

# The Utility of Oral Diabetes Medications in Type 2 Diabetes of the Young

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**Abstract: Background:** An estimated two-thirds of medications prescribed for use in pediatric patients have not been proven safe or effective for this patient population. Since 1995 a dozen orally administered diabetes medications or combination of medications for the management of type 2 diabetes mellitus have been approved by the Food and Drug Administration. Of these, only one (metformin) is approved for use in pediatrics. As the prevalence of children diagnosed with type 2 diabetes continues to rise, the need for adequate information regarding the safety, efficacy, and appropriate dosing of oral diabetes medications in the pediatric population likewise increases.

**Objective:** The purpose of this paper is to present the data available regarding the use of oral diabetes medications in a pediatric type 2 diabetes population.

**Methods:** A computerized literature search was performed using Medline and the Cochrane Database of Systematic Reviews.

**Results:** The Table consists of a summary of data regarding the use of oral antidiabetic agents in pediatric patients. These data include information regarding drug safety and efficacy and/or drug pharmacokinetic and drug dosing information.

**Conclusions:** Data concerning the safety and efficacy of oral diabetes medications to treat type 2 diabetes of the young is limited. Data currently available support the use of metformin as first-line drug therapy. Results of prospective studies over the next three to five years will better define the role of thiazolidinedione use as initial therapy in pediatric type 2 diabetes patients.

**Keywords:** Type 2 diabetes, pediatric, pharmacotherapy, safety, efficacy, medications.

An estimated two-thirds of medications prescribed for use in pediatrics have not been proven safe or effective for this patient population[1]. In addition, manufacturer product information rarely offers guidance for the appropriate pediatric dosing of these agents. While the "off-label" use of medications is not precluded by the Food and Drug Administration (FDA) [2], some data suggest a higher incidence of adverse drug events from the off-label use of drugs compared to those tested specifically for pediatric use [3]. Since 1995, a dozen orally administered diabetes medications or combination of medications for the management of type 2 diabetes mellitus (DM) have been approved by the FDA and subsequently marketed in the United States. Only one of these medications (metformin) is approved for use in pediatrics. As the prevalence of children diagnosed with type 2 diabetes continues to rise [4], the need for adequate information regarding the safety, efficacy, and appropriate dosing of oral diabetes medications in a pediatric population likewise increases. The purpose of this paper is to present the data currently available regarding the use of oral diabetes medications in type 2 diabetes of the young.

## METHODS

A computerized literature search was performed using Medline and the Cochrane Database of Systematic Reviews, the Database of Abstracts of Reviews of Effectiveness and the Cochrane Controlled Trials Register. Searches were conducted using the following search terms: type 2 diabetes mellitus, pediatrics, hypoglycemic agents, oral administration, medications, children, drug safety, and drug efficacy. In addition, individual searches consisting of the term children and each of the individual generic drug names were also completed. The resulting citations were reviewed for applicability by the authors. Titles that suggested the evaluation of drug safety or efficacy, or provided pharmacokinetic data for a pediatric population were retrieved for further review. The references of these articles were subsequently reviewed for additional relevant literature. All manufacturer package inserts of oral diabetes medications were also reviewed for information relating to their use in pediatrics. In addition, each manufacturer of currently available oral diabetes medications was contacted with the request to provide all available data regarding the use of its drug in a pediatric diabetes population. Finally, the Food and Drug Administration's Center for Drug Evaluation and Research, Pediatric Drug Development web page([www.fda.gov/cder/pediatric/index.htm](http://www.fda.gov/cder/pediatric/index.htm)) was accessed for pertinent information. In cases where controlled clinical trials of the agents in pediatric type two diabetes patients were

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**Table 1. Summary of Oral Diabetes Medication Use in Children.**

Oral Agent		Ref #	Age Range (yrs)	N	BMI	Dose Range	HbA1C Change	Study Conclusion
Biguanides	Metformin (Glucophage)	5	8-16	82	> 85 <sup>th</sup> % (28% were > 95 <sup>th</sup> %)	500mg QD – 1000mg BID	0.8%	Metformin was safe and effective for treating pediatric patients with type 2 diabetes.
		6	8-15	25	33.5 ± 9.6 kg/m <sup>2</sup>	500mg QD – 1000mg BID	4.4%	Metformin monotherapy was effective but short lived. T2DM management is as complex in children as in adults.
		7	16.3 ± 2.5 (mean)	35	>50 <sup>th</sup> %	1000mg BID	1.4%	Metformin was safe and effective for pediatric T2DM.
Sulfonylurea	Glipizide	11	12-15	6	14.2 kg/m <sup>2</sup> (mean)	2.5mg BID	Reduced	Role for glipizide in CF pts with IGT.
Biguanides / Sulfonylurea	Metformin / Glyburide (Glucovance)	9	10-16	N/A	N/A	N/A	N/A	Glyburide and Metformin PKs comparable between children, adolescents, and adults.
		10	9-16	167	> 50 <sup>th</sup> %	623 (Metformin) / 3.1mg (Glyburide) (mean)	0.8%	No difference between metformin, glyburide, and combo. Safety equivalent to adults.
- Glucosidase Inhibitors	Acarbose (Precose)	12	5-16	65	N/A	50-300mg daily in 2, 3, or 6 divided doses	1.1%	Efficacy in lowering post-prandial BG, urine glucose excretion, and HbA1C. Tolerability/safety equivalent to adults.
		13	11-18	11	N/A	200-300mg qd in 3 divided doses	0.8%	Insulin doses lowered and HbA1C improved.
		14	7-15	9	N/A	150-200mg daily in 2 divided doses	1 – 2.3%	Insulin doses lowered and HbA1C improved. Acarbose safe and effective.
		15	13 ± 1 (median)	12	N/A	50mg TID	N/A	Decreases in fasting and postprandial BG. No change in insulin doses. Good tolerability.
		16	N/A	12	N/A	50mg TID	N/A	Therapeutic place in CF pts with IGT.
		17	4-25 Months	6	N/A	12.5-50mg at meals	N/A	Effective reducing PP hypoglycemia in children s/p Nissen fundoplication; well tolerated aside from flatulence.
Thiazolidine dione	Rosiglitazone (Avandia)	18	9-19	5	32.2 ± 4.2 kg/m <sup>2</sup>	4 mg BID	N/A	ALT/AST levels remained WNL in patients with PCOS

**Table Legend**

Ref: Reference; N: number; BMI: Body Mass Index; QD: daily; BID: twice daily; TID: three times daily; T2DM: type 2 diabetes mellitus; IGT: impaired glucose tolerance; CF: cystic fibrosis; PKs: pharmacokinetics; N/A: not applicable; BG: blood glucose; HbA1C: glycosylated hemoglobin; PP: postprandial; ALT: alanine transaminase; AST: aspartate transaminase; WNL: within normal limits; PCOS: polycystic ovarian syndrome

unavailable, data regarding the use of the drug in any pediatric population was utilized.

**RESULTS**

The computer searches identified 279 potential references. Reference titles were reviewed of which 42 articles were considered relevant and retrieved for further review. Review of the retrieved articles resulted in the identification of 7 additional citations. Review of manufacturers' package inserts revealed no additional information regarding drug use in a pediatric population. A

request for information from the eight manufacturers of oral antidiabetes medications resulted in six responses, including information regarding four ongoing studies involving four different agents. Review of the FDA Pediatric Drug Development website resulted in the identification of two manufacturer-based submissions (both regarding the use of metformin) of oral diabetes drug use in a pediatric population.

Table 1 consists of a summary of data currently available regarding the use of oral antidiabetic agents in pediatric patients. These data include information regarding drug safety and efficacy and/or drug pharmacokinetic and drug

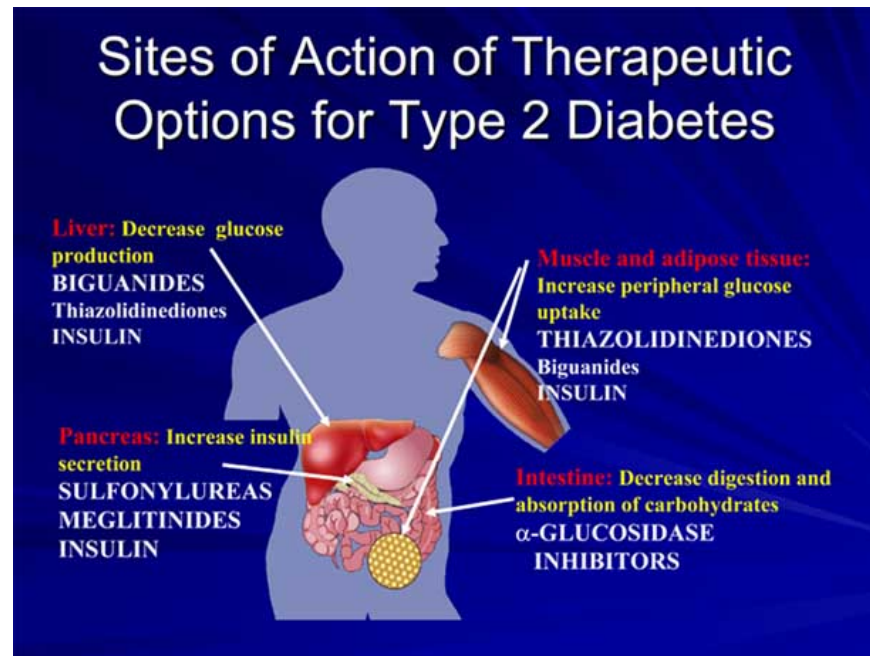


Fig. (1).

dosing information. Figure 1 illustrates each of the drug classes' mechanism of action.

### BIGUANIDE

The biguanide metformin is the only oral agent which has been approved by the FDA for treating pediatric type 2 diabetes mellitus. Metformin is indicated for the management of type 2 diabetes in children age 10-16 years at a daily dose of 1000-2000 mg in divided doses. The safety and efficacy of metformin in children has been reported in three recent publications. In a 16-week study, Jones *et al.* evaluated the safety and efficacy of metformin at doses up to 1000 mg twice daily in type 2 patients eight to 16 years of age with baseline fasting plasma glucose levels of 126-240 mg/dL and HbA1C values of  $\geq 7.0\%$  [5]. In a multicenter, double-blind, placebo-controlled study, eighty-two patients were randomized to receive metformin (n=42) or placebo (n=40). Therapy was initiated with 2 tablets per day (1000mg or placebo) and subsequently titrated at weekly intervals to the maximum dose of four tablets (2000mg or placebo) per day. Patients exceeding a fasting BG level of 230mg/dL at week two, 180mg/dL at week four, or 140mg/dL at week six received rescue sulfonylurea or thiazolidinedione therapy. The primary efficacy endpoint was change in FPG; changes in HbA1C, weight and lipids were pre-defined secondary efficacy variables.

An interim safety analysis planned for when half of the study subjects had completed eight weeks of therapy, found that 70% of placebo patients and 15.8% of metformin patients required rescue therapy. Based on the recommendations of the independent Data and Safety Monitoring Board (citing convincing efficacy results and lack of safety concerns) all subjects were subsequently switched to open-label metformin for the remainder of the 16

week study. At the end of the double-blind treatment, there was a mean difference in FPG of 64 mg/dL between the metformin and placebo groups ( $p < 0.001$ ). Mean HbA1C decreased from 8.3% at baseline to 7.5% in the metformin group, while the HbA1c in the placebo group decreased from 9.0% to 8.6% ( $p < 0.001$ ). Sixty-five percent of patients receiving metformin achieved HbA1C values of  $< 7\%$ , compared to 11% of patients receiving placebo. Compared to placebo, mean total cholesterol decreased by 10 mg/dL ( $p = 0.043$ ) in the metformin group. There were no significant differences between groups in change of mean LDL or HDL cholesterol levels, triglyceride levels, or weight. At 16 weeks, 65% of placebo patients required rescue medication compared to 9.5% of the metformin group. Eighty-three percent of the subjects randomized to metformin were taking 2000 mg/day at their last double-blind visit.

Ten metformin and six placebo treated patients discontinued therapy prior to 16 weeks. Three patients discontinued the study due to serious adverse events (1 metformin, 2 placebo), which were all subsequently judged to be unrelated to study medication. The most commonly reported adverse events were abdominal pain and nausea/vomiting: 25% of metformin subjects experienced abdominal pain compared to 12% of the placebo group, while 17% of the metformin group experienced nausea compared to 10% of placebo patients. No cases of hypoglycemia or lactic acidosis occurred during the study. The authors concluded that metformin is safe and effective for treating pediatric patients with type 2 diabetes.

Zuhri-Yafi *et al.* reported their experience with the use of oral agents in the treatment of type 2 diabetes of youth by conducting a retrospective chart review of 25 pediatric minority out-patients [6]. The study population, which was 8 to 15 years of age, was divided into three groups depending

on baseline blood glucose (BG) level and the presence or absence of ketonuria. Patients with ketonuria or BG levels consistently greater than 300 mg/dL were initiated on insulin therapy. Once controlled, metformin 500 mg once daily was added and increased by 500 mg weekly until a target dose of 1000 mg twice daily was reached. Insulin doses were weaned by 25% every week with each metformin dosage increase (as long as BG was maintained between 80-150 mg/dL). Patients without ketonuria and BG levels less than 300 mg/dL were placed on metformin and titrated as mentioned previously. Six months after the end of metformin titration, patients receiving metformin monotherapy with HbA<sub>1c</sub> values above 8% and consistently high BG levels were treated with additional anti-diabetic agents (typically insulin). Goal HbA<sub>1c</sub> for all groups was below 7.5%.

Eighteen of the 25 patients were initially treated with insulin therapy, the remaining seven patients were initially managed with metformin monotherapy. Most patients received a combination of insulin and metformin therapies by the end of the evaluation period, although two of the 18 patients initially treated with insulin were successfully converted to metformin monotherapy. Four of seven patients continued to receive metformin monotherapy, while the remaining three patients received combination oral hypoglycemic therapy of metformin with glyburide (n=2) or rosiglitazone.

The mean change in HbA<sub>1c</sub> for all patients was -2.9% from a mean baseline of 11.6%. Mean HbA<sub>1c</sub> fell 2.3% in the insulin/metformin group and 4.4% in the group of patients receiving oral hypoglycemic agents. Mean last-visit HbA<sub>1c</sub> values were 7% in 7 patients followed less than 12 months, 7.2% in 7 patients followed 1-2 years, and 9.8% in 11 patients followed more than 2 years. Treatments were well tolerated: there were no reported incidents of lactic acidosis related to metformin use, patients on sulfonylurea did not report hypoglycemia, and transaminase levels remained normal in the patient receiving rosiglitazone. The authors concluded that metformin is effective in treating type 2 diabetes mellitus in children but the effect may be short lived. The authors surmised that DM is likely to be as complex a disease to treat in children as it is in adults, and that metformin monotherapy would unlikely be enough for sustained effects.

Castells recently published his experience of the management of type 2 diabetes in children [7]. Thirty-five African American adolescents with a mean age of 16 years and average 2.5 year history of type 2 diabetes were non-randomly divided into treatment groups according to their pre-study treatment modalities: diet or metformin therapy (n=20), and insulin or a combination of insulin and metformin therapy (n=15). All patients were initially treated with insulin which was progressively weaned with the addition of metformin if euglycemia was obtained. After one year of treatment, HbA<sub>1c</sub> levels were compared.

Mean baseline HbA<sub>1c</sub> levels were  $8.4 \pm 1.8\%$  and  $10.9 \pm 3.1\%$  in the diet/metformin and insulin/metformin groups, respectively. After one year of follow-up, mean HbA<sub>1c</sub> levels decreased to  $7.0 \pm 2.8\%$  in the diet/metformin group and  $11.4 \pm 3.7\%$  in the insulin/metformin group, with 78% of the former group and 35% of the latter group

demonstrating a response (lowering of A1C) to therapy. No treatment side effects were reported.

Spiller and Quadrani utilized the Toxic Exposure Surveillance System of the American Association of Poison Control Centers to assess the toxic effects of metformin ingestions [8]. During the four year reporting period a total of 7121 such exposures were identified with 4072 cases meeting the study's inclusion criteria (metformin ingestion and follow-up to a known conclusion). Exposure by age identified 1095 (27%) cases occurring in patients less than 6 years of age, 172 (4%) cases in patients age 6-12 years, and 279 (9%) cases in patients 13-19 years of age. An "unintentional" cause of drug exposure occurred in 99% of patients under age 6 and 45% of patients age 6-12 years old. Children 12 or less years of age experienced "few adverse outcomes and no deaths" [8].

## SULFONYLUREAS

Data regarding sulfonylurea use in pediatrics is very limited. Bristol-Myers Squibb submitted one pediatric pharmacokinetic (PK) study and one pediatric safety and efficacy study of Glucovance, a fixed combination tablet of glyburide and metformin, to the FDA in July of 2003. The single dose PK study was conducted in male and female patients age 10-16 years and concluded that glyburide and metformin PKs (C<sub>max</sub>, T<sub>max</sub>, AUC, CL/F, V<sub>ss</sub>/F) were comparable between children and adolescent patients. The sponsor also concluded that there were no significant differences between glyburide and metformin PKs between this group and adults based on historic studies of the latter group [9].

The safety and efficacy of Glucovance were evaluated in a 26-week, double-blind, active control study of 167 pediatric patients with type 2 diabetes [10]. Mean age was 13.7 years (age 9-16 years), 65% of participants were female, and 52% of patients were drug naïve. Distribution by ethnicity was as follows: 62% Caucasian, 21% African-American, 13% Hispanic, and 4% Asian. Patients were randomized to receive glyburide monotherapy, metformin monotherapy or combination therapy as Glucovance. Mean baseline HbA<sub>1c</sub> values for the three groups were 7.70 – 7.99%. Inclusion criteria included greater than the 50<sup>th</sup> percentile for weight and inadequate glycemic control (defined as a HbA<sub>1c</sub> of >6.4% and mean fasting glucose < 350 mg/dL) despite an exercise/diet regimen, with or without a single agent hypoglycemic drug. Change in A1C level was the primary endpoint.

Mean final doses were 1500 mg in the metformin group, 6.5 mg in the glyburide group, and 623 mg/3.1 mg in the Glucovance group. At week 26, Glucovance (A1C reduction of 0.8 %) was not shown to be statistically superior to the metformin (mean A1C reduction of 0.5%) or glyburide (1.0% reduction) monotherapy groups (p>0.05). Drug naïve patients had greater responses in each of the groups compared to non-naïve patients (-1.35%, -0.92%, and -1.23% vs. 0.09%, 0.2% and 0.68%, respectively). Patients tolerated each therapy well, though patients receiving Glucovance had less gastrointestinal complaints than the metformin only group, metformin monotherapy was associated with less weight gain versus the other groups, and

glyburide monotherapy use was associated with hypoglycemia compared to the other groups. The authors stated that no unexpected safety findings were identified with Glucovance in this trial.

Other than the above trial, no data were available regarding the utility of sulfonylureas in children with type 2 diabetes. However, improved glucose tolerance was demonstrated with glipizide in a group of six lean (mean BMI 14.2 kg/m<sup>2</sup>) cystic fibrosis (CF) patients with impaired glucose tolerance [11]. The group, which included four adolescents aged 12-15 years, was given glipizide 2.5 mg twice daily for six months. Compared to baseline, improved glycemic control was seen at 3 and 6 months as evidenced by decreases in 24-hr urine glucose and HbA1C levels. No change in weight was seen at six months and therapy was generally well tolerated with "only occasional minor episodes of hypoglycemia". The authors concluded that the results of this study suggest that there is a role for sulfonylureas in the management of CF patients with impaired glucose tolerance.

### -GLUCOSIDASE INHIBITORS

The utility of the  $\alpha$ -glucosidase inhibitor acarbose (Precose<sup>®</sup>) has been described in six pediatric reports, though none has involved patients with type 2 DM. Spengler and Cagatary presented pooled data on the efficacy and tolerability of acarbose in 65 type 1 diabetic pediatric patients 5 to 16 years of age (mean 12.7  $\pm$  2.6 years) [12]. Approximately 90% of patients received a daily dose of 50 mg - 300 mg, typically in 2 or 3 divided doses. Duration of treatment varied from 1 day to greater than 135 days. Median fasting plasma glucose decreased by 8 mg/dL (4% decrease), median post-prandial plasma glucose decreased by 49 mg/dL (19% decrease), and median HbA1C fell by 1.1% from a baseline of 10.1% (11% decrease). Tolerability of the medication in children was comparable to that of adults with 50.7% of children vs. 57.9% of all patients reporting side-effects, 41% of children compared to 54.9% of all patients reporting intestinal symptoms (mainly flatulence), and 6.9% of children withdrawing from the study (2.7% because of intestinal side-effects), compared to 13% and 3.2% of all patients, respectively. The authors concluded that acarbose demonstrates efficacy in diabetic children and has similar tolerability in children compared to adults, with no major risk associated with drug treatment.

Henricks *et al.* investigated the 12-week efficacy of acarbose to reduce HbA1C and insulin requirements in eleven type 1 diabetes patients age 11 to 18 years [13]. In addition to an average baseline insulin dose of 0.97 units/kg per day, patients also received 200-300 mg of acarbose per day in 3 divided doses. Following 12 weeks of treatment, patients received placebo for another 12 weeks. After the addition of acarbose, the daily insulin requirement significantly decreased from 49.6 units to 46.5 units, and mean HbA1C significantly decreased from 8.3  $\pm$  1.8% to 7.5  $\pm$  1.4%. Mean 2-hour postprandial blood sugar did not significantly change from 176  $\pm$  80 mg/dl to 142  $\pm$  62 mg/dl. Average insulin requirements and HbA1C levels subsequently rose during the 12 week placebo period. The authors concluded that acarbose use was associated with

significant decreases in mean insulin requirements and HbA1C concentrations in pediatric patients with type 1 diabetes.

Bartsocas *et al.* evaluated the efficacy and tolerance of acarbose in nine type 1 diabetes patients aged 7 to 15 years [14]. The 12-week study consisted of two weeks of placebo, an 8-week period of acarbose 150 or 200 mg in two divided doses, followed by a 2-week placebo period. HbA1C, 2-hour postprandial blood glucose, complete blood cell counts, and liver functions tests were obtained at week 2 (baseline) and at week 10 (end of acarbose administration). Patients were instructed to report the occurrence of any side effects, changes in insulin dose requirements, or any deviations from their diet during the study. Three patients were withdrawn from the study prior to its completion though no reasons for study discontinuation were given. No drug side effects were reported. HbA1C levels decreased from a mean of 11.3% to a range of 9-10.3% after eight weeks of acarbose therapy, while postprandial sugars fell on average 22.5% (293 to 227 mg/dL). Mean insulin doses decreased by 5 units (11%) in 5 of six patients. Mean SGOT (AST) levels increased by 22% from 30 to 36.5 units. The authors concluded that acarbose should be considered a safe and effective adjunct in the treatment of type 1 DM.

Damjanova reported the results of a non-randomized study of acarbose in a group of patients with type 1 DM treated under hospital conditions [15]. Twelve patients, median age 13  $\pm$  1 years, were fed an isocaloric diet and received acarbose 50 mg three times daily for ten days prior to and following 10-day placebo periods. Fasting and postprandial blood sugars were subsequently compared. Mean morning fasting blood sugars decreased from 208  $\pm$  109 mg/dl at the end of the first placebo treatment to 149  $\pm$  57 mg/dl after ten days of acarbose therapy. Mean postprandial blood sugars likewise decreased from 293  $\pm$  83 mg/dl to 221  $\pm$  96 mg/dl and from 205  $\pm$  76 mg/dl to 178  $\pm$  85 mg/dl, following breakfast and lunch, respectively. Mean daily insulin doses did not change during the study. Tolerability of study medication was rated as "good".

Kentrup *et al.* investigated the efficacy of acarbose in 12 cystic fibrosis (CF) patients with impaired glucose tolerance (IGT) during a two-week hospital stay [16]. In a randomized, double blind, placebo-controlled, cross-over fashion, patients received acarbose 50 mg or placebo three times daily. After a two day observation period, patients received drug or placebo for five days, and were then switched to the alternative therapy for five days after a subsequent two day wash-out period. The administration of 1.75 gram/kg body weight (maximum 75 grams) enteral carbohydrate loads were followed by the measurement of glucose, c-peptide and insulin responses on day 2, 8, and 14 and compared. The mean and maximum values as well as area under the curve for glucose, c-peptide, and insulin were all significantly lower after acarbose treatment compared to baseline and after placebo therapy. Minor gastrointestinal complaints were experienced by 75% of patients receiving acarbose. The authors of this abstract concluded that acarbose has a therapeutic place in pediatric CF patients with IGT.

Ng *et al.* published an abstract reporting the ability of acarbose to treat post-prandial hypoglycemia in children

following Nissen fundoplication [17]. Six infants (age 4-25 months) status-post Nissen fundoplication for gastrointestinal reflux and with normal fasting glucose tolerance, were hypoglycemic at a median time of 120 minutes following a formula feeding. Growth hormone, diazoxide and cornstarch all failed to control hypoglycemia. Acarbose 12.5 mg was given before each patient's formula feeding and was titrated from 12.5 to 25 mg per feeding according to each patient's postprandial glucose response. Acarbose blunted the postprandial increases in insulin levels and eliminated postprandial hypoglycemia in all patients. Acarbose was well tolerated other than some mild flatulence.

### THIAZOLIDINEDIONES

Only one published report assessing the effects of a thiazolidinedione in a pediatric population was identified. Marcado-Asis *et al.* published an abstract regarding the utility of rosiglitazone in five obese patients age 9-19 years (mean  $12.8 \pm 4.2$  years) diagnosed with polycystic ovary syndrome (PCOS) [18]. All patients were obese (BMI  $32.2 \pm 4.9$ ) and had acanthosis nigricans. No patients were diagnosed with DM though all had baseline hyperinsulinemia. Impaired glucose tolerance was present in one patient. All patients were instructed to follow a diet and exercise program and each received rosiglitazone 4mg twice daily. Decreased hirsutism and fairer skin were observed in all patients. Normal menstruation was restored within 6 to 8 weeks in the two patients who had already reached menarche but experienced irregular menstruation. Alanine aminotransferase levels remained within the normal range in all patients. No additional safety information was provided in the abstract.

The results of randomized, controlled clinical trials regarding the use of glipizide, glimepiride, acarbose, miglitol, repaglinide, nateglinide, rosiglitazone, and pioglitazone in pediatric type 2 diabetes patients are unavailable. However, Aventis Pharmaceuticals, Inc. is currently conducting a comparison study of glimepiride (Amaryl<sup>®</sup>) to metformin (written communication received April 5, 2004) and Takeda Pharmaceuticals, Inc. recently initiated a pharmacokinetics trial of pioglitazone (Actos<sup>®</sup>) in pediatric type 2 patients (oral communication received April 19, 2004). Finally, retrospective descriptions by clinicians relating their experiences of the management of type 2 diabetes of the young have been published. These anecdotal reports have generally involved the use of metformin or sulfonylureas [19, 20].

The Department of Health and Human Services announced March 15, 2004 that a federal 5-year study has begun with the hope of determining the best treatment for children with type 2 diabetes. The TODAY (Treatment Options for type 2 Diabetes in Adolescents and Youth) study is the first clinical trial sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) of the National Institutes of Health (NIH) to focus on type 2 diabetes in youth. A second NIDDK-funded study, a prevention study, will seek to develop cost-effective interventions that can be widely applied in schools across the country to prevent youth-onset type 2 diabetes.

### DISCUSSION

Type 2 diabetes, formerly referred to as adult onset diabetes, has until the last decade been considered a disease of adults, not children. One of the earliest publications describing youth-onset type 2 diabetes appeared in 1979 involving a group of obese adolescent Pima Indians [21]. Prevalence rates of type 2 diabetes in children reported since have varied from 2-50 per 1000 in various populations [22], with one clinic reporting a 10-fold increase in youth-onset type 2 diabetes over a 12-year period [23]. Reports have also appeared describing the rising rate of type 2 diabetes of the young especially in minority populations [24].

Type 2 diabetes in children is occurring with an increased prevalence and at an earlier age, and, similar to adults, is closely linked to the national trend of increasing obesity [25, 26]. According to the National Health and Nutrition Examination Survey (NHANES), 15% of young people ages 6 to 19 are overweight, nearly triple the 1980 rate [27]. The term diabetes has been used to describe this profound relationship between obesity and type 2 diabetes. In addition to obesity (defined as a BMI greater than the 95<sup>th</sup> percentile for age and sex), several other risk factors of youth-onset type 2 diabetes have emerged, including physical inactivity, genetics, ethnicity, female sex, and puberty [28, 29]. Together, genetic susceptibility, a lack of physical activity and unhealthy eating patterns all play important roles in determining a child's weight and have helped fuel this explosion of type 2 diabetes of the young.

Other complications of overweight in children are also becoming clear. A study of very obese children suggests that half may have the metabolic syndrome. Metabolic syndrome is defined as the presence of three or more of the following cardiovascular risk factors: abdominal obesity, hypertension, hyperglycemia, high triglycerides, and low HDL-C levels [30]. Weir *et al.* examined the effect of varying degrees of obesity on the prevalence of the metabolic syndrome in a multi-ethnic, multi-racial cohort of 490 children and adolescents [31]. Baseline measurements included blood pressure and plasma lipid, C-reactive protein, and adiponectin levels. The authors administered a standard glucose-tolerance test to 439 obese (244 were moderately obese and 195 severely obese), 31 overweight, and 20 nonobese children and adolescents. The prevalence of the metabolic syndrome increased with the severity of obesity reaching 50% in severely obese youngsters and 39% of the moderately obese, compared to 0% in lean individuals. Two years later, seventy-seven of the study participants were evaluated a second time. Twenty-four of 34 still had metabolic syndrome, and 8 (24%) had developed type 2 diabetes. In addition, metabolic syndrome developed in 16 of the 43 children who did not initially have it. Data from autopsy studies have demonstrated the relationship of early coronary atherosclerosis with the presence of cardiovascular risk factors in the young [32]. Thus, evidence of increased cardiovascular risk, a phenomenon usually associated with middle age, is already present for many at this young age.

Due to the alarming increase in prevalence of type 2 diabetes, the American Diabetes Association (ADA) recommends screening all children considered at risk for developing this disease [33]. Children at high risk include

those who are overweight, are of an ethnic minority, have a family history of type 2 diabetes in first or second degree relatives, and/or have signs of insulin resistance (e.g. acanthosis nigricans). Screening is recommended to start at age 10 years or at the onset of puberty and repeated every two years. Fasting plasma glucose or a two-hour oral glucose tolerance test are considered acceptable screening tests.

There are currently no data comparing the efficacy of diet, exercise and drug therapy in the management of type 2 diabetes in the pediatric and adolescent populations. Since most patients with youth-onset type 2 diabetes are obese, lifestyle changes directed toward dietary and activity interventions with the goal of weight loss seem logical. Therefore, life style changes should be considered the cornerstone of therapy and should be encouraged in the initial management of all pediatric type 2 diabetes cases [34-36]. The fact that most oral agents have had a relatively short history of use and that their safety in children have not been proven also lends support that lifestyle intervention should be tried prior to pharmacotherapy, at least in asymptomatic patients. Indeed, lifestyle intervention programs have been found to be more effective than pharmacotherapy in preventing DM in obese adult patients with impaired glucose tolerance [37]. Prevention of obesity, and hence prevention of type 2 diabetes of the young, is of even greater national health interest, but the method of such prevention is currently undetermined.

The relationship of hyperglycemia and the risk of diabetes-related complications is well substantiated in adults with type 2 diabetes and data from the management of adults with type 2 diabetes support tight glycemic control to decrease microvascular and neurologic complications of the disease [38, 39]. Data regarding the benefits of tight glycemic control in children are currently unavailable. Despite this lack of definitive data, however, most clinicians would support tight glycemic control in young patients with type 2 diabetes with goals in children comparable to those of adults (i.e. fasting glucose levels of 80-120 mg/dl, bedtime blood sugars of 100-140 mg/dl, and HbA1c of less than 7%) [40].

The question of whether all oral therapies used in adults are appropriate to treat type 2 diabetes in children cannot currently be answered. It is apparent from the table that except for metformin and glyburide, there are no primary data regarding the safety and efficacy of oral diabetes agents in the treatment of type 2 diabetes of the young. Because childhood type 2 diabetes is in its infancy, the natural history of the disease, let alone comparative evidence-based data determining its optimal management, are unavailable. Appropriate treatment of children with type 2 diabetes is extremely important because complications due to poor glycemic control are likely to appear at a much younger age and incur an even greater human and economic cost than that typically seen with adults with type 2 diabetes because of an earlier onset of disease. Diabetes in adults is associated with impressive morbidity (diabetes is the number one cause of adult-onset blindness, non-traumatic amputation and end-stage renal disease [41]), increased mortality (the risk of cardiovascular and cerebrovascular events are two to four-fold higher in patients with diabetes compared to non-

diabetics [41]), and high medical costs (diabetes costs the healthcare system approximately \$132 billion annually in direct and indirect costs [42]). The aggressive treatment of high risk young patients therefore seems a worthwhile long-term investment because of the potential of reducing overall health risk, as well as decreasing future demands on finite health care resources.

Though dietary changes, exercise and behavior modification are recommended as first-line therapy for diabetes and obesity, drug therapy is often necessary to adequately control the disease. While it is unknown whether the natural history of diabetes in youth-onset type 2 diabetes is similar to that of adults, only 3% of adults in the United Kingdom Prospective Diabetes Study were able to maintain good glycemic control with diet and exercise [38]. Two reports in children have found that only 11% [43] and 22% [44] of youngsters, respectively, were able to control their diabetes with diet and exercise alone. This argues that most children will eventually require drug therapy. Certainly, accurate diagnosis and classification of diabetes in the young are imperative for determination of the appropriate management of these patients. For children with type 2 diabetes, the question remains: which oral medication should be initiated?

No uniform approach or guidelines to the management of type 2 diabetes of the young is available. As insulin resistance and hyperinsulinemia are harbingers of type 2 diabetes, therapies associated with weight loss and the lowering of endogenous insulin levels conceivably would be beneficial. Utilization of therapies that act to improve the concurrent metabolic abnormalities often associated with type 2 diabetes (e.g. hypertension, hyperlipidemia) intuitively seems reasonable. Alternatively, as the pathogenesis of type 2 diabetes in adults and in youth appear similar, treatments aimed at increasing insulin sensitivity or increasing insulin secretion seem logical to be effective. Indeed, metformin and glyburide have proven utility [10].

Obviously, the use of any medication in a pediatric/adolescent population is fraught with concerns including potential negative effects on normal growth patterns and neurologic development, the potential for hypoglycemia, and use in a potentially child-bearing population. The careful monitoring of children will be necessary then when any of these agents are initiated. For example, the use of growth charts is recommended to monitor the possible effects of these medications on patient height and weight; patients who become pregnant on therapy should immediately be switched to insulin therapy and carefully followed.

Arguably, pediatric patients require more aggressive therapy compared to adults due to the increased risk of diabetes-related complications from longer diabetes exposure. In addition, obesity has a greater risk for morbidity and mortality due to the accompanying diseases often associated with it (e.g. hypertension, dyslipidemia, diabetes mellitus, and atherosclerosis) [45]. These patients should therefore also be screened for hyperlipidemia and hypertension, and appropriately managed when present. The use of statin therapy and angiotensin converting enzyme

inhibitors are treatments of choice in the adult diabetes population [40].

Many clinicians use metformin as their first oral agent of choice despite the fact that no evidence-based, long-term outcome data for the treatment of type 2 diabetes in the young is available. Metformin has been proven safe and effective in pediatric type 2 diabetes and has an FDA approved indication for this population. In addition, the UKPDS demonstrated that in obese adults, metformin use was associated with a 32% reduction in any diabetes-related end-point [46]. Metformin also offers the advantages that it does not cause hypoglycemia, it typically lowers LDL-C and triglyceride levels, and its use is not associated with weight gain. Co-morbid conditions which would make the use of this drug contraindicated (e.g., renal disease, hepatic disease, severe respiratory disease, decompensated heart disease) are fortunately rarely seen in the pediatric population. Metformin use may be associated with nausea, diarrhea and/or abdominal pain, especially if the dose is not slowly in titrated.

Data regarding the safety and efficacy of sulfonylureas in pediatric type 2 diabetes are limited to one study involving glyburide [10]. While well tolerated in this one study, these agents are associated with hypoglycemia, weight gain, and a 5-10% per year secondary failure rate in adults [47]. The feasibility of the use of shorter-acting secretagogues (the meglitinides) in this patient population is even less well defined.

The alpha-glucosidase inhibitors (acarbose, miglitol) are relatively non-systemic agents that lower serum glucose levels by inhibiting post-meal carbohydrate absorption. Compared to other oral agents, these drugs demonstrate modest efficacy and are associated with significant gastrointestinal side effects. The use of acarbose in pediatric patients with type 1 diabetes has been associated with a significant incidence of flatulence and abdominal pain.

The thiazolidinedions (TZDs) represent a novel approach to the management of Type 2 diabetes. These drugs are believed to increase insulin sensitivity by activating the nuclear receptor peroxisome proliferator-activated receptor-gamma which results in increased glucose uptake in adipose and skeletal muscle and decreased hepatic glucose production. In addition to improved glycemic control, these drugs may possibly also preserve beta-cell function [48]. TZD use in adults is also associated with favorable effects on cardiovascular risk factors such as blood pressure, HDL-C, LDL-C oxidation, fibrinogen, PAI-1 levels, microalbuminuria, intra-abdominal fat, carotid intima-media thickness and cell wall inflammatory markers [49]. The anti-inflammatory properties of these compounds make them of investigative interest in the prevention and treatment of atherosclerosis and possibly other inflammatory conditions (e.g., inflammatory bowel disease) [50]. Finally, used as monotherapy TZDs do not cause hypoglycemia.

The FDA removed troglitazone, the first available TZD, from the market March 20, 2000 because of safety concerns regarding uncommon, but potentially life-threatening, idiosyncratic cases of liver dysfunction. The two currently available agents, rosiglitazone and pioglitazone, appear to be

hepatically safe in adults (liver function test elevations occur at a rate similar to that of placebo [51, 52]) but long-term safety in children has not been evaluated. TZDs are contraindicated in patients with liver disease and stage III or IV heart failure. The most common side effects of these agents in adults are weight gain and edema. While intra-abdominal body fat has been associated with hypertension, dyslipidemia, and cardiovascular disease, glitazone therapy has been shown to decrease intra-abdominal fat mass with redistribution to subcutaneous tissue [53]. Weight gain associated with glitazone use therefore may not increase cardiovascular risk while still allowing improvements in insulin sensitivity and glucose tolerance. Dietary compliance and increased physical activity would hopefully mitigate any TZD-induced weight gain in children. The mechanism of glitazone-induced edema is not fully understood and is probably multi-factorial including plasma volume expansion, increased endothelial permeability due to an increase in vascular endothelial growth factor, increased sympathetic nervous system activity, and altered interstitial ion transport [54]. Long-term data will be necessary for a final benefit-risk assessment of the use of these agents in children.

There are economic, ethical, legal, scientific and practical reasons for the relative lack of approval of drugs in the pediatric population [55]. The FDA Modernization Act was passed by Congress in 1997 in an attempt to encourage the pharmaceutical industry to test their products in the pediatric population. This law required the FDA to develop, prioritize, and publish a list of approved drugs for which additional pediatric information may produce health benefits in the pediatric population. In addition, this law also provided marketing incentives to drug manufacturers who conduct studies of drugs in children. A portion of this amendment, known as the Pediatric Exclusivity Provision, provides the drug maker with six months of additional patent exclusivity in return for conducting pediatric studies. It is likely due to this pharmaceutical incentive (e.g. extended patent life) that the limited data we have is currently available. The Pediatric Research Equity Act of 2003, an amendment to Section 505A of the Federal Food, Drug and Cosmetic Act, now authorizes the FDA to require research be carried out by the pharmaceutical industry regarding drug safety, efficacy and dosing information of medications used in the pediatric population. Lack of pediatric information (e.g. testing and labeling) can result in adverse reactions because of overdoses, a lack of therapeutic effect because of underdosing or refusal by caregivers and/or patients to use the drug because of the lack of information. Lack of testing in pediatric populations (especially the very young) also results in lack of drug formulations (e.g., liquids, chewable tablets, sprinkle capsules) that may be more suitable for this population thereby denying this population access to potentially important medications [56].

Studies to better define the risk/benefit ratio of oral diabetes medications in pediatric patients are clearly needed. Fortunately, two trials assessing the utility of oral diabetes agents in the treatment of pediatric and adolescent type 2 diabetes are underway. The 5-year, 12 center TODAY study will determine the optimal treatment for children with type 2 diabetes. In this study, 750 children age 10 to 17 years who are within two years of initial diagnosis will be evaluated.

Participants will be randomly assigned to one of three treatment groups consisting of metformin alone, metformin and rosiglitazone in a fixed dose combination, or metformin plus intensive lifestyle changes (consisting of 30 minutes of daily exercise and a goal of losing 7-10% of body weight). The TODAY study's main goal is to determine how well and for how long each treatment approach controls blood glucose levels. The study will also evaluate: the safety of the treatments; the effects of the treatments on insulin production, insulin resistance, body composition, nutrition, physical activity and aerobic fitness, assess comparative risk for the development of eye, kidney, nerve, and heart disease, compare quality of life and psychological outcomes, assess the influence of individual and family behaviors on treatment response; and compare the cost-effectiveness of the treatments [57].

The second of two NIDDK-funded efforts focusing on type 2 diabetes in children is a prevention study called the Studies to Treat or Prevent Pediatric Type 2 Diabetes Study Group (STOPP-T2D). This study is designed with the goal of determining whether a population (school)-based, multifaceted program can bring about behavior change and help curb the epidemic of overweight and other risk factors for diabetes and cardiovascular disease. A pilot trial of that study, announced June 6<sup>th</sup> 2004, at the American Diabetes Association's 64th Annual Scientific Sessions, involved 1,700 eighth grade children in Texas, North Carolina and California. The population, which was 52% Hispanic, 23% African American, 15% Caucasian, 3% Native American, and 10% from other ethnic groups, had an average age of 13.6 years. Height, weight, waist circumference and blood pressure were measured and fasting blood samples were drawn for analysis of glucose, insulin, and lipid levels. The pilot study found that more than half of these children had one or more problems, such as being overweight or having cholesterol, blood pressure or blood glucose abnormalities that place them at high risk for diabetes and premature cardiovascular disease. Overall, 49.3 percent of children had a BMI above the 85th percentile for their age and gender (overweight), and 40.2% had pre-diabetes. The planned study will deliver a three-year intervention, starting in 6th grade, and will consist of three components: (1) enhanced physical activity in the school by increasing the time devoted to moderate-vigorous activity in gym class; (2) environmental change in the school targeting the food service, by changing foods available in the cafeteria and vending machines; and (3) behavior curriculum aimed at increasing physical activity in and out of school, decreasing sedentary behavior out of school, and changing dietary habits [58].

## CONCLUSION

Data concerning the comparative safety and efficacy of oral diabetes medications in the treatment of youth-onset type 2 diabetes are currently unavailable, but a high priority for such data exists and needs to be gained through controlled, randomized long-term studies. Aggressive management of young diabetes patients is imperative as the lifetime risk of diabetes-related complications and potentially early mortality can be expected to increase due to the long-term exposure to disease. This approach must

include overall good metabolic control as these patients often have concurrent cardiovascular risk factors (e.g., hypertension, hyperlipidemia) that are often already present at the time of diabetes diagnosis. Lifestyle changes promoting healthy living (e.g., improved diet, increased physical activity) should be encouraged in addition to the initiation of any pharmacotherapy regimen. Data currently available support the use of metformin as first-line drug therapy. Results of prospective studies over the next three to five years will better define the role of TZD use as initial therapy in the management of type 2 diabetes of the young.

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## CONFLICTS OF INTEREST

The authors report no conflict of interest.

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