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An Audit of Pediatric Type 2 Diabetes Management in a Single Institution

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Abstract

Objectives: To assess clinical and demographic characteristics of children & adolescence diagnosed with type 2 diabetes and review their management.

Methods: This is descriptive audit of data collected from diabetes database and case records of patients between January 2007 to May 2015. Patients included were aged between 10 and 18 years old at diagnosis; with at least 1-year duration of T2DM. Treatment was either single therapy with insulin or OHA, or combination therapy with both insulin and OHA. Comparison was made between patients on single *vs.* combination therapy (Group 1) and patients on insulin-only *vs.* OHA-only therapy (Group 2).

Results: Of 70 subjects, 18 were started on insulin, 30 on OHA & 22 on combination therapy. In Group 1, mean HbA1c at diagnosis was significantly lower in patients on single than combination therapy [9.47 ± 3.18 *vs.*12.4 ± 1.42%; p<0.001], while in Group 2 it was lower in OHA than insulin therapy [7.91 ± 2.06 *vs.* 12.2 ± 2.95%; p<0.001]. Patients initiated on combination therapy were more likely to be younger (p=0.021) and have higher HbA1c (p<0.001) than those on single therapy. Mean weight at diagnosis was not significantly different in Group 1, but in Group 2 it was significantly higher in those on OHA than insulin [75.5 ± 21.1 *vs.* 55.8 ± 18.0 kg; p=0.004]. Reduction in HbA1c at one year was seen across all treatment groups, a greater reduction is seen in those on combination treatment as compared to those on insulin alone.

Conclusion: Significant reduction in HbA1c is seen in all treatment groups; those started on combination therapy had greater reduction in HbA1c than those on insulin alone.

Keywords: T2DM; OHA; Insulin; Single therapy; Combination therapy

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Introduction

The rise in the incidence of type 2 Diabetes Mellitus (T2DM) in children has been a global phenomenon within the past two decades. While conventionally viewed as an adult disease, the onset of T2DM has been shifting towards the younger age group. A study in United States published in 2005 found that the disease which used to account for 3% of newly diagnosed DM in children and adolescents in 1990s, today accounts for up to 45% of the new-onset cases [1]. The same trend is witnessed across the world, even more so in Asia. In Singapore, it was reported that there was greater than 5 times increase of T2DM cases diagnosed in 2000 compared to 1997 [1], and numbers are expected to be greater now. The cause of this rising trend has been attributed mainly to the rise in prevalence of obesity. Increasing attention has been placed in this area of clinical practice as it potentially translates to earlier onset of micro- and macro-vascular complications in these patients, which in turn leads to greater healthcare burden.

While there have been guidelines established to aid in the diagnosis and management of T2DM [2,3], variations still exist among physicians in practice. Locally in Singapore, there are limited studies done on T2DM in the pediatric population. Diagnosis of T2DM is usually made based on a mixture of clinical and laboratory features which suggest insulin resistance. Unlike in adults, the diagnosis of T2DM in children is not as straightforward as there may be overlapping clinical features of insulin deficiency and insulin resistance. Phenotyping of Asian children is made more difficult with the rising prevalence of obesity which can coexist with T1DM; while children with T2DM can also present with beta cell failure.

Majority of the patients are asymptomatic and picked up on screening tests done on background of obesity; a small proportion presents with symptoms of hyperglycemia and few presents acutely

with diabetic ketoacidosis. In the acute presentation, most pediatric patients are started on insulin therapy which aims to rapidly bring down blood glucose levels. The subsequent treatment regimen-whether insulin-only, Oral Hypoglycemic Agent (OHA)-only or combined insulin and OHA therapies-depends largely on patient's clinical progress and glycemic control. All patients are initiated on lifestyle modification.

The American Diabetes Association Standard of Medical Care 2016 states that the general goal of treatment of T2DM in children and adolescents is to achieve HbA1c of <7.5% for all age groups, in addition to managing co-morbidities [4]. Period of insulin therapy is recommended in children (i) with ketosis or ketoacidosis until post-prandial glucose level is near normal, (ii) in whom the distinction between type 1 or type 2 diabetes is unclear and (iii) whose random blood glucose >13.9 mmol/L or HbA1c >9%. In patients who do not need to start with insulin, metformin should be initiated. Lifestyle modifications including exercise, balanced diet and maintenance of healthy weight apply to all children.

Many studies in recent years support early initiation of insulin therapy as a means to achieve better long-term glycemic control by preserving pancreatic beta cell function [5-8]. Chronic exposure to high glucose levels with resultant increased oxidative stress leads to impaired endogenous insulin secretion and production of mediators which contribute to development of micro- and macro-vascular complications [9]. With such emerging findings, the traditional approach of starting with OHA in patients with lower HbA1c at diagnosis may be gradually replaced by a bold approach of early insulin initiation. Some of the patients who were given insulin early on in their illness have shown to maintain good glycemic control even after insulin was stopped. With this treatment approach, we can aim to minimize the number of patients who fall into the cycle of poor glycemic control and high insulin requirements. However as the general population is still averse to the idea of regular injections, this may take time to be widely practiced or accepted.

This retrospective audit aims to describe the demographics, clinical characteristics and laboratory features of children diagnosed with T2DM in relation with their treatment regimen.

Methodology

Data collection

The data was collected from diabetes database and case records of patients on regular follow-up at Kandang Kerbau (KK) Women's and Children's Hospital, between January 2007 and May 2015. The following data was collected: gender, race, age, weight and height, HbA1c, DKA or non-DKA at presentation, C-peptide, antibody levels, treatment initiated and subsequent changes in treatment regimen at 3 month, 6 month and 1 year from disease onset.

Patient population

Patients included in this audit had age of diagnosis between 10 to 18 years, at least 1 years' duration of diabetes and phenotypic characteristics of Type 2 diabetes (i) BMI at diagnosis >2SDS for age and gender, (ii) antibody negative (GAD and ICA) and (iii) family history of first degree relative with Type 2 diabetes.

Laboratory measurements

The HbA1c assay is measured with ionic exchange High-Pressure Liquid Chromatography (HPLC) on a D-10 system (BIO-RAD). The samples were processed utilizing Abbott Diagnostics' Architect i1000 assay to measure the level of C-Peptide. The level of GAD and ICA is measured with Enzyme-linked Immunosorbent Assay (ELISA). GAD greater than 0.8 U/mL indicates the presence of autoantibody. BMI was calculated by weight (kg) divided by square measured of height (m). BMI SDS was calculated. ICA positive indicates the presence of autoantibody.

Diabetes treatment

At initiation of treatment, those on oral therapy are prescribed metformin 500 mg once or twice daily dosing, while those on insulin therapy are started on basal-bolus regime. Choice of basal insulin varies between NPH and Insulin analogues (Lantus or Levemir), while Novorapid is used as the pre-meal bolus insulin. Combination therapy includes both the basal-bolus regime and metformin. For comparison of outcomes, the subjects divided into two main groups depending on the treatment received for the initial 3 months after diagnosis; single *vs.* combination therapy (Group1); and within single therapy insulin *vs.* OHA (Group 2). Lifestyle management, including dietary modification and maintenance of physical activities, applied to all our patients. All subjects underwent mandatory counseling by an experienced Diabetes Dietician, including calorie prescription for age and weight loss. They were also scheduled to see the Diabetic Nurse Educator (DNE) who provides lifestyle advice.

Statistical analysis

Statistical analyses were conducted using SPSS version 19.0. The association between treatment regimens with demographics and clinical features was tested using multivariable logistic regression. All P values were two-tailed, with P<0.05 considered to be statistically significant (Table 1).

Results

A total of 70 children with T2DM were included in this audit and majority were females (61.4%, n=43). There were more patients of Malay ethnicity (64.2% Chinese, 22.9% Malay and 10% Indians) as compared to the general local population (74.3% Chinese, 13.4% Malays, and 9.1% Indians) [10]. Only 4 out of 70 patients had Diabetic Ketoacidosis (DKA) at presentation, of which 2 were placed on combination therapy and other 2 on insulin-only therapy. Majority of patients were asymptomatic and diagnosed on screening tests on the background of obesity.

Association between treatment regimen with demographics and clinical features

Single therapy *vs.* combination therapy (Group 1): Of the 70 patients, 22 were given combination of insulin and OHA therapy while 48 were given either insulin or OHA. The mean age at diagnosis was lower in the combination therapy group than the single therapy group (12.41 ± 1.76 *vs.* 13.52 ± 1.75, p<0.05). Mean HbA1c at diagnosis was lower in the single therapy group than combination therapy (9.47 ± 3.18 *vs.* 12.4 ± 1.42%, p<0.001). The mean weight at diagnosis however was not significantly different between the two groups. Patients with higher HbA1c and younger age at diagnosis were more likely to be on combination therapy than single therapy (HbA1c at diagnosis: adj* OR=1.84, 95% CI [1.25, 2.71], p<0.05; Age at diagnosis: adj* OR=0.62, 95% CI [0.38, 0.99], p<0.05). There was no relationship between gender, race or C-peptide level and the choice of therapy even after adjustment.

Insulin *vs.* OHA (Group 2): Of the 48 patients on single therapy, 18 were placed on insulin while 30 were on OHA. The mean age at diagnosis was not significantly different between the two subgroups.

Table 1: Demographics and clinical characteristics of patients with type 2 diabetes sorted according to treatment regimen.

	Total (N=70)	Combination therapy	Single therapy	P-value	Insulin-only therapy	OHA-only therapy	P-value
N (%)		22 (31.4)	48 (68.6)		18 (37.5)	30 (62.5)	
Gender							
Male	27 (38.5)	8	19		6	13	
Female	43 (61.5)	14	29		12	17	
Race							
Chinese	45 (64.3)	11	34		10	24	
Malay	16 (22.9)	7	9		6	3	
Indian	7 (10)	3	4		1	3	
Others	2 (2.8)	1	1		1	0	
Type of presentation							
DKA	4 (5.7)	2	2		2	0	
NKDA	66 (94.3)	20	46		16	30	
Mean age at diagnosis (years)	13.2	12.4	13.5	0.016	13.6	13.5	0.785
Mean weight at diagnosis (kg)	67.7 (n=64/70)	65.8 (n=21/22)	68.6 (n=43/48)	0.528	55.8 (n=15/18)	75.5 (n=29/30)	0.004
Mean HbA1c at diagnosis (%)	10.3	12.4 (n=21/22)	9.47 (n=47/48)	<0.001	12.2 (n=17/18)	7.91	<0.001
HbA1c at 1 year (%)	8.35 (n=69/70)	8.97 (n=21/22)	8.18	0.189	10.1 (n=15/18)	7.21	0.001
Change in HbA1c (%)	NA	-3.26 ± 2.09	-1.24 ± 1.72	<0.001	-2.24 ± 2.01	-0.755 ± 1.35	0.02

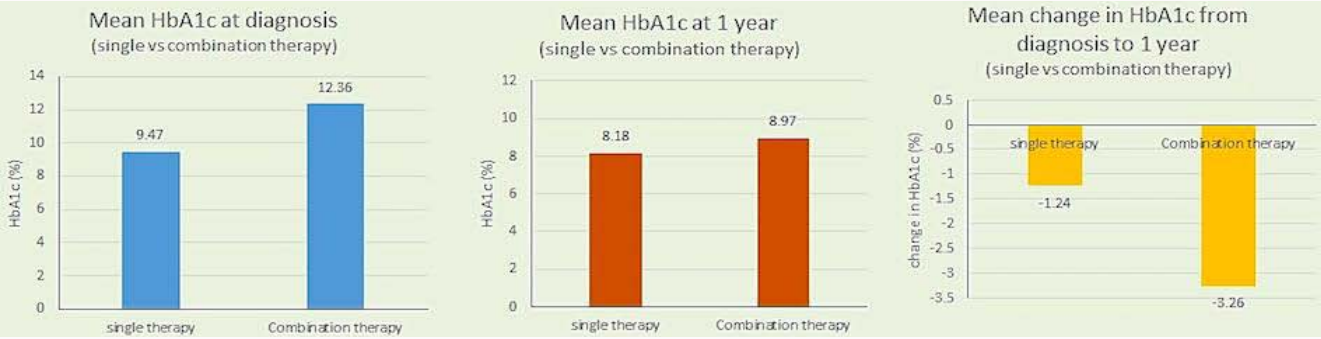

Figure 1: Change in HbA1c in patients on single *vs.* combination therapy from diagnosis to 1 year (Group 1); a) Mean HbA1c at diagnosis, b) Mean HbA1c at one year, c) Mean change in HbA1c from diagnosis to 1 year.

However, the mean HbA1c at diagnosis was significantly lower in the OHA than insulin group (7.91 ± 2.06 *vs.* 12.24 ± 2.95%, p<0.001). The mean weight at diagnosis was also significantly higher in those on OHA than insulin (75.46 ± 21.13 *vs.* 55.83 ± 17.97 kg, p<0.05). Patients with higher HbA1c and older at diagnosis were less likely to be on oral therapy (HbA1c at diagnosis: adj* OR=0.51, 95% CI [0.32, 0.82], p<0.05; Age at diagnosis: adj* OR=0.50, 95% CI [0.24, 1.03], p<0.05). Again, there was no relationship between gender, race or C-peptide level and the choice of therapy even after adjustment.

Change in HbA1c within the respective treatment groups

The change in HbA1c from diagnosis to 1 year between patients on combination therapy, insulin-only and OHA-only therapy was different. For those on combination therapy, the change in HbA1c was 3.26% (26.4% reduction), while those on insulin-only was 2.24% (18.3% reduction) and OHA-only 0.76% (9.55% reduction).

Single therapy *vs.* Combination therapy (Group 1): The change of HbA1c from diagnosis to 1 year between patients on single therapy and combination therapy was significantly different. For participants on single therapy, the reduction in HbA1c was 1.24% (13.1% reduction) *vs.* 3.26% (26.4% reduction) [p<0.001] for those in the combination therapy (Figure 1).

Insulin *vs.* OHA (Group 2): The change of HbA1c from diagnosis to 1 year between patients on insulin *vs.*OHA therapy was significantly different. Those on insulin-only the reduction in HbA1c was 2.24% (18.3% reduction) *vs.* 0.76% (9.55% reduction) [p=0.02] for those on OHA-only (Figure 2).

Change in treatment regimen within the respective treatment groups

Of the 22 patients who were started on combination therapy, 17 remained on combination therapy at the end of 1 year while the remaining 5 (22.7%) patients were converted to OHA only. Of the 18 patients who were started on insulin therapy, 3 (16.7%) were converted to OHA at the end of 1 year, 4 stayed on insulin while 11 were converted to combination therapy. This suggests that proportion of patients who were able to come off insulin at the end of 1 year was higher in the combination therapy group as compared to those started on insulin-only.

Of the 30 patients who were started on OHA therapy, 28 remained on OHA at the end of 1 year, 1 was converted to combination

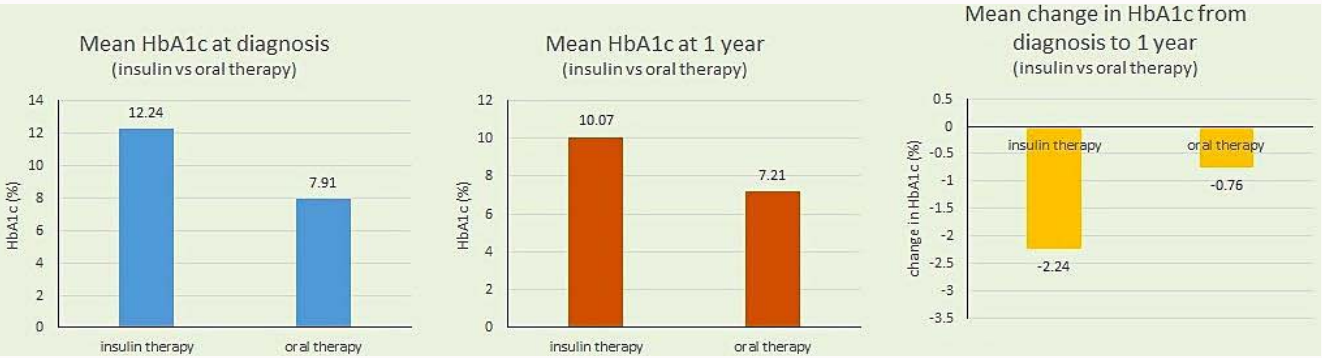

Figure 2: Change in HbA1c in patients on insulin *vs.* oral therapy from diagnosis to 1 year (Group 2) a) Mean HbA1c at diagnosis, b) Mean HbA1c at one year, c) Mean change in HbA1c from diagnosis to 1 year.

therapy while 1 managed to be taken off all medications and relied on lifestyle modification alone. This group represents patients who likely have a lower degree of beta cell failure at diagnosis and more insulin resistance, which can be improved with metformin. This is also consistent with findings of lower mean HbA1c at diagnosis and higher mean weight at diagnosis in this group.

Discussion

Factors affecting choice of therapy at diagnosis

Treatment of T2DM in adults has been a well-studied topic but the same cannot be said of the pediatric population. While oral hypoglycemic agents are often the first-line treatment in adults with newly diagnosed T2DM, metformin remains as the only oral medication formally approved for use in children with T2DM. A significant proportion of our pediatric patients are treated with insulin at presentation. One main reason is that insulin therapy helps to rapidly bring down glucose level and euglycemia can be achieved within a shorter period of time; this is especially important for patients who present young or are symptomatic. This aggressive approach allays, to some extent, the fears of hyperglycemia-induced micro- and macro-vascular complications, which would logically set in earlier in life if one were diagnosed with diabetes at a young age. Another reason lies in the overlapping presentations of Type 1 and Type 2 DM in children, resulting in physicians treating some T2DM cases as insulin deficiency, especially when Type 1 is in fact the more common entity in children.

The ISPAD guidelines suggest that patients who are metabolically stable i.e. HbA1c<9% and without symptoms should be started on metformin 500 mg daily and titrated weekly, while those who are metabolically unstable should be started on NPH or basal insulin with or without metformin; lifestyle change should be initiated in all patients from diagnosis. In our center, treatment regime was also selected based on phenotypic characteristics of the patient.

HbA1c – higher HbA1c more likely given combination than single therapy; and within single therapy, more likely insulin than OHA

Patients with higher HbA1c at diagnosis are considered to be "metabolically unstable" as there is greater degree of hyperglycemia, and they are also more likely to be in hyperglycemic state for a longer duration of time before presentation. Sustained hyperglycemia is likely to have caused greater extent of beta cell failure and insulin deficiency (by theory of glucose toxicity) and insulin treatment is hence the preferred choice. On top of that, combination therapy is preferred because there is a synergistic effect between providing insulin and increasing insulin sensitivity. A meta-analysis comparing combination therapy (metformin and insulin) *vs.* insulin-only therapy in T2D showed that the former resulted in greater reduction in HbA1c, less weight gain and lower insulin dose required to maintain acceptable glycemic control [11].

Age - younger patients more likely given combination than single therapy

The children who are started on combination therapy are slightly younger than those on single therapy (12.41 ± 1.76 *vs.* 13.52 ± 1.75, $p<0.05$). Younger children usually present with symptoms of hyperglycemia, in contrast to the older children who are more likely to be diagnosed from screening tests. Insulin is needed in younger patients to treat the hyperglycemia and symptoms associated with it. If the clinical phenotype of the patient is distinctly like T2D at presentation then metformin is added to insulin therapy. It is less common for a younger patient to be started on metformin alone due to the way they tend to present.

Weight – higher weight more likely given OHA than insulin

The glucose-lowering effect of metformin occurs primarily via the suppression of hepatic gluconeogenesis. Over the years, the effect of metformin on weight in patients with diabetes has not been conclusively proven. However most evidence still point towards metformin resulting in weight loss (though often modest) in patients who are obese when compared to placebo, especially with good adherence to metformin therapy [12]. Insulin on the other hand has anabolic effects and has been shown to cause weight gain albeit with better glycemic control in general [13]. Children with T2D and obesity are likely to have underlying insulin resistance and metformin inevitably becomes the treatment of choice in view that further weight gain can aggravate the insulin resistance state.

Early initiation of insulin

The concept of glucose toxicity, a well-established entity in animal models, is believed to be the mechanism through which pancreatic beta cell failure occurs. Chronic exposure to high glucose levels causes increased oxidative stress to the beta cells, resulting in cellular dysfunction with decreased expression of the insulin gene, ultimately leading to reduced insulin secretion by the pancreatic beta cells. It has also been demonstrated that even when good glycemic control is maintained subsequent to the period of hyperglycemia, the products of oxidative stress and mitochondrial damage remain up regulated for an extended duration of time, supporting the concept of

metabolic memory [9,14]. Presence of these products contributes to development of micro and macrovascular complications of diabetes. A study by Engerman et al. [15] compared dogs subjected to 2.5 years of poor glycemic control followed by 2.5 years of good glycemic control with dogs subjected to 2 months of poor glycemic control followed by treatment with insulin to maintain good glycemic control for the remaining 5 years the latter group exhibited significantly less signs of retinopathy. This understanding leads us to wonder if early treatment of T2DM with insulin actually allows us to provide better glycemic control in the long run by preserving beta cell function as much as possible, and reduce the rates of vascular complications.

In this retrospective audit, we have seen that patients who were started on insulin within the first 3 months of diagnosis (namely those on combination and insulin-only therapies) showed significant improvement in glycemic control at the end of 1 year. Measuring insulin and C-peptide levels and comparing them between patients treated early with insulin *vs.* those without insulin may provide more conclusive evidence on the effects of treatment on beta cell function.

The effect of intensive short-term insulin therapy in patients with T2DM was studied in a randomized, parallel group trial in 2008 [8]. The study population was randomly assigned to one of three treatment groups-continuous subcutaneous insulin therapy, multiple daily insulin injections and oral treatment. Pharmacological treatment was stopped once patient achieved sustained normoglycemia for 2 weeks and glycemic control was followed up upon. At 1 year, it was found that 51% of those who had received continuous insulin and 45% of those who had received multiple daily insulin injections remained normoglycemic compared to 27% of patients randomized to the oral treatment group. Patients who were given continuous insulin therapy had an increase in beta cell function of 160% *vs.* 105% for those treated with oral agents (measured using the homeostasis model assessment of basal beta cell function, HOMA B).

With increasing number of studies providing results in favor of early insulin treatment, the traditional notion of following a stepwise progression from conservative oral therapy to insulin therapy in treatment of T2DM has been challenged. Patients often correlate the type of treatment to the severity of their disease i.e. only "severe" diabetes should require insulin injections. This mindset may serve as a barrier for physicians to promote early insulin therapy to patients with newly diagnosed T2DM. Education hence plays a pivotal role in adjusting the perceptions of the general public and encouraging acceptance of insulin injections for the benefit of better long-term glycemic control.

Limitations of Audit

I. One of the limitations is the lack of serial C-peptide measurements of the subjects during the course of diabetes. Having C-peptide levels would allow us to analyze the relationship between residual beta cell function and HbA1c as well as the resultant change in treatment regime. It will provide evidence on the benefit of early initiation of insulin in preserving beta cell function in the long run. It will also be interesting to follow up on the glycemic control of the patients over a longer term (for example, up to 5 years, instead of 1 year), as that would give us more information on their long-term outcomes.

II. Diabetes is a disease that is closely linked to lifestyle and the results of this audit could be further enhanced if there was an objective assessment of patients' attitudes and behavior, which might have influence their treatment outcomes.

III. In our local population, IA-2 antibody is uncommon hence only anti-GAD and anti-islet cell antibodies levels are taken as part of our clinical phenotyping.

Conclusion

Patients with younger age or higher HbA1c at diagnosis are more likely to be started on insulin and metformin, rather than insulin or metformin alone. Patients who have higher weight at diagnosis are more likely to be started on metformin alone rather than insulin alone.

Insulin-only, OHA-only and combination therapy all lead to significant reduction in HbA1c. From our audit, there is suggestion that combination therapy may be more effective in lowering HbA1c compared to insulin-only regime.

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