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The Dilemma of Diagnosing Type-2 Diabetes Mellitus [T2DM] in Overweight Children and Adolescents

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Abstract

American Diabetes Association [ADA] has recommended that diabetes should be diagnosed when HbA_{1c} is ≥6.5%. Subjects with HbA_{1c} of 6.0 to < 6.5% were at the highest-risk for developing diabetes. Objectives: To determine the sensitivity and specificity of $HbA_{1c} \geq 6.5\%$ to diagnose Type 2 Diabetes Mellitus [T2DM] in overweight children and the adolescents as compared to an oral glucose tolerance test. Retrospective chart review was done from January 2004-December 2008, and search criteria included overweight children who had OGTT and HbA_{1c} done. Based on OGGT we divided the data into normal, impaired and diabetic groups.

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The results shows that HbA_{1c} cut-off of ≥ 6.5% had a specificity of 96% and a sensitivity of 40% in accurately diagnosing patients with T2DM. Sixty percent of T2DM and 44.60% of impaired OGTT subjects would show a normal glycemic status if only HbA_{1c} is used to diagnose them. Homeostasis Model of Assessment - Insulin Resistance [HOMA-IR], Quantitative Insulin Sensitivity Check Index [QUICKI] and HbA_{1c} levels were statistically significant between normal versus diabetic and normal versus impaired groups [$p<0.05$]. Due to the low sensitivity of the HbA_{1c} test in diagnosing diabetes, it may result in missed or delayed diagnosis of T2DM if used exclusively to diagnose diabetes.

Keywords: HbA1c; OGTT; diagnosis of Type-2 Diabetes mellitus [T2DM]; overweight children and adolescents

1. Introduction

Blood glucose measurements have been the corner stone of diagnosing diabetes. The criteria for diagnosing diabetes have changed over the last three decades. WHO has published several guidelines for the diagnosis of diabetes since 1965 [1-3]. The oral glucose tolerance test (OGTT] has been used for over ninety years in clinical medicine [4]. It was in 1979 that National Diabetes Data Group [NDDG] included OGTT criteria for the diagnosis of diabetes with a fasting plasma glucose [FPG] ≥126 mg/dL or a 2-h plasma glucose ≥200 mg/dL on more than one occasion, in a patient with classic symptoms of diabetes, a single random plasma glucose ≥200 mg/dL is considered diagnostic [5]. The level of glycemia was chosen since it was associated with the specific microvascular complication of diabetic retinopathy. The 2-h plasma glucose ≥200 mg/dL was chosen based on the development of this diabetic complication in 77 of 1,213 subjects followed for 3–8 years after a baseline OGTT [6]. The International Expert Committee [IEC] proposed new diagnostic criteria based on measurement of HbA_{1c} ≥6.5% for diabetes and 6.0–6.4% for "high risk" of progression to diabetes [7]. The American Diabetes Association [ADA] subsequently proposed HbA_{1c} ≥6.5% for the diagnosis of diabetes and 5.7–6.4% for the highest risk to progress to diabetes [8].

The potential utility of HbA_{1c} in diabetes care is first mentioned in the 1985 WHO report [3]. Since then there have been arguments for and against using HbA_{1c} for the diagnosis of diabetes. HbA_{1c} determination is convenient, does not require fasting and is not affected by day-to-day variability of glucose values e.g. stress and illness [9, 14]. The relationship between HbA_{1c} and the prevalence of retinopathy is similar to that of plasma glucose, which was originally reported in Pima Indians [15] and has been observed in several populations including Egyptians [16], NHANES study in the USA [17], Japanese [18], and Australians [19] and more recently in the DETECT-2 analysis [20]. These studies were carried out in the adult population, and the HbA_{1c} diagnostic cut-offs were also recommended for the children and the adolescents. There is a lack of data in the pediatric population regarding the utility of HbA_{1c} in diagnosing diabetes and in identifying the individuals at a high risk for developing diabetes. Our study aims to determine the sensitivity and specificity of $HbA_{1c} \geq 6.5\%$ to diagnose T2DM in overweight children and the adolescents as compared to OGTT. We will also observe the distribution of our patient population based on having HbA_{1c} range being normal range, high risk for developing diabetes r and in the diabetics.

2. Material and Methods

Retrospective chart review was done from January 2004-December 2008. The search criteria included overweight children with BMI ≥ 85^{th,} who had a previous OGTT and a simultaneous HbA_{1c}. The children usually get one OGTT at the initial visit with a simultaneous HA_{1c} level to determine the glycemic status. The study protocol was approved by The Children's Mercy Hospitals & Clinics institutional review board.

OGTT is done as a part of screening process for the determination of dysglycemia in overweight children BMI ≥ 85th percentile. Subjects may also have clinical signs of insulin resistance including acanthosis nigricans and or family history of T2DM in first or second-degree relatives. None of the subjects in the study had any anemia or hemoglobinopathies listed in their past history. These children were not on any medications for weight loss or oral antihyperglycemic agents like metformin. The lifestyle of these children was sedentary with no involvement in an active exercise program. Sex, race, birth weights, gestational age and maternal gestational diabetes status were also available in the data.

OGTT was done at The Children's Mercy Hospitals & Clinics [CMH], after a 10-h overnight fast. A standard OGTT was administered in a dose of 1.75 g of glucose per kilogram of body weight [up to a maximum of 75 g] was performed in all subjects to establish the glycemic status, as previously described [18]. Whole blood was obtained to determine the blood glucose and the HBA1c values through a peripheral venous blood draw.

HbA_{1c} was performed by the principle of high performance liquid chromatography [HPLC] using a Tosoh Automated Glycohemoglobin Analyzer HLC-723G8 with intra- and inter-assay coefficients of variation [CVs] ≤1.4%. Blood glucose were measured by using Analyzer: Vitros 5600 analyzer by calorimetric method with intra- and inter-assay CVs ≤0.8%, and insulin was measured using chemiluminescent immunoassay using iulite 2000 system with intra- and inter-assay CVs ≤3.6%.

Based on OGTT we divided the data into normal, impaired and diabetic groups. Impaired glucose tolerance [IGT] is defined as 2-h glucose after the OGTT 140–199 mg/dL. Diabetes was diagnosed based on a fasting glucose of >125 mg/dl or a 2-h plasma glucose ≥200 mg/dL during an OGTT [16, 17]. The prediabetes group included patients with either fasting glucose level between 100-125 mg/dl or IGT. The study was approved by the institutional review board of the Children's Mercy Hospitals and Clinics and written consent was not obtained since it is a retrospective study.

Continuous demographic variables and outcome variables were summarized by mean and standard deviation. We compared the continuous variables among the normal group, impaired group and diabetic group using Analysis of Variance [ANOVA]. Pearson and Spearman correlation coefficients were calculated between HbA_{1c} and other outcome variables. For comparison of categorical variables by group, Chi-squared analysis was used. We created receiver operator characteristic [ROC] curves to assess diagnosis accuracy. Multivariate analyses were performed using general linear model [GLM] and logistic regression. Statistical significance was claimed at 95% confidence level [$p<0.05$]. Statistical analysis was performed using SAS 9.2 [Cary, NC] and SPSS 20. HOMA-IR was calculated using the formula HOMA-IR= Glucose x Insulin/405, with glucose in mg/dl. QUICKI was calculated using the Formula: [1/log(fasting insulin micro unit/ml + 1/ log(fasting glucose mg/dl].

3. Results

A total of 628 charts were reviewed. Among these subjects, 368 [58.6%] are Caucasians, 167 [26.6%] are African Americans [AA] and 94 [14.9%] are mixed races, including Hispanics and Asians, etc. The demographic features of the groups are in [Table 1].

Table 1: Clinical features of the study population

	All subjects (n=628)	Normal (n=537)	Impaired (n=78)	Diabetic (n=13)	P-value
Age	12±3.2	11.9±3.2	12.9±2.7	13±2.9	0.01
BMI Z-score	2.4±0.5	2.4±0.5	2.4±0.4	2.1±0.5	0.11
OGT glucose 0 min	83.4±11.1	82.2±8.2	89±13.2	99.4±42.6	<.0001
OGT glucose 120 min	111±32.7	101±17.6	160±17	243±38.2	<.0001
OGT insulin 0 hr	23.6±20.5	21.8±18.9	34±24.9	37.6±30.7	<.0001
OGT insulin 120 min	131±122	109±82	266±216	219±168	<.0001
QUICKI	0.32±0.04	0.32±0.04	0.3±0.04	0.3±0.03	<.0001
HOMA	5±4.6	4.5±4.1	7.6±6.2	8.1±7.8	<.0001
Cholesterol (mg/dl)	160±34	160±34	160±30.8	184±49.4	0.06
LDL (mg/dl)	95.1±28.6	94.8±28.6	94±26.4	115±39.6	0.06
TG (mg/dl)	131±81.1	128±78.3	148±98	148±77.1	0.13
HDL (mg/dl)	40.3±10	40.8±10.1	37.4±9.8	39.9±6	0.03
ALT (U/L)	35±21.3	33.8±18.1	42.7±34.9	37.7±25.4	0.005
AST (U/L)	31.7±16.6	31.7±16	32.9±20.4	26.7±14.1	0.51
$HbA_{1c\ (\%)}$	5.5±0.6	5.5±0.4	5.8±0.6	6.8±1.6	<.0001

HbA_{1c} cut-off of ≥ 6.5% had a specificity of 96% and a sensitivity of 40% in accurately diagnosing patients with type-2 diabetes. Sixty percent of T2DM and 44.60 % of impaired OGTT subjects would show a normal glycemic status if only HbA_{1c} is used to diagnose them. There was only one subject with fasting blood glucose level greater than 125 mg/dl, and also had 2 hours OGTT glucose level of ≥ 200 mg/dl. Twenty nine [4.61] subjects had an impaired fasting glucose level and out of these six [21%] of them also had a 2 hour glucose level of ≥ 200 mg/dl.

We did not detect association between HbA_{1c} and birth weight or gestational age by univariate and multivariate analysis. Caucasian had significantly higher birth weights as compared to AA children [3.4 ± 0.7 vs. 3.2 ± 0.8, p=0.02]. There is no sex difference in HbA_{1c} or birth weight. There was significantly positive association between HbA_{1c} and diastolic blood pressure [dbp] [spearman rho=0.14, p<0.01]. There was significant association between birth weight and BMI- Z score [Spearman rho=0.15, p<0.01] and between birth weight and

diastolic blood pressure [dbp] [Spearman rho=0.11, p=0.03]. No race and sex differences are present by gestational age [GA]. HOMA-IR and QUICKI were statistically significant between normal versus diabetic and normal versus impaired groups but not when comparing impaired versus diabetic groups [p<0.05]. GA is not associated with the OGTT status. No significant difference was found for BMI-z score. Small for gestational age [SGA] subjects are more likely to have HbA_{1c} >5.7 [impaired or Type II] p=0.05 [60% vs. 52% vs. 78%]. There is very weak agreement between HbA_{1c} status and OGTT status. When comparing Caucasians versus AA race groups, AA had a higher BMI Z-score, ALT and HbA1c levels [P<0.01] [Table 2].

Table 2: Ethnic difference of the study population

	Caucasian (n=368)	AA (n=167)	Others (n=94)	P-value*
Age	11.8±3.3	12.5±2.7	11.8±3.3	0.03
BMI Z-score	2.4±0.6	2.4±0.4	2.4±0.6	0.70
OGT glucose 0 min	82.8±9.7	84.3±13.4	84±11.6	0.15
OGT glucose 120 min	111±31.1	113±34.5	113±35.3	0.44
OGT insulin 0 hr	21.1±19.2	26.4±21.1	28.4±23	0.002
OGT insulin 120 min	117±114	150±121	148±144	0.005
QUICKI	0.32±0.04	0.31±0.04	0.31±0.04	0.003
HOMA	4.4±4.3	5.6±4.9	5.9±5.2	0.004
Cholesterol (mg/dl)	162±33.9	158±33.1	158±36.1	0.16
LDL (mg/dl)	94.8±28	97.2±29.1	92.9±30.2	0.40
TG (mg/dl)	145±93.3	100±52.7	136±56.4	<0.0001
HDL (mg/dl)	40.1±9.8	41.4±10.4	39.3±10	0.21
ALT (U/L)	35.5±17.9	29.2±12.3	44.1±37.8	0.0001
AST (U/L)	31.5±13.3	29.1±16.5	37.9±25.1	0.10
$HbA_{1c\ (\%)}$	5.4±0.4	5.7±0.7	5.6±0.5	<0.0001

* compare Caucasians vs AA

AA group had a lower triglyceride [TG] levels [P<0.01]. They also had a higher fasting glucose and insulin levels, and HOMA-IR and a lower QUICKI suggestive of an increased insulin resistance. [P<0.01] [Table 2]. We calculated the weighted Kappa statistic in Tables 3 and 4 to measure agreement between HbA1c and OGTT. The results show that HbA1c level was more consistent with 2 hours blood glucose level on OGTT in AA as compared to Caucasians [Kappa: 0.06 vs. 0.27 in Table 3; 0.05 vs. 0.32 in Table 4].

In AA group two-hour post- glucose measurements have a stronger correlation than individual HbA_{1c} measurements, which are most likely related to higher insulin resistance as shown by the HOMA-IR and the QUICKI values [Table-2]. Females had higher BMI z-score, triglyceride. ALT and the AST levels [Table-5].

Receiver operating characteristic [ROC] curves were used to evaluate how well the A1c and baseline [0h] glucose can predict impaired OGTT patients defined by 2h OGTT [Figure 1].

Table 3: Comparison of subjects HA1c status and diagnosis based on the OGTT

All subjects				
OGTT	HbA1c < 5.7 %	HbA1c : 5.7-6.49%	HbA1c: ≥ 6.5%	Weighted Kappa for Agreement
Normal (n=402)	278 (69.2%)	119 (29.6%)	5 (1.2%)	0.19 (0.11 - 0.27)
Impaired(n=65)	29 (44.6%)	24 (36.9%)	12 (18.5%)	
Diabetic(n=10)	2 (20%)	4 (40%)	4 (40%)	
Caucasians				
OGTT	HbA1c < 5.7 %	HbA1c : 5.7-6.49%	HbA1c: ≥ 6.5%	Weighted Kappa for Agreement
Normal (n=232)	175 (75.4%)	55 (23.7%)	2 (0.9%)	0.06 (-0.05 - 0.17)
Impaired(n=38)	26 (68.4%)	9 (23.7%)	3 (7.9%)	
Diabetic(n=4)	2 (50%)	2 (50%)	0 (0%)	
AA				
OGTT	HbA1c < 5.7 %	HbA1c : 5.7-6.49%	HbA1c: ≥ 6.5%	Weighted Kappa for Agreement
Normal (n=114)	63 (55.3%)	48 (42.1%)	3 (2.6%)	0.27 (0.15 - 0.39)
Impaired(n=20)	2 (10%)	11 (55%)	7 (35%)	
Diabetic(n=3)	0 (0%)	0 (0%)	3 (100%)	

Table 4: Distribution of study subjects based on OGTT and HA1c status

All subjects				
OGTT	HbA1c < 6 %	HbA1c : 6.0-6.49%	HbA1c: ≥ 6.5%	Weighted Kappa for Agreement
Normal (n=402)	347 (86.3%)	50 (12.4%)	5 (1.2%)	0.22 (0.12 - 0.32)
Impaired(n=65)	44 (67.7%)	9 (13.9%)	12 (18.5%)	
Diabetic(n=10)	4 (40%)	2 (20%)	4 (40%)	
Caucasians				
OGTT	HbA1c < 6 %	HbA1c : 6.0-6.49%	HbA1c: ≥ 6.5%	Weighted Kappa for Agreement

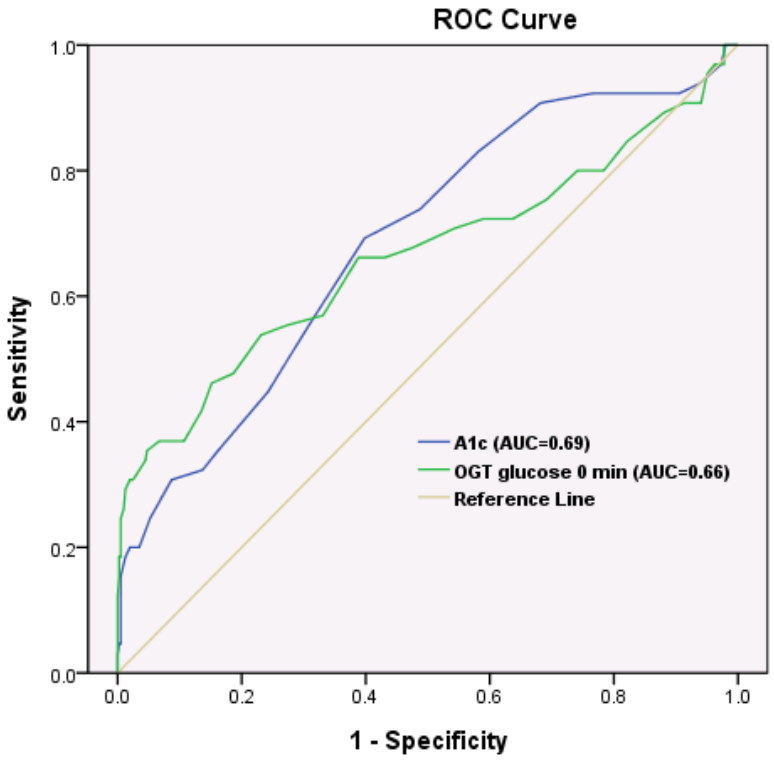
Normal (n=232)	208 (89.7%)	22 (9.5%)	2 (0.9%)	0.05 (-0.04 - 0.20)
Impaired(n=38)	31 (81.6%)	4 (10.5%)	3 (7.9%)	
Diabetic(n=4)	3 (75%)	1 (25%)	0 (0%)	
AA				
OGTT	HbA1c < 6 %	HbA1c : 6.0-6.49%	HbA1c: ≥ 6.5%	Weighted Kappa for Agreement
Normal (n=114)	89 (78.1%)	22 (19.3%)	3 (2.6%)	0.32 (0.16 - 0.48)
Impaired(n=20)	9 (45%)	4 (20%)	7 (35%)	
Diabetic(n=3)	0 (0%)	0 (0%)	3 (100%)	

Table 5: Gender differences of the study population

	MALE (n=453)	FEMALE (n=176)	P-value
Age	11.9±3.1	12.2±3.3	0.38
BMI Z-score	2.3±0.5	2.6±0.6	<0.0001
OGT glucose 0 min	82.8±12.0	84.9±8.4	0.04
OGT glucose 120 min	111.4±33.4	111.6±30.8	0.94
OGT insulin 0 hr	24.2±22.1	22.2±15.7	0.28
OGT insulin 120 min	134.5±127.8	120.6±105.1	0.20
QUICKI	0.32±0.04	0.32±0.04	0.92
HOMA	5.0±5.0	4.7±3.5	0.44
Cholesterol (mg/dl)	160.0±33.7	161.5±34.8	0.63
LDL (mg/dl)	95.8±28.6	93.5±28.7	0.40
TG (mg/dl)	122.3±70.2	154.3±100.7	<0.0001
HDL (mg/dl)	41.2±10.0	38.1±9.7	0.001
ALT (U/L)	32.0±16.7	42.3±28.5	<0.0001
AST (U/L)	29.8±13.9	36.6±21.2	<0.0001
$HbA_{1c\ (\%)}$	5.5±0.6	5.5±0.5	0.78

The AUC for A1c is 0.69 [95% CI: 0.61 - 0.76], indicating A1c does not provide an accurate prediction of the impaired OGTT patients. The AUC for baseline [0h] glucose is 0.66 [95% CI: 0.58 - 0.75]. There are no significant differences between the ROC curves for A1c and baseline [0h glucose]. ROC curve was also used to evaluate how well the A1c and baseline [0h) glucose can predict diabetic OGTT patients defined by 2h OGTT

[Figure 2].



Area Under the Curve

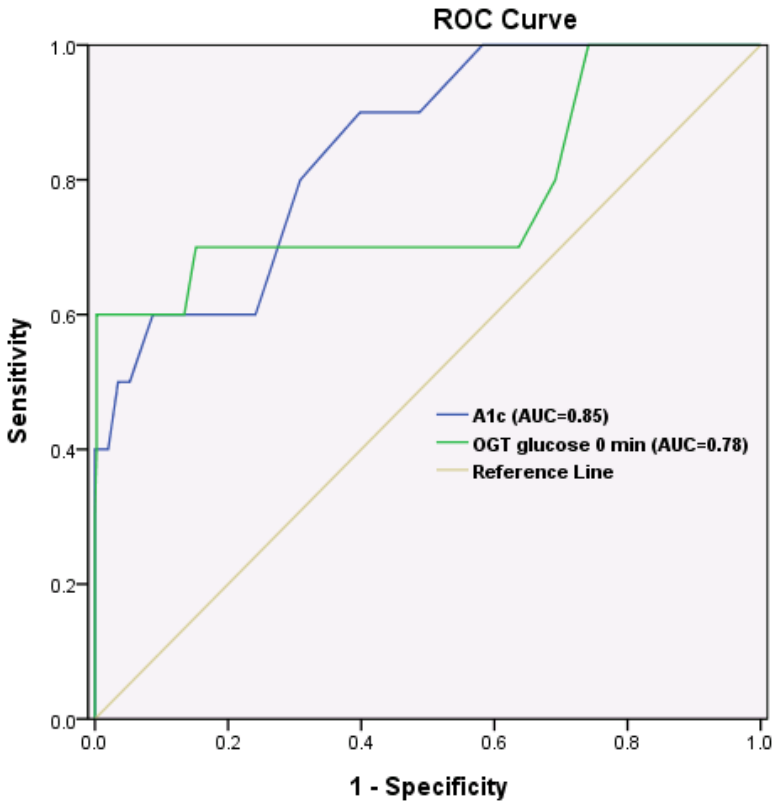
Test Result Variable(s)	Area	Std. Error	P-value	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
A1c	0.686	.037	<0.001	0.614	0.758
OGT glucose 0 min	0.664	.044	<0.001	0.578	0.750

Figure 1: ROC Curve for HbA1c in Prediction of Normal vs. Impaired by OGTT 2 hours

The AUC for A1c is 0.85 [95% CI: 0.73 - 0.96]. Since diabetic patients are profoundly different from the normal subjects, we saw a better ROC curve for diabetic patients [Figure 2] as compared the impaired patients [Figure 1]. Despite the high AUC, there is no good cutoff for A1c that yields high sensitivity and specificity to predict diabetic patients. For instance, if we choose A1c cutoff as 6.05, we only have sensitivity = 0.6 and specificity =091. The AUC for baseline [0h] glucose is 0.78 [95% CI: 0.58 - 0.97].

4. Discussion

There are several points in favor of and against using HbA_{1c} for diagnosing diabetes. HbA_{1c} indicates chronic hyperglycemia, and can be a predictor of chronic complications of diabetes [21]. It has been shown to be better than FPG and 2-h OGTT in adult Saudi population when used as a screening tool for newly diagnosed diabetes and pre-diabetes [22].



Area Under the Curve

Test Result Variable(s)	Area	Std. Error	P-value	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
A1c	0.847	0.059	<0.001	0.732	0.962
OGT glucose 0 min	0.775	0.100	0.003	0.580	0.970

Figure 2: ROC Curve for HbA1c in Prediction of Normal vs. Diabetic by OGTT 2 hours

HbA_{1c} can be obtained at any time of the day and can be used to guide management of diabetes [14]. It has a very low pre-analytical variability. Two-hour post- glucose measurements have a weaker correlation than individual HbA_{1c} measurements [23].

However, even in western countries, the standardization of HbA_{1c} assay is not optimal while blood glucose assay is standardized easily in most places of the world [10]. The cost of HbA_{1c} assay is very high and cannot be used in poor and under-developed countries where the prevalence of diabetes is very high. The diagnosis of diabetes may be delayed if HbA_{1c} is used, since its measurement involves the measurement of glycation of the proteins, which is a result of elevated blood glucose levels. These glycation proteins may not be high enough in the beginning of the disease process [11]. The hemoglobin glycation can be affected by the environmental parameters, such as lipid peroxidation and hereditary factors [24]. HbA_{1c} cannot be used in patients with abnormal hemoglobin traits or rapid turnover of the red cells [11]. It will be a bigger issue in the under developed countries which have a higher prevalence of anemia and hemoglobinopathies [25]. There are also racial differences in HbA_{1c} levels [26].

The OGTT has its own drawbacks as well, the most important is a lack of reproducibility, it is inconvenient to perform in the clinical setting since the patient has to be fasting, does not guide about the treatment of IGT or diabetic patients [27].

The two-hour OGTT glucose levels document an impairment of β-cell function, which also correlate with cardiovascular disease [28]. HbA_{1c} fails to recognize the patients with an impaired glucose tolerance test and has low sensitivity to diagnose diabetes [29].

Insulin resistance precedes the development of diabetes and is a presenting feature of obesity, metabolic syndrome, and many cardiovascular diseases. A delayed diagnosis will mean a delay in interventions for the management of Diabetes which can cause multi-organ damage [12]. Contrary to $HbA_{1c,}$ fasting blood glucose and the insulin levels measured during OGTT also help in calculating the HOMA-IR and QUICKI which give an assessment of insulin resistance and future risk for developing diabetes [30].

Our study showed a sensitivity/specificity of 40%/96% in diagnosing patients with type-2 diabetes, which is similar to the data Lee et al, showed that $HbA_{1c} \geq 6.5\%$ had sensitivity/specificity of 75/>99% [31]. Lee et al compared HbA1c with fasting plasma glucose and 2 hour OGTT glucose values for pre-diabetes and diabetes diagnosis in the adolescents; they showed that HbA_{1c} had less than acceptable test performance for children with prediabetes. It showed lower sensitivity for diagnosing diabetes if $HbA_{1c} \geq 6.5\%$ was used. It also showed that two out of three patients with diabetes would be missed if the ADA recommendation of 6.5% for the diagnosis of diabetes was used since the subjects had HbA_{1c} levels of 5.1 and 5.2% [31].

Nowicka et al showed that there was a poor agreement between HbA_{1c} and OGTT in diagnosing diabetes in children and adolescents with HbA_{1c} having a sensitivity of 62% [32].

Our data indicate that using HbA_{1c} exclusively for the diagnosis of diabetes will miss 40% of the diabetics and 20% of patients at risk for developing diabetes [table 3]. This will also be true in the new onset diabetics since HbA_{1c} measures the chronic hyperglycemia [10].

Our data also indicates that 13.4% of patients a normal OGTT may have HbA_{1c} greater than 6%. Thirty one percent of patients may have an HbA_{1c} greater than 5.7% and would have a normal OGTT status. Furthermore

44% of patients with HbA_{1c} <6 % and 44.6 % with an HbA_{1c} less than 5.7% have an impaired glycemic status on the OGTT. Failure to identify these high-risk groups on HbA_{1c} testing will cause a probable delay in implementing an effective prevention strategy and diagnosis of diabetes [table 4]. About 1.2 % with a normal OGTT and 18.5% of impaired OGTT status subjects have an $HbA_{1c} \geq 6.5$ %. Our study also showed that in AA group Two-hour post- glucose measurements have a stronger correlation than individual HbA_{1c} measurements.

The limitations of the study include its retrospective design. The data was obtained from a single-center. A follow-up study on the participants was not performed because of the lack of funding but it's a possibility in the future. The strengths include relatively large sub-sets of obese children in the study and simultaneous HbA_{1c} and OGTT measurements.

5. Conclusion

Due to the low sensitivity of the HbA_{1c} test in diagnosing diabetes, it may result in missed or delayed diagnosis of T2DM if used exclusively to diagnose diabetes. However the use of HbA1c in AA's may be more indicative of their glycemia status.

Since the glucose level measurements are inexpensive, widely available and assays are standardized in most parts of the world, we recommend that OGTT should be used to diagnose diabetes using the standardized OGTT. W e further recommend that due to the sub-optimal reproducibility of the OGTT it should be used with HbA_{1c} test to diagnose diabetes. HbA_{1c} can be a good tool to monitor the compliance to treatment of diabetes and the glycemic status.

We recommend doing further prospective studies with larger sample size to clarify and improve the recommendations for diagnosing diabetes.

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