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Treatment regimens and glycosylated hemoglobin levels in youth with type 1 and type 2 diabetes: data from SEARCH (United States) and YDR (India) registries

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Abstract

Objective: To compare treatment regimens and glycosylated haemoglobin (A1c) levels in type 1 (T1D) and type 2 diabetes (T2D) using diabetes registries from two countries – SEARCH for Diabetes in Youth (SEARCH) in the U.S. and the Registry of People with Diabetes with Youth Age at Onset (YDR) in India.

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Author Contributions: N.T, D.D, V.M, R.F.H and E.J.M.-D conceptualized the study and oversaw the data harmonization. C.W.H., P.P., T.C.O., S.P.I., M.G.K. and A.A. harmonized and transformed data into the common data model (OMOP). R.P.W contributed in categorizing treatment regimens. C.W.H., T.C.O., and S.P.I analysed the data. A.A and V.M prepared the first draft of the manuscript and provided oversight for study analyses. All authors reviewed and edited the manuscript and contributed to discussion. All authors have read and approved the final manuscript.

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Methods: The SEARCH and YDR data were harmonized to the structure and terminology in the Observational Medical Outcomes Partnership (OMOP) Common Data Model (v5). Data used in the analyses were from youth with physician-diagnosed T1D and T2D between 2006-2012 for YDR, and 2006, 2008 & 2012 for SEARCH and were <20 years at the time of diagnosis. We compared diabetes treatment regimens and A1c levels across the two registries.

Results: We included 4,003 T1D (SEARCH=1,899; YDR=2,104) and 611 T2D (SEARCH =384; YDR=227) youth for this analysis. The mean A1c was higher in YDR compared to SEARCH (T1D: 11.0 ± 2.9 vs. 7.8 ± 1.7%, p<0.001; T2D: 9.9 ± 2.8 vs. 7.2 ± 2.1%, p<0.001). Among T1D youth in SEARCH, 65.1% were on a basal/bolus regimen, whereas in YDR, 52.8% were on once/twice daily insulin regimen. Insulin pumps were used by 16.2% of SEARCH and 1.5% of YDR youth with T1D. Among T2D youth, a majority were on metformin only, followed by insulin+any oral hypoglycemic agents and insulin only in both SEARCH and YDR.

Conclusion: Efforts to achieve better glycemic control for both T1D and T2D youth are urgently needed in order to reduce the risk of long term complications.

Keywords

Diabetes Registry; type 1 diabetes; youth onset type 2 diabetes; A1c levels

INTRODUCTION

Diabetes is reported to be increasing in younger age groups in India[1,2] and the United States (U.S.)[3-6]. This has long-term implications for increasing the burden of complications, health care costs, and risk of diabetes in future generations. The health care delivery system in India is a mix of both public and private health-care service providers with the latter providing almost 80% of the health care[7]. The U.S. does not have a universal healthcare program, unlike other developed countries[8], and health care facilities are largely owned and operated by private sector businesses. In the U.S., 58% of community hospitals are non-profit, 21% are government-owned, and 21% are for-profit. Healthcare coverage is provided through a combination of private health insurance and public health coverage (e.g. Medicare, Medicaid)[9]. Any drawbacks in the health care delivery system in both the countries will reflect in the treatment pattern of any disease condition.

The treatment options for type 1 diabetes (T1D) and type 2 diabetes (T2D) are very different. Differences in treatment patterns, both within and between countries are also likely to exist. Unlike the U.S., India has very limited data on the treatment patterns in both T1D and T2D. Comparing treatment regimens among youth with T1D and T2D in the U.S. and India will highlight differences in day to day management of diabetes and the potential impact on glycemic control. In this analysis, we compare treatment regimens in the U.S. and India and corresponding glycosylated haemoglobin (A1c) levels in youth with T1D and T2D ascertained by the SEARCH for Diabetes in Youth (SEARCH) study registries and Registry of People with Diabetes with Youth Age at Onset (YDR).

METHODS

Data for this analysis were obtained from the collaborative partnership between SEARCH for Diabetes in Youth (SEARCH) registry in the U.S. and the Registry of People with Diabetes with Youth Age at Onset (YDR) in India.

SEARCH for Diabetes in Youth

SEARCH is a multi-ethnic, population-based registry with five sites across the U.S. ascertaining physician-diagnosed non-gestational incident diabetes cases among individuals aged 19 years or younger. More detailed information about SEARCH is published elsewhere[10-12]. Each site conducts active surveillance under the Health Insurance Portability and Accountability Act (HIPAA) waivers of consent using networks of endocrinologists, healthcare providers, hospitals and community health centers, and clinical and administrative data systems along with electronic medical records. Cases are confirmed as valid after review of medical records or by the referring physician. All registered participants are asked to complete an Initial Participant Survey (IPS) (average response rate for incident cases 2006-2012, 82%). Participants diagnosed in 2006, 2008 and 2012 were invited to participate in an in-person baseline research visit (IPV) (average response rates between 46%, and 65%), where data were obtained on sociodemographic characteristics, height, weight, medications, glucose control and other risk factors for diabetes-related complications, including laboratory measurements. Blood samples (A1c) were taken and analysed at a central laboratory. For the purposes of this manuscript, the IPV baseline research visit is referred to as the baseline visit.

Registry of People with Diabetes with Youth Age at Onset

The YDR registry is an observational multicenter clinic-based registry enlisting all cases of physician-diagnosed diabetes, diagnosed at the age of 25 years or younger, who were registered at a designated registry reporting center on or after January 1, 2000, residing within assigned geographical areas. More detailed information about YDR is published elsewhere[13]. Individuals are classified into various diabetes categories based on the assessment of the principal investigator at the reporting center using symptom-based clinical criteria agreed upon by the registry expert group prior to initiation of data collection in 2006. YDR data collection is coordinated by the Indian Council of Medical Research through regional collaborating centers and their interacting reporting centers. All individuals have a proforma (registration and clinical extract) completed by the participant and physician to obtain information on socio-demographics, clinical profile, anthropometrics and laboratory measurements of the individual. Data from the period 2000-2006 were collected retrospectively in a structured format from medical records; while data from 2006-2012 were collected prospectively and completed by both the participant and physician at the time of registration, which is referred to here as the baseline visit. There are eight regional collaborating centers across India who provide cases to YDR. For this project, data from three of the eight regional collaborating centers (one in Chennai (Madras Diabetes Research Foundation) and two in New Delhi (All India Institute of Medical Sciences (AIIMS) and the University College of Medical Sciences, Delhi)) were used. Both previously treated and

untreated cases were included. For the purposes of this manuscript, the baseline registration visit is referred to as the baseline visit.

Data Harmonization

The SEARCH and YDR data were harmonized to the structure and terminology in the Observational Medical Outcomes Partnership (OMOP) Common Data Model. Additional details of data harmonization are provided in a previous article by Hockett et al. within this special edition.

Demographic and Clinical Characteristics—Age at diagnosis (in years) was calculated using participant's date of birth and date of diagnosis, which were obtained from self-report and medical record abstractions, respectively. Age at baseline visit was calculated using the participant's date of birth and date of the baseline visit. Diabetes duration (in months) is the time from the date of diabetes diagnosis to the date of the baseline visit. Youth's sex was self-reported at the baseline visit.

Diabetes type (T1D and T2D) and date of diagnosis were obtained from medical records. For SEARCH participants, height and weight were measured at the baseline visit. Hemoglobin A1c was measured from a fasting blood draw taken at the baseline visit. Blood samples were obtained only if there was no episode of diabetic ketoacidosis within the prior month. Specimens were processed at the site and shipped within 24 h to the Northwest Lipid Metabolism and Diabetes Research Laboratories in Seattle, Washington, which serves as the study's central laboratory. Medications and treatment were self-reported at the baseline visit. For YDR, height and weight were obtained clinically at the respective reporting centers, using standardized protocols. A1c was obtained from the most recent clinical encounter prior to the baseline visit (analyzed locally). Data on medication and treatment were obtained clinically at the respective reporting centers by self-reported and/or medical records. Body mass index (BMI) was calculated as kg/m^2 and BMI z-scores were calculated using the World Health Organization Child Growth Standards reference data[14].

Categorization of treatment regimens and A1c levels—For T1D youth, treatment regimens were grouped into five categories – insulin pump (SEARCH=pump; YDR=pump); basal/bolus regimens (SEARCH= basal/bolus regimens; YDR=multidose); multiple daily injections without basal insulin (MDI) (SEARCH=MDI; YDR=thrice a day); once daily or twice daily regimens (SEARCH=older regimens; YDR=once a day or twice a day); and unknown regimens/no information (SEARCH=unknown or missing; YDR=unknown or missing). For T2D youth, treatment regimens were grouped into five categories – metformin only (SEARCH=metformin only; YDR=biguanides); other oral hypoglycemic agents (OHAs) (which also included two or more OHAs) (SEARCH=other oral; YDR=sulphonylureas, glitazones, alpha glucosidase inhibitor, meglitinide analogues or DPP-4 inhibitor); insulin only (SEARCH=insulin only; YDR= regular, intermediate acting, premixed, long acting analogue, short acting analogue and premixed analogue); insulin + any OHAs (including metformin) (SEARCH=insulin+metformin or insulin+other oral; YDR=any insulin and any oral); and no medications/no information (SEARCH=none or missing; YDR=no treatment selected).

Hemoglobin A1c levels were grouped into three categories—less than 7.5% (9.4 mmol/L), 7.5% to 9.0% (9.4 to 11.8 mmol/L), and greater than 9.0% (11.8 mmol/L)) based on ISPAD guidelines[15].

Statistical Analysis

For the current analysis, we included incident T1D and T2D cases diagnosed between 2006 and 2012 among youth aged <20 years at diagnosis for YDR, and a subset of SEARCH participants diagnosed with diabetes in 2006, 2008, and 2012 and who completed a baseline visit. This sample selection aligned the clinical information in both registries.

For continuous variables, mean values ± standard deviation are presented. Two-sample t-tests were conducted to assess differences in continuous variables between the two registries. For categorical variables, counts and percentages are presented. Chi-square tests were used to determine differences in variables of interest across the two registries. All the statistical analysis was conducted using SAS statistical software v9.4 (SAS Institute, Inc, Cary, North Carolina). P-values <0.05 were considered significant.

RESULTS

Table 1 presents the relevant clinical characteristics by diabetes type in SEARCH and YDR. For youth with T1D, mean age at baseline visits (11.0 ± 4.3 vs. 10.9 ±5.1 years, p=0.346) and age at diagnosis (10.1 ± 4.3 vs. 10.4 ± 4.9 years, p=0.048) were similar in SEARCH and YDR respectively. For T2D, a significant female preponderance was seen in the SEARCH, but not the YDR. Among SEARCH youth, the duration of diabetes until the baseline visit was higher compared to YDR for both T1D (10.3 ± 7.4 vs. 6.2 ± 9.7 months, p<0.001) and T2D (13.3 ± 8.2 vs. 7.0 ± 10.5 months, p<0.001). The mean A1C of youth with T1D (11.0% ± 2.9% vs. 7.8% ± 1.7%, p<0.001) and T2D (9.9% ± 2.8% vs. 7.2% ± 2.1%, p <0.001) were higher in YDR youth compared to those in SEARCH.

Table 2 shows the treatment regimens for youth with T1D and T2D in SEARCH and YDR. For SEARCH youth with T1D, 65.1% were on a basal/bolus regimen, whereas in YDR only 23.5% were on a basal/bolus regimen. About 53% of YDR youth were on a once or twice daily regimen compared to 2% in SEARCH youth. Insulin pumps were used by 16.2% of SEARCH youth, but only 1.5% of YDR youth. For youth with T2D, 43.0% of SEARCH youth were on Metformin only and 26.3% were on Insulin + any OHA, compared to 30.0% and 13.7% in YDR youth, respectively.

Categories of glycemic control, based on A1c levels at the baseline visit, are shown for youth with T1D and T2D in SEARCH and YDR, by treatment regimen (Figures 1a & 1b). Among SEARCH youth with T1D, in each category of treatment regimen, around 40 to 50% met the recommended glycemic control target of ≤7.5% (58 mmol/L), whereas in YDR only 10 to 15% were in the target range. For youth with T2D, according to treatment regimens, 40 to 90% of SEARCH youth met the recommended A1C target of ≤7.5% whereas in YDR only 10 to 45% met the target. Mean A1c levels were uniformly higher in YDR youth when compared to SEARCH youth among both T1D and T2D, regardless of regimens used (Figures 2a & 2b).

DISCUSSION

We found important and significant differences between SEARCH and YDR in treatment patterns for youth with T1D: a majority of SEARCH youth with T1D were on basal/bolus insulin regimens or were using insulin pumps, whereas most YDR youth were treated with once or twice daily insulin regimens. For youth with T2D, in both the registries, the first line of treatment was metformin only followed by insulin and insulin + any OHAs. We also found that A1C levels were higher in YDR youth than SEARCH youth, for both T1D and T2D, irrespective of the regimens used.

Type 1 Diabetes

A variety of insulin formulations and pre-mixed human insulins and analogs are available in both countries. Most patients with T1D need multiple daily injections, a basal/bolus regimen or an insulin pump[16-19]. In SEARCH, 65.0% of T1D youth were on basal/bolus regimens while only 23.5% of YDR youth with T1D were using such a regimen. Moreover, there were significant differences in usage of insulin pumps between US and India (16.2% vs 1.5%, $p<0.001$). While in the US, paediatric patients with T1D commonly use insulin pumps for insulin delivery; in India, pumps are very expensive and the cost is not reimbursable or covered by insurance, thus limiting their use. Factors like motivation level, family support, and cognitive skills may also influence the use of insulin pumps in Indian children and adolescents[20]. While this was not directly studied here, the main reasons for differences in the treatment pattern for youth with T1D between the two registries is likely to be related to differences in provider practices and the health care delivery systems between the two countries, and not to major differences in availability of insulin types and formulations.

Among the insulin pump users in SEARCH, a substantial proportion (45.5%) had good glycemic control (<7.5%), although this was not observed among the smaller number of YDR youth using pumps (12.5%). In a retrospective analysis of 33 patients (17 with T1D and 16 with T2D) who were on insulin pumps and were followed up for a mean duration of 3.4 years, a significant reduction in HbA1c was observed after initiating pump therapy with a reduction in frequency of severe hypoglycaemia with no instances of diabetic ketoacidosis[21]. A previous report by SEARCH found that youth with T1D that used an insulin pump had lower A1C levels and less hospitalizations without any hypoglycemic episodes[22]. Taken together, these findings suggest that insulin pump therapy for youth with T1D offers a better chance at adequate glycemic control.

Type 2 Diabetes

The majority of youth with T2D in both registries were on approved treatment regimens (i.e. metformin and insulin). More than 30% of the SEARCH and YDR youth with T2D were on insulin or insulin + any OHAs. Unlike T1D, an insulin-containing regimen is generally not the first-line of treatment for T2D, unless the patient presents in diabetic ketoacidosis (DKA) or has a high A1c (>10%) at the time of diagnosis[23]. When oral treatment fails, insulin is recommended to improve glycemic control. Studies in adults have suggested that early insulin treatment in T2D reduces the risk of chronic vascular complications[24,25], but long-term data in youth are limited.

In SEARCH, 60-70% of T2D youth were at the recommended glycemic target of <7.5%, whereas in YDR, 20 to 30% met the target regardless of the treatment regimen used. In both the registries, the recommended glycemic control target could not be reached by all, which may be due to their pubertal status. Glycemic control deteriorates during puberty due to increase in lean body mass, which increases insulin requirement leading to insulin resistance. Certain behavioural changes and psychosocial issues occurring during adolescence also further worsens glycemic control[26]. Therefore, physicians need to identify barriers to achieving optimal glycemic control in order to prevent the development of vascular complications. It is recommended that adolescents with T2D should have two to four A1c measurements per year because adolescents may require insulin therapy more rapidly than adults[27]. SEARCH had a higher percentage of youth in the insulin + any OHAs group which may be one of the reasons for the lower A1c levels in SEARCH compared to YDR. Among YDR youth, the mean A1c levels were greater than 7.5% for all treatment regimens.

The TODAY study, a clinical trial of U.S. adolescents with T2D, reported that metformin monotherapy maintained optimal glycemic control only in half of the youth and demonstrated that the addition of rosiglitazone, but not intensive lifestyle intervention, was superior to metformin alone[23,28]. In another study, glimepiride was shown to reduce A1c levels but was not equivalent to metformin. Moreover, it stimulated weight gain; it is not approved by the Food and Drug Administration for youth with T2D[29,30]. There are clinical trials on new oral hypoglycemic agents including DPP-4 inhibitors (sitagliptin, saxagliptin, and linagliptin), and several of the new injectable agents, including GLP-1 agonists (such as exenatide and liraglutide). However, these drugs are not yet approved for youth with T2D. Our study suggests that more aggressive treatments are needed in youth with T2D to bring their glycemic control within target range.

A nationwide Indian study of adults (ICMR-INDIAB) covering four Indian states, showed that higher A1c levels were observed in the oldest age group studied (20–24 years)[31]. In the U.S., the T1D Exchange, a large registry of youth diagnosed with T1D from 67 centers across the U.S., showed glycemic control among patients 8–18yrs old worsened over time[32]. In this paper, we found that more than 40% of youth with T1D or T2D (aged 19 years or younger) had A1c levels above 7.5%, indicating a substantial burden of suboptimal glycemic control, almost regardless of treatment regimen.

There are several limitations to our study. First, in both registries, the treatment regimens captured at the time of the baseline visit were self-reported and did not capture adherence and compliance. In YDR, data from only three centers (Chennai and two in New Delhi) were included and results may not be fully representative of the larger population of youth with diabetes in India. Since data were not shared across registries, we were not able to conduct multivariate analyses, which would have allowed us to control for differences between the two registries (such as the longer diabetes duration to baseline visit in SEARCH vs YDR). These findings only reflect the treatment patterns and A1c levels of youth at the time of inclusion into the registries, within the first year of diagnosis. In some centers in the U.S., for example, over time, up to 50-70% of T1D youths are being treated with pumps and this later treatment is not captured in this analysis[33]. Additionally, ADA targets of care were

updated in 2014 and the findings reported here reflect glycemic control during a period of time with slightly different standards of care in the U.S. Finally, and importantly, A1c levels were not standardized across registries. While SEARCH used standardized techniques and a central certified laboratory[34], this was not the case for YDR and could explain some of the differences seen in A1c levels between SEARCH and YDR. It is however, likely that the more aggressive treatment regimens in the U.S. explain the relatively more optimal A1c levels achieved among SEARCH youth. The major strength of our study rests on the fact that this is the first attempt to harmonize and compare two youth diabetes registries internationally, including youth with both T1D and T2D.

Development of microvascular complications is closely linked to suboptimal glycemic control in both T1D and T2D. The high A1c levels in youth with both forms of diabetes is of concern, as these individuals are likely to be exposed to a longer period of hyperglycaemia, compared with subjects with onset of diabetes later in life. Indeed, among youth with T2D, complications may sometimes be present even at the time of diagnosis of diabetes[1,35-37]. Moreover, in such youth, rapid progression of complications is sometimes observed within 5 years of diagnosis[38-40]. Regardless of treatment regimens used, A1c levels for the majority of youth in SEARCH and YDR are above the ADA recommended levels, particularly in YDR. This glycemic burden may put them at high risk of developing complications during the prime of their life unless immediate steps are taken to improve diabetes care in youth and lower the A1c levels. Treatment efforts should aim for better glycemic control in both countries in order to prevent long term complications.

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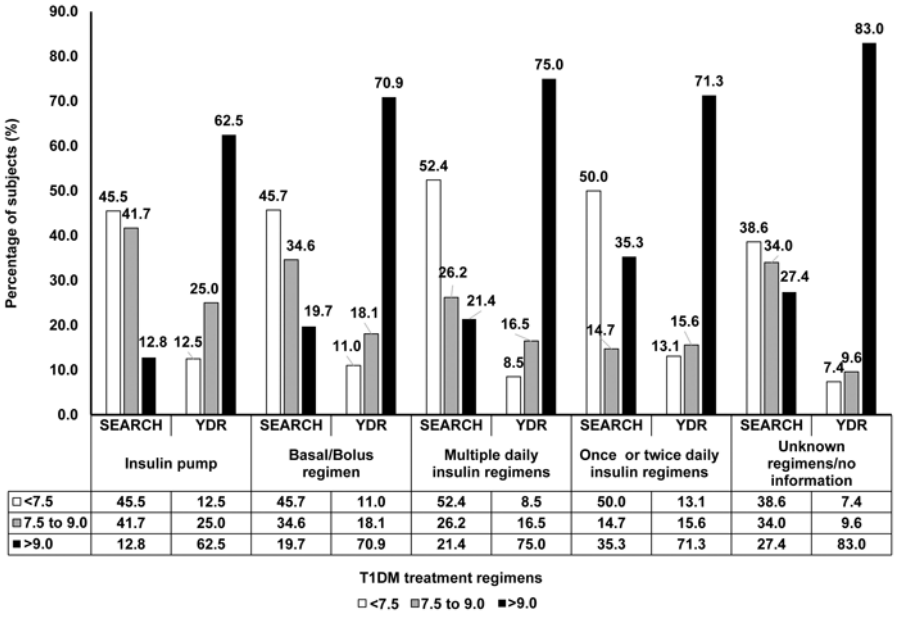

	Insulin pump		Basal/Bolus regimen		Multiple daily insulin regimens		Once or twice daily insulin regimens		Unknown regimens/no information	
	SEARCH	YDR	SEARCH	YDR	SEARCH	YDR	SEARCH	YDR	SEARCH	YDR
<7.5	45.5	12.5	45.7	11.0	52.4	8.5	50.0	13.1	38.6	7.4
7.5 to 9.0	41.7	25.0	34.6	18.1	26.2	16.5	14.7	15.6	34.0	9.6
>9.0	12.8	62.5	19.7	70.9	21.4	75.0	35.3	71.3	27.4	83.0

Figure 1a.

Glycemic control by treatment regimen in SEARCH (2006, 2008, 2012) and YDR (2006-2012) for T1D

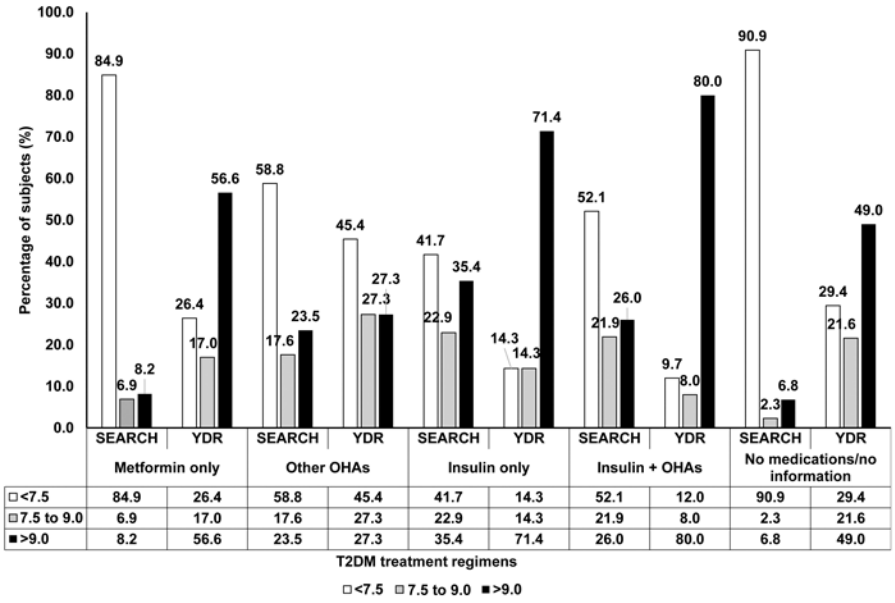

Figure 1b.

Glycemic control by treatment regimen, in SEARCH (2006, 2008, 2012) and YDR (2006-2012) for T2D

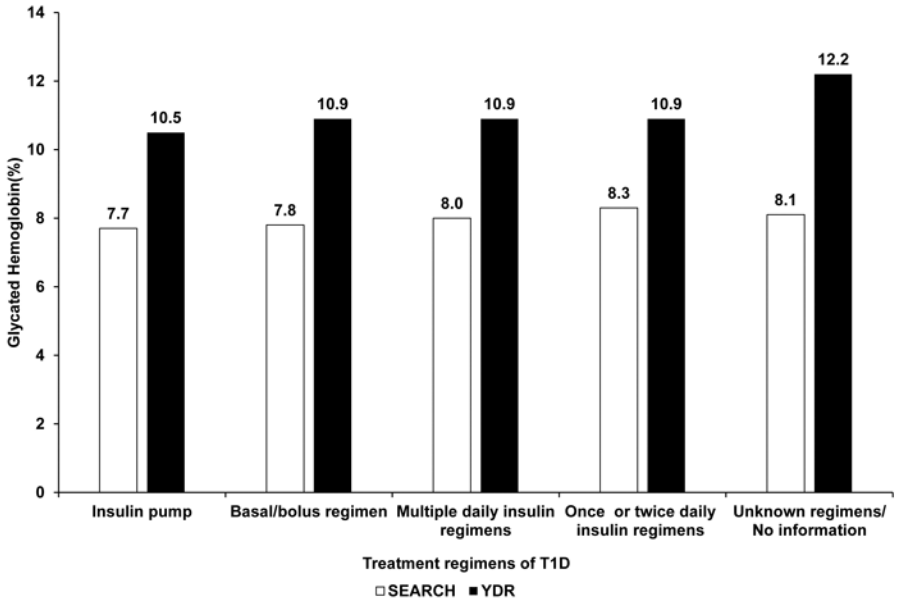

Figure 2a.

Mean levels of A1c levels by treatment regimen in SEARCH (2006, 2008, 2012) and YDR (2006-2012) for T1D

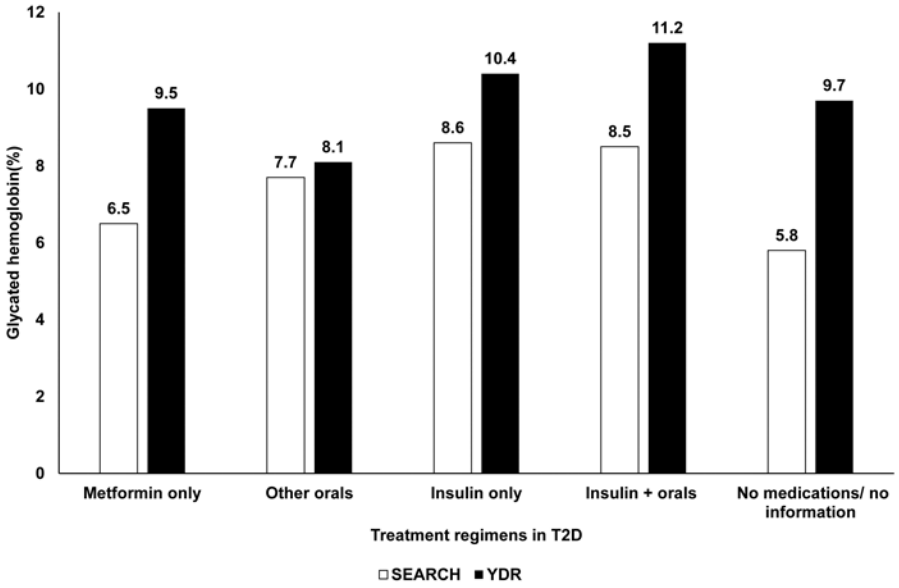

Figure 2b.

Mean levels of A1c levels by treatment regimen in SEARCH (2006, 2008, 2012) and YDR (2006-2012) for T2D

Table 1:

Demographic and clinical characteristics youth diagnosed with T1D and T2D in SEARCH (2006, 2008, 2012) and YDR (2006-2012), by diabetes type

Variables	Type 1 diabetes (n=4,003)			Type 2 diabetes (n=611)		
	SEARCH* (n=1,899)	YDR (n=2,104)	p-value	SEARCH* (n=384)	YDR (n=227)	p-value
Age at diagnosis (yrs), mean (SD)	10.1 ± 4.3	10.4 ± 4.9	0.048	14.4 ± 2.7	16.1 ± 2.8	<0.001
Age at baseline visit (yrs), mean (SD)	11.0 ± 4.3	10.9 ± 5.1	0.346	15.6 ± 2.8	16.6 ± 2.9	<0.001
Gender (female), n (%)	870 (45.8)	990 (47.1)	0.432	240 (62.5)	111 (48.9)	0.001
Duration of diabetes at baseline visit (months), mean (SD)	10.3 ± 7.4	6.2 ± 9.7	<0.001	13.3 ± 8.2	7.0 ± 10.5	<0.001
BMI z-score (WHO) at baseline visit, mean (SD)	0.7 ± 1.2	−0.5 ± 1.6	<0.001	3.2 ± 1.1	1.7 ± 2.1	<0.001
A1c at baseline visit, mean (SD)	7.8 ± 1.7	11.0 ± 2.9	<0.001	7.2 ± 2.1	9.9 ± 2.8	<0.001
A1c Categories, n (%)			<0.001			<0.001
Less than 7.5%	797 (42.0)	151 (7.2)		260 (67.7)	41 (18.1)	
7.5 to 9.0%	620 (32.6)	214 (10.2)		50 (13.0)	29 (12.8)	
Greater than 9.0%	355 (18.7)	959 (45.6)		64 (16.7)	98 (43.2)	
Missing	127 (6.7)	780 (37.1)		10 (2.6)	59 (26.0)	

SD – standard deviation; BMI – body mass index; WHO – World Health Organization; A1c – glycated haemoglobin

* a subset of SEARCH participants diagnosed with diabetes in 2006, 2008, and 2012 and who completed a baseline visit.

Table 2:

Treatment regimens for T1D and T2D youth in SEARCH (2006, 2008, 2012) and YDR (2006-2012), by diabetes type, n (%)

Treatment regimens	Type 1 diabetes (n=4,003)			Type 2 diabetes (n=611)			
	SEARCH (n=1,899)	YDR (n=2,104)	p-value	Treatment regimens	SEARCH (n=384)	YDR (n=227)	p-value
Insulin pump	307 (16.2)	31 (1.5)	<0.001	Metformin only	165 (43.0)	68 (30.0)	0.001
Multiple daily injections insulin regimen	47 (2.5)	295 (14.0)	<0.001	Other OHAs	20 (5.2)	15 (6.6)	0.472
Basal/bolus regimen	1,237 (65.1)	494 (23.5)	<0.001	Insulin only	49 (12.8)	43 (18.9)	0.039
Once or twice daily insulin regimens	38 (2.0)	1110 (52.8)	<0.001	Insulin + any OHAs	101 (26.3)	31 (13.7)	<0.001
Unknown regimens / no information	270 (14.2)	174 (8.3)	<0.001	No medications / no information	49 (12.8)	70 (30.8)	<0.001

OHA – oral hypoglycaemic agents