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Research Article

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HbA1c Level at the Time of Diagnosis of Type I Diabetes Mellitus: A Retrospective Study

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ABSTRACT

Diabetes Mellitus (DM) is the most common metabolic disease occurs during childhood and its incidence varies between different communities and nationalities at an increased rate of global prevalence. HbA1c level in high-risk patients with Type II diabetes mellitus allows early diagnosis and management of diabetes and delaying long - term complication of diabetes. This study was conducted to highlight the importance of HbA1c as a confirmatory test for diagnosing Type I diabetes in children. 844 diabetic children and adolescent participated in this study. The present study also examined HbA1c level at the time of diagnosing DM and its relation to parameters, including age, sex, duration of diabetic symptoms, parents' educational level, and mode of presentation. The mean age of the study group was 8.9 ± 4.4 years; 47.9% were females and 52.1% were males in which. 98% of them were Libyan. 63% of the patients had family history of diabetes mellitus either Type I or II. 26.8% of the patients were presented with ketosis while 78.8% of others had classical diabetic symptoms. 95.6% of the target patients had duration of 1-3 weeks signs and symptoms before presentation.

95.6% of the patients had HbA1c >6% at time of diagnosis with a mean of 11.2% for all age groups of P value (0.000), which is statistically significant. The study concludes that HbA1c is significantly raised at the time of diagnosis of diabetes mellitus and it can be used as a diagnostic test as well as a test of glycemic control for diabetic patients. Moreover, HbA1c can be used to identify children who are at risk to develop DM either Type I or II.

Keywords - *Diabetes Mellitus; HbA1c; Glycemic control.*

INTRODUCTION

Diabetes Mellitus is the most common metabolic disease in childhood and its incidence varies between different communities and nationalities. The incidence of DM-type I is increasing worldwide. The estimated prevalence in childhood is around 2 million individuals in the western world.[1-3] The estimated annual incidence is 15 new cases per 100,000 in children less than 18 years of age; the prevalence of DM increases with increasing age. Recent estimates indicate there were 171 million people in the world with diabetes in the year

2000 and this is projected to increase to 366 million by 2030. Diabetes is a condition primarily defined by the level of hyperglycemia giving rise to risk of micro vascular damage (retinopathy, nephropathy and neuropathy). It is associated with reduced life expectancy, significant morbidity due to specific diabetes related micro-vascular complications, increased risk of macro-vascular complications (ischemic heart disease, stroke and peripheral vascular disease), and diminished quality of life. Only ten years ago, Type II DM was considered extremely rare in children in contrast to what is recently revealed that one third of those who are less than 18 years old have been diagnosed with such metabolic disease.

Early diagnosis of DM allows the opportunity to intervene at an earlier age and possibly prevent diabetes and its long-term complication.[4] So, HbA1c level in high-risk patients with Type II diabetes allows early diagnosis and management of diabetes and delaying long-term complication. Type I DM develops as the result of cumulative auto-immune destruction of pancreatic β cells, mainly in genetically predisposed individuals.[5] The DCCT study is generally regarded as providing strong evidence of the of role of hyperglyceamia in

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diabetic micro-vascular disease, but the question remains about extrapolating its results to the management of patients with NIDDM.[6] The incidence of micro-vascular complication is lower in NIDDM than IDDM, and the largest controlled trial to date of treatment of NIDDM (the University Group Diabetes Program Study) found no effect of improved glucose control with insulin or drug therapy on retinopathy.[7] Males and females are equally affected; there is no correlation with socioeconomic status.

Hemoglobin A1c (HbA1c) is an important test recommended by the American Diabetes Association (ADA) and other diabetes organizations worldwide, for management of patients with diabetes mellitus.[8] The United Kingdom Prospective DiabetesStudy (UKPDS) and Diabetes Control and Complications Trials (DCCT) have showed the direct relationship between HbA1c and the risk for complications due to hyperglycemia.[9,10] The amount of stable HbA1c measured in the blood of a patient is directly proportional to the average glucose concentration over the previous 6 weeks. The average amount of HbA1c changes in a dynamic way and indicates the mean blood glucose concentration over the life span of the red blood cell.[11,12] HbA1c gives as indication of chronic hyperglycemia rather than being a test of glycaemia at a single point in time. Recent glycaemia has the largest influence on the HbA1c value, with 50% of HbA1c formed in the month prior to the sampling and 25% in the month before that.[13] It therefore seems logical that such a test would be appropriate in diagnosing a disease characterized by chronic hyperglycemia and a gradual progression to complications.

It is a relatively convenient test because it does not require the patient to fast and only uses a single blood sample. This is an important consideration, in that it may enable improved uptake of testing and improved detection of diabetes, given the large proportion of diabetes cases that go undiagnosed.[14]

HbA1c may be determined 2-4 times per year to assess control in diabetics (normal range: 4%-6%). It is now recognized that glycosylation of a wide variety of proteins occurs when exposed to high concentration of glucose; the chemical properties and, therefore, function of these proteins; which form advanced glycation and product (AGES), are altered. This phenomenon may explain some of the long-term complications of diabetes.[15-17] HbA1c may provide more information in people with borderline fasting blood glucose values.[16,17] A large clinical study [the United Kingdom Prospective Diabetes Study] has shown that better glycemic

control (HbA1c < 7%) resulted in reduced cardiovascular and micro-vascular complications.[18]

In the past, the results of the DCCT could not be extrapolated widely because of differences in methodology and a lack of standardization between laboratories.[19] The National Glycohemoglobin Standardization Program (NGSP) has standardized more than 95 percent of the assays used in the US to the DCCT standard. A1C values are influenced by red cell survival. Thus, on the one hand, falsely high values in relation to a mean blood glucose values can be obtained when red cell turnover is low. On the other hand, rapid red cell turnover leads to a greater proportion of younger red cells and falsely low A1C values.[23,24]Depending upon the methodology, the values may be high in patients with abnormal hemoglobin's (such as HbF and HbS) and those with end-stage renal disease.[21] Therefore, this study was conducted to see the level of HbA1c at the time of diagnosis and correlate that with the duration of signs and symptoms, family history of diabetes mellitus, and the level of family education and presentation.

This study aims to highlight the importance of HbA1c as a confirmatory test at the time of diagnosing Type I DM. It further investigates the correlation between two variables, such as the duration of signs and symptoms of diabetes and its mode of presentation, and the level of HbA1c at diagnosis.

MATERIALS AND METHODS

This retrospective study was carried out in the pediatric endocrine department at Tripoli Medical Center, where all newly- diagnosed diabetic children and adolescent from 1st-Jan. 1999 to 30th-Jun 2006 (7.5 Years period) were included. 844 children and adolescent were tested for HbA1c at the time of diagnosis.

The laboratory method used for determination of HbA1c is immunological in vitro assay in whole blood on automated clinical chemistry analyzer, where HbA1c levels value greater than or equal to 6% are considered high.

We looked at age distribution (which was divided into 4 subgroups: <1-4, 5-9, 10-15, and 16-19) sex, residency, nationality, mode of presentation, the duration of signs and symptoms, hospital stay, and family's level of education. Patients were categorized into two categories: category (A), where one of the parents' educational level was above the preparatory school; and category (B), where one of them has the level of preparatory school or below and it is influence on onset of DM, family history

of diabetes mellitus either type I or II, mode of presentation were studied. Then, these variables were analyzed in relation to HbA1c level when the diagnosis is made.

RESULTS

All medical records of diabetic children and adolescents (1111 records) registered in the pediatric endocrine clinic (at Tripoli Medical Centre) during the period from the 1st of January 1999 to the 30th of June 2006, were reviewed during the study period. The files contained the result of HbA1c at the time of diagnosis were also included in this study (844 records). The results will be presented as the following headlines: HbA1c level at diagnosis, Socio-demographic characteristics of the patients, and the clinical presentation. The HbA1c level at diagnosis ranged from 6.2% to 27% with mean level of 10.7±3.2 in which 95.6% of the patients had a HbA1c> 6% (Figure 1).

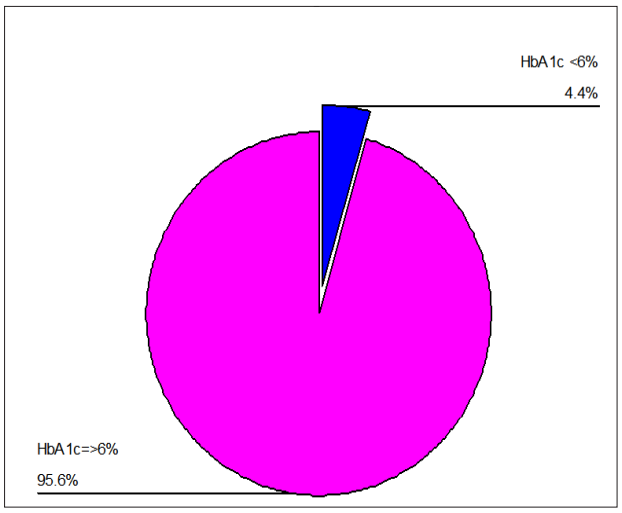

Figure 1: HbA1clevel at time of diagnosis.

The age at presentation of the patients included in this study ranged between 3 months and 19 years, with mean age 8.9±4.4years, (44%) of the cases aged (10-15 years), followed by (32%) for the age group (5-9 years), children aged (1-4 years) made (19%) of the total cases, the lowest percentage was for the ages < one year and (16-19 years), by using nonparametric Chi-square. The difference between these 5 categories was statistically significant (*P* = 0.000) (Figure 2).

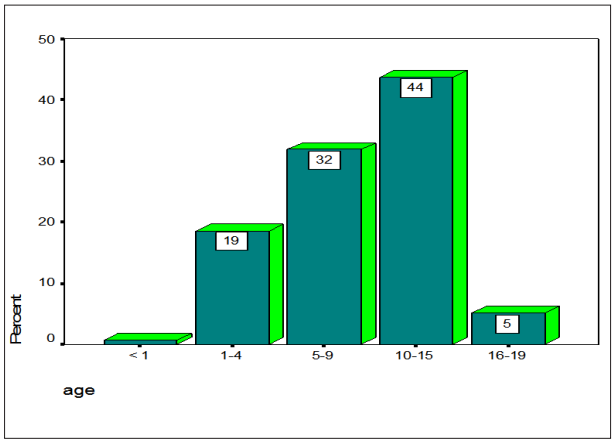

Figure 2: Age distribution.

By studying the relation between HbA1c at time of diagnosis and age of patients, we found that HbA1c level was higher in older age groups. The level of normal HbA1c that was taken into consideration reached the percentage of lower that six for all age groups. The highest level was 11.4%±3.4 for the age group (16-19 years), and the lowest level was 7.3%±1.7 for patients aged less than one year. By using one sample T test, the difference between the mean HbA1c for each age group and the normal HbA1c was statistically significant for all age groups, except for those aged less than one year, where (*P* = 0.132) (Table 1).

About half (52.1%) of the patients under study were males, female patients made 47.9%, with male to female ratio =

1.09:1(Figure 3). By studying the age at diagnosis with sex of the participants, we found that the mean age of males = 8.9±4.5 years, and for females = 9±4.2 years. By using student T test for independent samples, the difference between these two means were not statistically significant (*P* =0.613). By analyzing the sex of the target patients in accordance with the age groups, there was almost no difference in sex distribution for each age group (Figure 4).

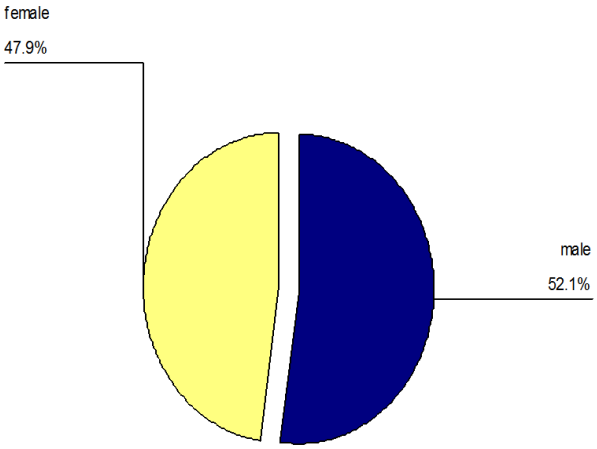

Figure 3: Sex distribution.

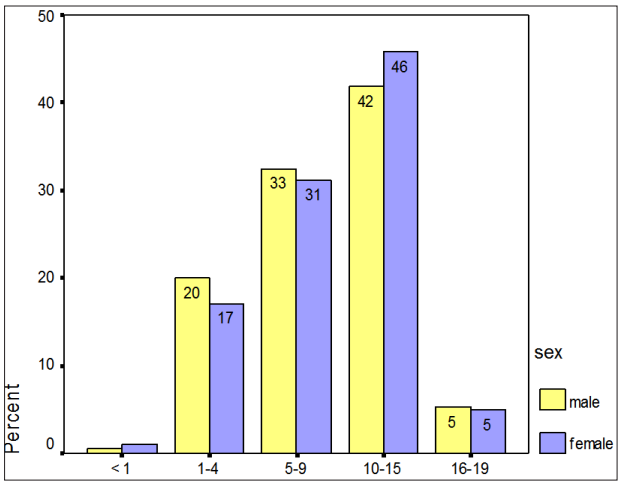

Figure 4: Age distribution according to sex.

The fast majority of the diabetic children under study were Libyan (98%), foreigners made only 2% (Figure 5). Although the clinic is located inside Tripoli, about half (48.2%) of the patients live outside Tripoli district (Figure 6).

About (30%) of the diabetic cases were diagnosed in the preschool age; the other (70%) were studying in different levels; 40% in primary schools, 25% in preparatory schools, and (5%) in secondary schools (Figure 7). Family history of DM was positive in 63% of the cases; 15% was positive for type I DM, 41% for type II, and 7% for both type I and II, and 29% had no family history of DM (Figure 8).

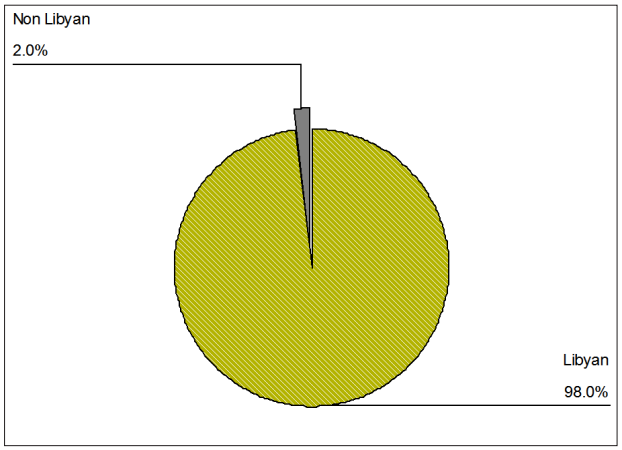

Figure 5: Diabetic cases' nationality.

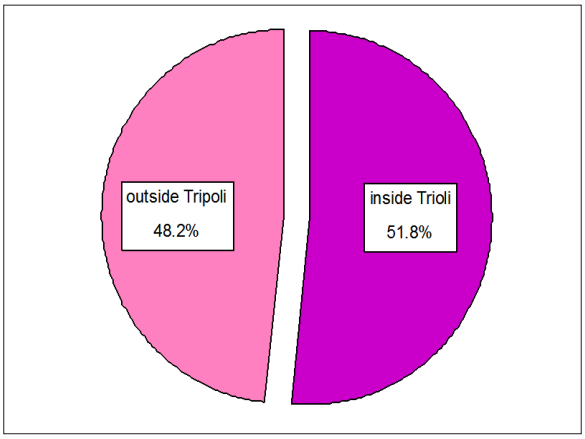

Figure 6: Site of residence.

Family vlevel of education in relation to the HbA1c levels showed that 555 patients (65.7%) fell into category A (with good level of education) and their mean HbA1c level was 12.1%. 20% of those patients presented with ketosis, while

45.8% with classic presentation. Nevertheless, 289 patients (34.3%) fell into category B (with limited level of education) and their mean HbA1c was 13.1%.7.82% of them had ketotic presentation, whereas 27.42% had classic signs and symptoms at presentation. All patients in the two categories had mean duration of signs and symptoms of 3 weeks (Table 2).

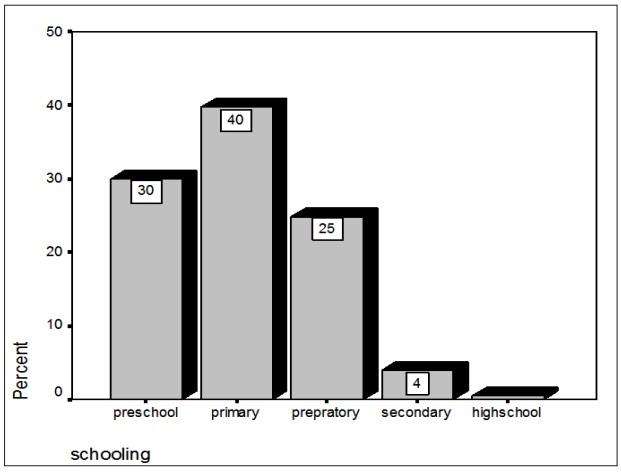

Figure 7: Schooling level.

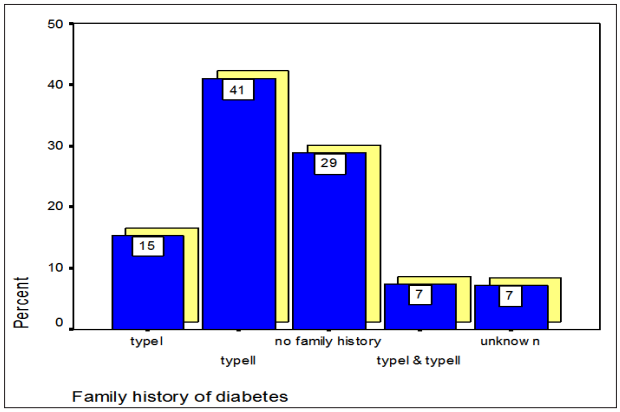

Figure 8: Family history of diabetes.

The presenting signs and symptoms were classified as classical (poly urea, polydipsia, and weight loss) and diabetic ketoacidosis (DKA). The results revealed that 26.8% of the cases presented with DKA, while 68.8% of others with classical signs and symptoms of diabetes mellitus (Figure 9). The mean age of patients presented with DKA was 8.7±4.7 years, whereas the mean age of other patients presented with classical symptoms was 9±4.2 years. By using student T test for independent samples, the difference between these two means was statistically not significant ($P = 0.292$) (Figure 10).

This study found out that 4.4% of the patients were presented to the clinic after a month from the development of signs and symptoms, whereas 95.6% of others were presented there with less than a month (Figure 9).

Table 1: Distribution of cases by age group and mean HbA1c at the time of diagnosis.

Age groups	% of age groups	HbA1c Mean±SD	Normal HbA1c	*P* value
<1year.	0.7%	7.3±1.7		0.132
1-4years.	18.6%	9.8±2.3	Is less than	0.000
5-9years.	31.9%	10.2±3.1	6%	0.000
10-15years.	43.7%	11.3±3.3	For all age groups.	0.000
16-19years.	5.1%	11.4±3.4		0.000

Table 2: Education level and clinical presentation.

Family level of education	Number of patients	Percentage	Mean HbA1c	Ketotic presentation	Classic presentation
Category A	555	65.7%	12%	20%	45.8%
Category B	289	34.3%	13%	7.82%	27.42%

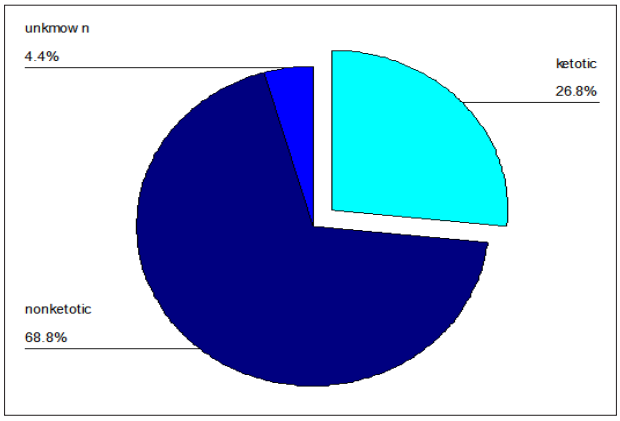

Figure 9: Mode of presentation.

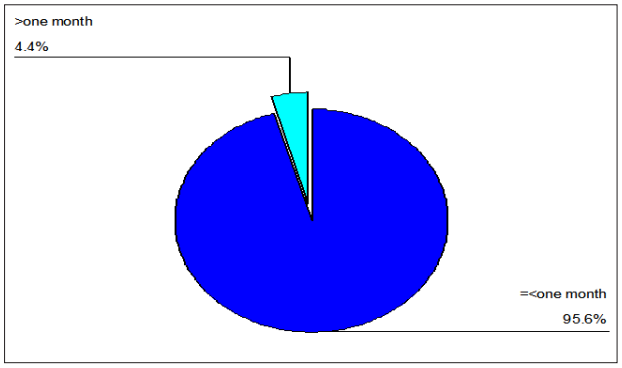

Figure 10: Duration of signs and symptoms.

The relationship between the level of HbA1c at time of diagnosis and duration of signs and symptoms was statistically significant (P =0.000), except for those who were presented after 17-20 weeks duration of developing signs and symptoms (P =0.489) (Table 3).

Table 3: HbA1c at time of diagnosis and duration of signs and symptoms.

Duration of signs and symptoms	Frequency	HbA1c Mean ±SD	*P* value
1-4 weeks	671(79.5%)	10.6±3.1	0.000
5-8weeks	28(3.3%)	10.1±3.3	0.000
9-12weeks	25(3%)	10.3±3.1	0.000
13-16weeks	15(1.8%)	11.5±4.6	0.000
17-20weeks	2(0.2%)	8.8±3.8	0.489
≥20weeks	14(0.7%)	11.7±3.1	0.000

DISCUSSION

Diabetes is one of the most common chronic diseases of childhood, the prevalence of type 1 DM continues to increase around the world even though it still affects less than 0.5 % of the population.26 We have noted that in our Centre the annual incidence was 6.5/100000 in 1989 and raised up to 18/100000 in 200627, with increased annual incidence in Libyan children. We have also noticed that HbA1c was high at presentation of young diabetics irrespective of their age, sex and family level of education.

In retrospective audit of outcomes two years post-diagnosis in children presenting in Diabetic Ketoacidosis (DKA) compared to "walking wounded" at Queens Medical Center, Nottingham.26 The study examined HbA1c at presentation and two years post presentation. 114 (out of current 256) of its 1patients diagnosed with diabetes between 2000 and 2004 were identified.

Average HbA1c at presentation was (11.01%) in contrast to our HbA1c at presentation was (12.1%). Patients who presented in DKA in Nottingham study had initial HbA1c of (10.77%), whereas in our study was (10.8%). However, patients presented in non DKA in Nottingham study had an initial HbA1c of (11.12%), while those who presented in non DKA in this study had an initial HbA1c of (10.6%).

Splitting HbA1c results by gender and presentation state, the results of Nottingham study revealed that there was a difference between girls and boys. To be more specific, girls had higher HbA1c at presentation (11.87%) than boys (10.24%). A similar result was detected in our study, asHbA1c for girls was (10.95%±3.1), and for boys reached (10.4%±3.15).

Our study showed that the majority of diabetic children and adolescent had high HbA1c at time of diagnosis irrespective of their gender, age, family level of education, mode of presentation. Those patients who had a parent with good level of education sought medical advice earlier. HbA1c at diagnosis inversely related to the duration of signs and symptoms. The raised HbA1c level at the time of diagnosis was seen by the Endocrinology team 10 years ago. This can be explained by asymptomatic phase of DM exists before the development of its signs and symptoms. As There is no treatment for asymptomatic phase in type 1, and no role of using HbA1c as a screening tool, except for research purpose in genetically susceptible patients. Nonetheless, HbA1c can be used to predict type 2 diabetes mellitus in high risk families, as in type 2 DM in which early detection means prevention of micro-vascular complication.

There has been interest in the use of HbA1c values for screening and identification of impaired glucose tolerance and diabetes.
The HbA1c value may also be considered in combination with the fasting blood glucose value, particularly in the light of the changing epidemiology of diabetes with the new criteria for diagnosis of DM.

HbA1c is an important test for monitoring glyceamic control in diabetics. It can be used as a screening test for early detection of diabetes mellitus, especially in high-risk patients with type 2. HbA1c is not yet recommended for diagnosis (although it may be later when assays are standardized worldwide), but from our study we can recommend HbA1c for diagnosis of type I and II DM.

CONCLUSION

HbA1c was significantly high at time of diagnosis and was not influenced by age, sex, family level of education. It is high irrespective of short duration of diabetic signs and symptoms. The presented data provided evidence that high HbA1c level at diagnosis could be deployed as a diagnostic test in diabetic children and adolescents. Early diagnosis of DM means prevention of acute complication and therefore decreases the mortality.

RECOMMENDATIONS

HbA1c level should be checked with a Random Blood Sugar(RBS) at diagnosis of type 1 DM; where high HbA1C mean100% confident that the patient is diabetic. HbA1c can be used as a screening test with high-risk groups for detecting the development of type 2 DM. The task of managing childhood diabetes is good metabolic control, preventing morbidity and mortality, and assuring good quality of life.

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