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Review

Treatment for Childhood Type 2 Diabetes

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Abstract. Urine glucose screening at school implemented in Japan is useful for detecting childhood type 2 diabetes at the early stage of the disease. Most patients detected by the screening can improve hyperglycemia and reduce overweight within one to three months by changing lifestyle with diet and exercise. For patients who are unable to alter their lifestyle and for those who have hyperglycemia despite maintaining these changes, a variety of oral hypoglycemic agents, including α-glucosidase inhibitors, sulfonylureas, glitinides, metformin, thiazolidenediones, and insulin are available. Metformin is considered to be the most effective oral agent as monotherapy for Japanese young persons with type 2 diabetes, because most of them are obese with insulin resistance. The approach to insulin therapy in patients with type 2 diabetes often differs from that most frequently used in patients with type 1 diabetes. Adjustment of the dose of insulin at each injection using sliding scales or algorithms is not required in most cases. In some cases, combination therapy with metformin and sulfonylureas or use of insulin is more effective for stabilization of blood glucose values. Therapeutic means for childhood type 2 diabetes should be variable depending on each patient's characteristics.

Key words: childhood type 2 diabetes, lifestyle changes, diet and exercise, oral hypoglycemic agents, metformin, insulin

Introduction

Various reports have shown that the number of children with type 2 diabetes has increased worldwide in recent years and continues to increase (1–3). It is noteworthy that several racial and ethnic groups are at a particularly high risk for developing type 2 diabetes, including African-Americans and Asians (2, 3). In Japan, we demonstrated an increased frequency of type 2 diabetes among school children residing in Tokyo as detected by urine glucose screening and confirmed by the oral glucose tolerance test (4, 5). A similar trend was noted in Yokohama and Osaka (6). According to the data from these studies, the annual incidence of type 2 diabetes is estimated at approximately 3–5 per 100,000 school children in Japan. Concurrently, the increased prevalence of obesity among Japanese school children is notable (5, 7). Lifestyle changes, including westernization of eating habits, increased consumption of animal protein and fat (5) and a decrease of physical activity, have been implicated in the increasing prevalence of childhood obesity. Most children with type 2 diabetes have excessive body weight. There seems to be a strong relationship between childhood obesity and the development of type 2 diabetes. Thus, the increase of type 2 diabetes in

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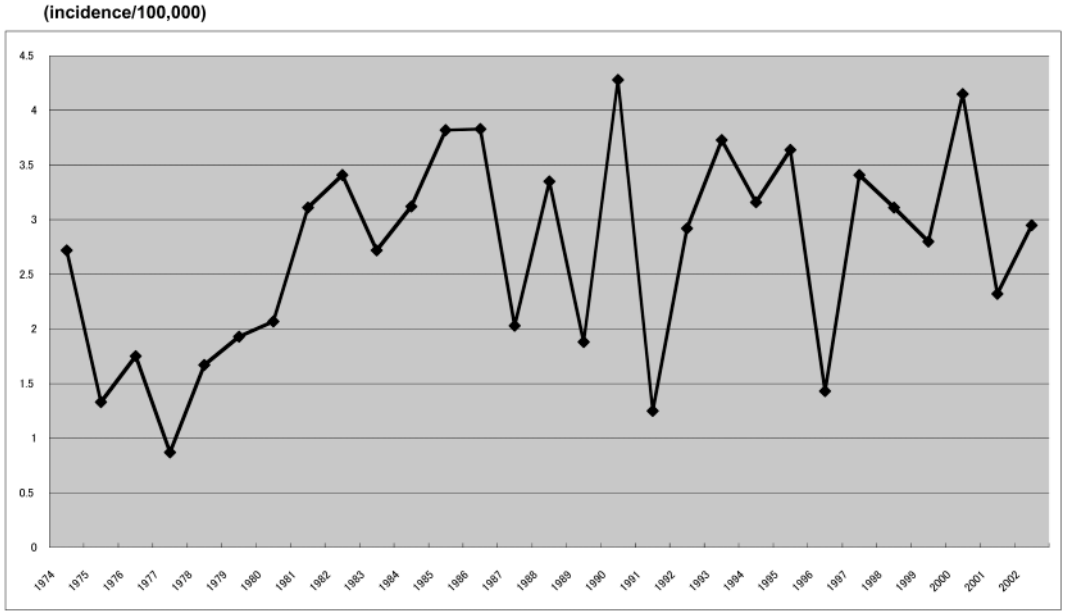

Fig. 1 Serial changes in the incidence of childhood type 2 diabetes detected by urine glucose screening at school in Tokyo.

childhood is an evolving problem and it is critical to develop a strategy to treat type 2 diabetes in childhood. However, treatment for type 2 diabetes varies and it has not been established for children and adolescents. This paper presents some possible therapeutic approaches to improve glycemic control for type 2 diabetes in childhood.

Clinical Features of Children with Type 2 Diabetes at Diagnosis

We have detected numerous children with type 2 diabetes by urine glucose screening at school in Tokyo (4, 5). If the first and second tests are positive for urine glucose, the oral glucose tolerance test is performed for diagnosis of diabetes. The incidence of type 2 diabetes during the last two decades was estimated at 2.8/100,000 school children/year in Tokyo (Fig. 1). According to our accumulated data, approximately 80% of children with type 2 diabetes have an obesity rate of more than 20% at diagnosis. The tendency to excessive overweight is more notable in boys. The incidence of type 2 diabetes is significantly higher in junior high school children than in primary school children (6.4 vs. 0.78/100,000 school children/year, $p<0.01$). A family history of type 2 diabetes is strongly associated with the development of childhood type 2 diabetes. The frequency of a history of type 2 diabetes in first- or second-degree relatives is above 50%. Most children with type 2 diabetes have no or minimum symptoms of hyperglycemia at diagnosis, however, some patients initially show metabolic decompensation such as diabetic ketoacidosis requiring insulin therapy.

Treatment for Children with Type 2 Diabetes

The ideal goal of treatment is physical and emotional well-being and near normalization of blood glucose values. Successful treatment is defined as cessation of excessive weight gain with normal linear growth, controlling of an emotional condition and improvement of glycemia: i.e. fasting blood glucose of 90 to 130 mg/dl,

Table 1 Therapeutic approaches for childhood type 2 diabetes

Diet
1) Energy intake For patients whose obesity rate exceeds 20%, energy intake should be reduced to about 90 to 80% of the energy requirement for age-matched healthy children. For patients whose obesity rate is 10 to 20%, energy intake should be reduced to 95 to 90%.
2) Composition of energy source Carbohydrate: Fat: Protein= 53 to 55%: 30%: 15 to 17%
3) Restriction of energy intake should be relaxed when glycemic control as well as obesity rate improve.
Exercise
Energy consumption from exercise should be maintained at no less than 10% of total energy intake.
Pharmacological therapy
Oral hypoglycemic agents or insulin should be introduced when diet and exercise therapy are found to be insufficient and patients have HbA1c over 8.0%.

postprandial blood glucose of less than 180 mg/dl and HbA1c<7.0% (8). Dietary and exercise regimens are often recommended as the initial therapeutic approach, with progression to oral hypoglycemic agents and finally insulin if hyperglycemia remains uncontrolled (9). Therapeutic approaches for childhood type 2 diabetes in our clinic are shown in Table 1. We start with lifestyle changes through dietary management and exercise. Most patients improve hyperglycemia within one to three months after introduction of lifestyle changes. Some patients, however, continue hyperglycemia and require pharmacological therapy (7). We prescribe oral hypoglycemic agents or insulin to patients who continue high levels of HbA1c over 8.0%.

Some practitioners recommend beginning insulin therapy immediately in patients who have ketoacidosis or severe symptoms of hyperglycemia (10). It has been suggested that initial therapy with insulin can be helpful in overcoming the toxic effects of hyperglycemia, interrupting the vicious cycle whereby hyperglycemia increases peripheral insulin resistance and decreases endogenous insulin secretion leading to worsening of hyperglycemia (11, 12).

Lifestyle Changes with Diet and Exercise

Weight loss induced by low-calorie diets and exercise programs is a principal therapeutic means for obese patients with type 2 diabetes. Caloric restriction improves glucose tolerance initially by decreasing hepatic glucose output. Later, peripheral sensitivity to insulin is increased through reductions in lean and adipose mass (13, 14). The majority of patients can improve hyperglycemia through diet and exercise during a relatively short period. Near normalization of blood glucose with reduced weight gain is achieved in most patients by a relatively modest diet regimen: i.e. caloric reduction of 5 to 10% of the energy requirement for age-matched healthy children with an adequate composition of energy source. Strict restriction of food intake impairs childhood physical development and is likely to lead with time to a drop out of patients (14). It is difficult to maintain diet and exercise regimens consistently. Family support is indispensable for sustaining diet and exercise programs.

Oral Hypoglycemic Agents

For patients who are unable to change their lifestyle through weight loss and increased

Table 2 Available oral hypoglycemic agents

Variable	Name	Daily dose	Indication for clinical use	Side effects
α-glucosidase inhibitors	acarbose boglibose	50–300 mg 0.2–0.9 mg	early state with mild postprandial hyperglycemia	gastrointestinal symptoms
Sulfonylureas	tolbutamide glibenclamide gliculazide glimepiride	250–1500 mg 1.25–10 mg 40–160 mg 1–6 mg	non-obese or mildly obese and maintaining residual β cell function	gastrointestinal symptoms, hypoglycemia, weight gain
Glitinides	nateglinide	90–270 mg	postprandial hyperglycemia and maintaining residual β cell function	hypoglycemia, weight gain
Biguanides	metformin	250–750 mg (1000–1500 mg maximum in US)	Obese and hyperinsulinemia with insulin resistance	gastrointestinal symptoms, lactic acidosis (rare)
Thiazolidenediones	pioglitazone	15–60 mg	Obese and hyperinsulinemia with insulin resistance. Not recommended for pediatric use	weight gain, liver dysfunction, edema

physical activity and for those who make these changes but continue to have poor glycemic contorol, a variety of oral hypoglycemic agents are now available (Table 2). Because the pathophysiology of type 2 diabetes in children appears to be similar to that of type 2 diabetes in adults, it is reasonable to assume that such agents will be effective in children (2).

The available oral hypoglycemic agents and their mechanisms of action are as follows:

α-Glucosidase inhibitors (acarbose and boglibose) work by inhibiting the absorption of carbohydrates in the small intestine. They lower postprandial hyperglycemia and are helpful for improving glycemic control especially for patients at an early stage of diabetes. α-Glucosidase inhibitors can be widely used in combination with other oral agents or insulin (15, 16). The most common side effects are gastrointestinal symptoms, which can be tolerated by most patients. No major systemic adverse effects exist.

Sulfonylureas (tolbutamide, gliclazide, glibenclamide, glimepiride) promote endogenous insulin secretion and are useful for reducing hyperglycemia in non-obese or mildly obese patients with type 2 diabetes, who maintain residual β-cell function, because the primary action of sulfonylureas is to enhance endogenous insulin secretion (17). Obesity is likely to be aggravated when sulfonylureas are inappropriately used in patients under insufficient dietary management with increasing huperinsulinism and insulin resistance (17). First-generation (tolbutamide) and second-generation (gliclazide, glibenclamide) sulfonylureas differ in potency but are thought to be equally effective (17–19). Newer sulfonylureas (glimepiride) are thought to exert their hypoglycemic effect by increasing peripheral sensitivity to insulin in addition to stimulating insulin secretion.

In general, sulfonylureas are well tolerated with gastrointestinal complaints, being the most frequent adverse effects. Skin reactions,

abnormal liver function and hematologic complications have been reported but are uncommon. Hypoglycemia is the most common severe side effect of sulfonylureas (20). The hypoglycemic potential of sulfonylureas can be potentiated by certain drugs that displace them from plasma protein binding sites, such as salicylates and sulfonamides. Conversely, phenytoin and barbiturates can decrease the action of the sulfonylureas (17, 21). In adults, secondary failure of sulfonylureas is common, and the frequency increases with duration of the disease. Worsening insulin resistance or increased impairment of β-cell function has been implicated in over half of the cases, but in the remainder the cause is unknown (12, 17). When sulfonylurea failure occurs, various therapeutic options exist, including another oral agent with a different mechanism of action such as metformin, changing to insulin therapy, or using a combination of sulfonylureas plus insulin.

Glitinides (nateglinide) are nonsulfonylureas that promote insulin secretion in a manner similar to that of sulfonylureas, but their onset of action is briefer and the duration of action is shorter (9). Nateglinide, one of glinitides, alone and in combination with metoformin is reported to be useful for improving glycemic control by reducing mealtime glucose levels in adults with type 2 diabetes (22). On the other hand, glitinides are new oral agents and most pediatricians are not familiar with their use, so that their hypoglycemic efficacy has not been ascertained.

Metformin is approved for pediatric use in the U.S. It is used as the initial oral agent and has the advantage of inducing a significant decrease in HbA1c by 1.2% and fasting blood glucose by 3.6 mmol/l (64.8 mg/dl) in the absence of severe hypoglycemia in pediatric patients with type 2 diabetes (23). In addition, it has been demonstrated that weight is either decreased or remains stable, and plasma lipid profiles improve (23–26). The mechanism of the action of metformin differs from that of sulfonylureas. Metformin does not promote insulin secretion, but decreases hepatic glucose output and peripheral insulin resistance (24–26). Metformin is thought to be essentially effective for patients with insulin resistance associated with overweight. For Japanese young persons with type 2 diabetes, metformin is considered to be most effective as monotherapy, because most of them are obese. We introduced metformin therapy for pediatric use 5 years ago, now 15 patients have received metformin at doses of 500 to 1,000 mg daily. If monotherapy with metformin is not successful over a reasonable period (i.e., 3–6 mo), several alternatives can be considered. Combination therapy with metformin plus sulfonylureas or insulin is more effective than either agent used alone in some cases. The glycemic control in patients with metformin alone or a combination with sulfonylureas or using insulin in our clinic is shown in Table 3.

The most common side effects of metformin are gastrointestinal symptoms, which are significantly reduced with the passage of time and appropriate time schedule (23, 25, 26). Lactic acidosis is uncommon and usually is restricted to patients with underlying renal or hepatic dysfunction or cardiac disease (24–27). Metformin should not be used in patients with known hepatic disease, renal dysfunction, hypoxemic conditions, or severe infections. Metformin should be temporarily discontinued with any acute illness associated with dehydration or hypoxemia. Insulin should be used if glycemic control deteriorates acutely (2, 27).

Thiazolidenediones (troglitazone) is not used in Japan, because it has been associated with fatal hepatic failure (28). Pioglitazone is reported safer for practical use, however, its routine use in children is not recommended until safety information is available. Unfortunately, we do not have any data for clinical efficacy and safety for

Table 3 Glycemic control in treatment with metformin alone or in combination with sulfonylureas or insulin at our clinic

Treatment	N	HbA1c (%)
metformin	5	5.2, 5.8, 6.2, 6.8, 7.5
metformin plus insulin	4	6.4, 6.6, 6.6, 7.8
metformin plus gliclazide	2	6.8, 7.4
metformin plus glibenclamide	8	5.4, 6.0, 6.9, 7.0, 7.7, 7.7, 7.9, 8.5

under line: HbA1c<7.0%.

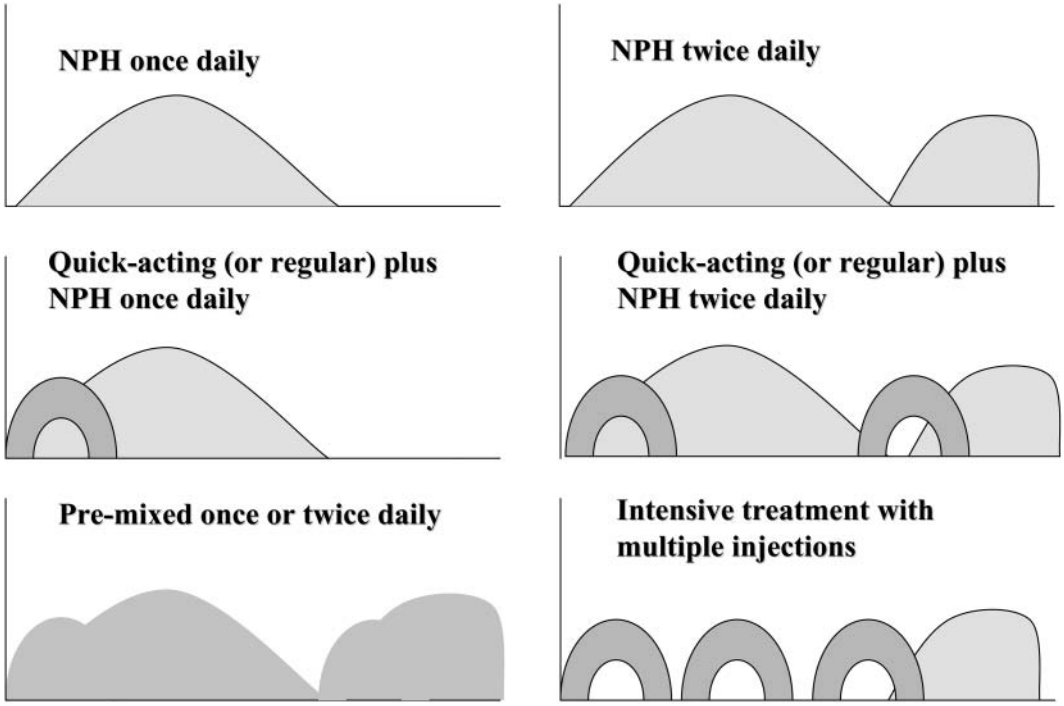

Fig. 2 Insulin regimens for the treatment of type 2 diabetes.

pediatric use.

Insulin

Insulin is the oldest hypoglycemic agent. In the 1980s, oral agents were practically not used and insulin was the only hypoglycemic agent approved for pediatric use in Japan. Nowadays, despite the clinical use of oral hypoglycemic drugs in pediatric patients, quite a few patients with type 2 diabetes receive insulin therapy (9, 29). The various insulin regimens used in patients with type 2 diabetes are shown in Fig 2. There are insufficient data to help determine the best one, because residual β cell function is heterogenous in type 2 diabetes. Once-daily injection of intermediate insulin at bedtime or before breakfast (10) seems uncommon for pediatric use. Twice-daily injections in combination with intermediate- and rapid acting insulin (10, 13) or pre-mixed regimens have been used to good effect. However, a minority of patients with deranged metabolic

Table 4 Recent preparations of insulin for children with type 2 diabetes at our clinic

Case (age at investigation)	Treatment just before insulin	Diabetic duration at introduction of insulin (yr)	Insulin regimens (breakfast/ lunch/dinner)
case 1 (23)	Sulfonylureas	3	30R/ - /R
2 (22)	Sulfonylureas	3	30R/ - /40R
3 (25)	Diet, Exercise	3	30R/ - /30R
4 (28)	Diet, Exercise	4	50R/R/50R
5 (22)	Diet, Exercise	4	50R/ - /30R
6 (22)	Sulfonylureas	7	30R/ - /30R
7 (18)	Diet, Exercise	3	30R/ - /30R
8 (31)	Sulfonylureas	13	30R/ - /30R
9 (16)	Metformin, Sulfonylureas	4	Q/Q/Q combined with metformin
10 (27)	Sulfonylureas	10	30R/ - /30R combined with metformin
11 (15)	Metformin	3	QN/-/QN combined with metformin

30–50R: premixed insulin, R: regular insulin, N: NPH insulin, Q: quick-acting insulin analogue.

control and deficient β cell capacity need intensive insulin therapy similar to type 1 diabetes.

The approach to insulin therapy in patients with type 2 diabetes often differs from that most frequently used in patients with type 1 diabetes. Adjustment of the dose of insulin at each injection using sliding scales or algorithms is not required in most cases, because their residual β cell function is not exhausted. Insulin resistance is a central feature of most forms of type 2 diabetes, and accordingly insulin requirement to control hyperglycemia is often very high (10, 13). High doses of insulin, however, lead to hyperinsulinemia resulting in weight gain while hyperglycemia is not reduced. Appropriate use with an adequate dose of insulin under sufficient dietary management is essential to achieve glycemic goals in type 2 diabetes.

Combination therapy with insulin and various oral hypoglycemic agents has also been advocated. In some studies, the addition of oral agents to insulin regimens was shown to achieve better glycemic control compared with insulin alone or to reduce the required dose of insulin (9, 10, 13, 30, 31). Modified insulin therapy, including a combination with oral hypoglycemic agents, and its metabolic effect in our clinic are shown in Table 4. The use of pre-mixed insulin once or twice daily or a combination with insulin and metformin seems to be useful for glycemic control in most of children with type 2 diabetes. However, some patients, who have lost endogenous insulin secretary capacities, need intensive insulin treatment similarly to the management of type 1 diabetes.

Conclusion

Children with type 2 diabetes show clinical heterogeneity and therapeutic approaches to them patients are considered to be heterogeneous. Most patients can improve hyperglycemia by changing lifestyle with diet and exercise. On the other hand, some need either oral hypoglycemic agents or insulin therapy for their glycemic control. Therapeutic means for childhood type 2 diabetes should be variable depending on each patient's characteristics.

Considerable number of children who were treated with diet and exercise dropped out because many children while not feeling ill, did not realize immediate benefits from lifestyle changes through

diet and exercise, and recognized no gain from the treatment. Adherence is the most important factor for the management of childhood type 2 diabetes, and a good patient-family-pediatrician relationship should be maintained to encourage good glycemic control (7).

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