituted so as to detect early predisposition to diabetes so it can be addressed at first sight.

References

[1]. *Increased prevalence of Down's syndrome in individuals with type.* **Bergholdt, R, et al.** 6, Denmark : Springer-Verlag, 2006, Vol. 49.

[2]. *A Human Type 1 Diabetes Susceptibility Locus Maps to Chromosome 21q22.3.* **Concannon, Patrick, Onengut-Gumuscu, Suna and Todd, John A.** NA, Australia : DIABETES, 2008, Vol. 57. NA.

[3]. **Karp, Gerald.** *Cell and Molecular Biology Concepts and Experiments.* New York : John Wiley and Sons Inc, 2003. ISBN 0-471-26890-9.

[4]. **Read, Andrew and Donnai, Dian.** *New Clinical Genetics.* Manchester UK : Scion Publishing Limited, 2007. ISBN 1-904842-31-6.

[5]. **Klug, William S and Cummings, Michael R.** *Concepts of Genetics 6th ed.* New Jersey : Prentice-Hall, 2000. ISBN 0-13-0816-26-4.

[6]. Down syndrome. *Mayo Clinic.* [Online] Mayo Foundation for Medical Education and Research, April 7, 2011. [Cited: January 10, 2012.] http://www.mayoclinic.com/health/down-syndrome/DS00182/DSECTION=complications.

[7]. **Hozyasz, Kamil K, Pyrzak, Beata and Szymanska, Marta.** The coexistence of Down syndrome and a triad consisting of: coeliac disease, insulin dependent diabetes mellitus and congenital hypothyroidism. *Down Syndrome Education Online.* [Online] April 2010. [Cited: January 9, 2012.] http://www.down-syndrome.org/case-studies/2062/.
[8]. **Badiu, Corin, et al.** Autoimmunity Puzzle in Down Syndrome. *Down Syndrome Education Online.* [Online] January 2010. [Cited: January 9, 2012.] http://www.down-syndrome.org/case-studies/2138/.
[9]. **VAN GOOR, J C and MASSA, G G.** Increased incidence and prevalence of diabetes mellitus in Down's syndrome. *Archives of Disease in Childhood.* [Online] BMJ Publishing Group Ltd & Royal College of Paediatrics and Child Health, NA NA, 1997. [Cited: JANUARY 9, 2012.] http://adc.bmj.com/content/77/2/183.14.full. ISSN 14682044.
[10]. Diabetes Signs: The Big 3 signs. *Diabetes.co.uk.* [Online] The Global Diabetes community, January 2012. [Cited: 01 27, 2012.] http://www.diabetes.co.uk/The-big-three-diabetes-signs-and-symptoms.html.
[11]. Diabetic Ketoacidosis. *PubMed Health.* [Online] A.D.A.M Medical Encyclopedia, June 28, 2011. [Cited: January 27, 2012.] http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0001363/.
[12]. Health Calculators. *Med India.* [Online] Med India Network for health, NA NA, NA. [Cited: January 27, 2012.] http://www.medindia.net/patients/calculators/bloodsugar_chart.asp.
[13]. *Type 1 diabetes and other autoimmune disorders in Down's syndrome.* **Sheild, Julian.** NA, London UK : University of Bristol, 2001, Vol. NA. NA.
[14]. *Down's syndrome in diabetic patients aged <20 years:an analysis of metabolic status, glycaemic control and autoimmunity in comparison with type 1 diabetes.* **Rohrer, T R, et al.** 6, Germany : Springer-Verlag, 2010, Vol. 53. ISSN 00125-010-1686-z.
[15]. *Obesity in adults with Down syndrome:a case–control study.* **Melville, C A, et al.** 2, Leicester UK : Journal of Intellectual Disability Research, 2005, Vol. 49. doi: 10.1111/j.1365-2788.2004.00616.x.
[16]. *Down's syndrome and diabetes.* **JEREMIAH, D E, et al.** 4, Wakefield : Cambridge University Press , 2009, Vol. 3. ISSN 0033291700054258 .
[17]. *Insulin resistance in an 18-year-old patient with Down Syndrome presenting with hyperglycaemic coma,hypernatraemia and rhabdomyolysis.* **Hoorn, E J, De Vogel, S and Zietse, R.** 3, The Netherlands : Blackwell Publishing Ltd , 2005, Vol. 283.
[18]. *Islet Autoimmunity in Children With Down's Syndrome.* **Gillespie, , Kathleen M, et al.** 11, UK : Diabetes , 2006, Vol. 55.
[19]. *Insulin resistance in adolescents with Down syndrome: a cross-sectional study.* **Fonseca, Cristina T, Amaral, Daniela M and Márcia, G.** 6, UK : Biomed Central, 2005, Vol. 5. doi:10.1186/1472-6823-5-6.
[20]. *Down syndrome and coexistent autoimmune diseases.* **Chistiakov, Dimitry.** 2, Pittsburgh : University of South Bohemia , 2007, Vol. 5. ISSN 1214-0287.
[21]. *Type 1 Diabetes Mellitus and Down's Syndrome: Prevalence, Management and Diabetic Complications.* **Anwar, A J, Walker, J D and Frier, B M.** 2, Edinburgh UK : Diabetic Medicine, 2004, Vol. 15. DOI: 10.1002/(SICI)1096-9136(199802)15:2<160::AID-DIA537>3.0.CO;2-J.
[22]. **Burtis, Carla, Ashwood, Edward R and Bruns, David.***Tietz Text Book of Clinical Chemistry and Molecular Diagnostics 4th ed.* Missouri USA : Eslevier Saunders, 2006. ISBN 0-7216-0189-8.