Clin Pediatr Endocrinol 2013; **22**(1), 1–8

Original Article

Pharmacologic Treatment Strategies in Children with Type 2 Diabetes Mellitus

Tatsuhiko Urakami[1], Remi Kuwabara[1], Masako Habu[1], Ayako Yoshida[1], Misako Okuno[1], Junichi Suzuki[1], Shori Takahashi[1], and Hideo Mugishima[1]

[1] *Department of Pediatrics, Nihon University School of Medicine, Tokyo, Japan*

Abstract. We treated 80 obese and 28 nonobese children diagnosed as having type 2 diabetes mellitus (T2DM). Among these patients, 26 obese and 23 nonobese children were assigned to pharmacologic therapies during the course of diabetes. Pharmacologic therapies were started if the HbA1c (NGSP) value exceeded 7.0% despite dietary and exercise management. For the 26 obese patients, metformin alone or in combination with an additional medication was frequently used. Only 2 patients independently received sulfonylureas (SUs) in the form of glimepiride. In addition, 9 patients were treated with basal insulin supported with oral hypoglycemic drugs (OHDs) or biphasic premix insulin. On the other hand, the 23 nonobese patients were frequently treated with insulin alone or in combination with an additional medication followed by SUs. The nonobese patients tended to require pharmacologic therapies, in particular insulin, at an earlier stage of diabetes as compared with the obese patients. New antidiabetic drugs, DPP-4 inhibitors and GLP-1 receptor agonists, seemed to exert positive effects on glycemic control without occurrence of hypoglycemic episodes in some patients regardless of the type of diabetes. These results suggest that pharmacologic treatment strategies in childhood T2DM should be tailored to individual patient characteristics.

Key words: type 2 diabetes, obese, nonobese, pharmacologic therapies

Introduction

Treatment of childhood type 2 diabetes mellitus (T2DM) is a critical issue because the number of children with T2DM has dramatically increased worldwide in recent decades (1, 2). Successful treatment is defined as cessation of excessive weight gain with normal linear growth, control of emotional conditions, and improvement of glycemia, i.e., fasting blood glucose less than 130 mg/dl, postprandial blood glucose less than 180 mg/dl, and HbA1c level less than 7.0% (NGSP) (3). Lifestyle modification such as a well-balanced diet and adequate physical activity with the aim of reducing body weight are usually recommended as an initial therapeutic approach. If the treatment goals of these diet and exercise regimens are not met, pharmacologic therapies using oral hypoglycemic drugs (OHDs) and finally insulin therapy are introduced for children with T2DM (4, 5).

We presently prescribe a variety of pharmacologic therapies depending on the patient's characteristics. The use of OHDs could differ between obese and nonobese children with T2DM. Thus, we examined the current status of

Received: July 23, 2012
Accepted: October 3, 2012
Correspondence: Dr. Tatsuhiko Urakami, Department of Pediatrics, Nihon University School of Medicine, 1-8-13 Kandasurugadai, Chiyoda-ku, Tokyo 101-8309, Japan
E-mail: urakami.tatsuhiko@nihon-u.ac.jp

Table 1 Therapeutic approaches for children withT2DM at Nihon University Hospital

- Lifestyle (diet and activity) modifications in the entire family.
- Dietary management.
  a) Limiting of high-fat, high-caloric density foods and drinks.
  b) Restriction of daily caloric intake by 10% in moderate-severe obesity and by 5% in mild obesity.
  c) Composition of food: C 53–57%, P 15–17%, F 30%.
- Exercise management.
  Negotiated and enjoyable exercise prescription to exhaust 5–10% of daily caloric intake.
- Pharmacological therapies including oral hypoglycemic drugs and insulin should be started if the HbA1c (NGSP) value exceeds 7.0% despite of dietary and exercise management.

pharmacologic therapies independently in these two patient groups at the pediatric clinic of Nihon University Hospital in Tokyo.

Subjects and Methods

We treated 108 children, 51 males and 57 females, diagnosed as having T2DM at the pediatric clinic of Nihon University Hospital, as of April 1, 2012. Their mean age at the time of the study was 18.8 ± 7.8 (10.1–32.0) yr, and that in their mean age at the diagnosis of diabetes was 12.6 ± 5.7 (9.1–15.2) yr, with the mean diabetic duration being 7.2 ± 4.5 (1.0–20.0) yr. Of these children, 101 (93.5%) were diagnosed as having T2DM by urine glucose screening at schools. All the patients with T2DM were negative for any diabetes-related autoantibodies including islet cell antibodies (ICA) and anti-glutamic acid decarboxylase (GAD) antibodies at the time of diagnosis and during the course of the disease.

Among these 108 patients, 80 were obese and 28 nonobese. Forty-nine of these patients, 13 males and 36 females, with a mean age of 23.0 ± 5.8 yr, and a mean duration of diabetes of 12.5 ± 3.5 yr, were given pharmacologic therapies during the course of diabetes management. The mean HbA1c value in the 49 patients using pharmacologic therapies was 7.0 ± 0.7% (NGSP). Among these 49 patients, 26 were obese and 23 nonobese. Overall frequencies of progression to pharmacologic therapies in the obese and nonobese patients were 32.5% and 82.1%, respectively. The frequency of pharmacologic therapies was significantly higher in nonobese patients than in obese patients (p=0.0005). The current pharmacologic status was compared between the two patient groups.

We used percent overweight as an index of obesity in this study. The percent overweight was calculated as (current weight – sex-, age- and height-matched ideal weight) / sex-, age- and height-matched ideal weight × 100 (%). Subjects with a percent overweight above 20% were judged to be obese (6).

Therapeutic approaches for T2DM at our clinic are shown in Table 1. The majority of patients showed amelioration of hyperglycemia through diet and exercise modification during a relatively short period of 1–3 mo. Near normalization of blood glucose levels accompanied by reduction of body weight was achieved in most patients by applying a relatively modest diet regimen, i.e., caloric restriction of 5–10% of the energy requirement for age-matched healthy children with an adequate energy source composition. Excessive restriction of food intake impairs physical development in childhood and is likely to lead to patient withdrawal from the regimen over time (3, 4). Some patients, however, continued to be hyperglycemic and required pharmacologic therapies. For patients who were unable to change their lifestyles with regards to dietary management and increased physical activity or those who made these changes but continued to have poor glycemic control and HbA1c levels of

Table 2 Antidiabetic medications in 26 obese children with T2DM

Regimens	N	Female	HbA1c (%)
Insulin alone	5	4	7.6 ± 0.6
Insulin + Metformin	4	2	7.1 ± 0.2
Metformin alone	6	4	6.4 ± 0.4
Metformin + α-GI	2	1	6.6 ± 0.3
Metformin + SU	3	2	7.1 ± 0.1
Metformin + TZD	1	1	5.2
SU alone	2	2	5.7 ± 0.1
DPP-4 inhibitor + SU	1	0	8.1
DPP-4 inhibitor + Metformin	1	1	6.7
GLP-1 agonist + Metformin	1	1	6.8

more than 7.0% (NGSP), a variety of OHDs and/or insulin injections were introduced depending on the patient's condition.

HbA1c was measured by an HPLC method, and the value of HbA1c (%) was estimated as a National Standardization Program for Glycocylated Hemoglobin (NSPG)-equivalent value (%) and calculated using the formula, HbA1c (%) = HbA1c (Japan Diabetes Society: JDS) + 0.4%, considering the relational expression of HbA1c (JDS) measured by the previous Japanese standard substance and measurement method and HbA1c (NGSP).

The results were expressed as the mean value ± SD. Frequency and mean values were compared using the χ^2 test or Mann-Whitney U-test to detect differences between the data, respectively. $p<0.05$ was considered to be statistically significant.

Results

Pharmacologic therapies in obese children with T2DM

Table 2 shows various pharmacologic regimens prescribed to 26 obese children with T2DM. All the patients were initially treated with a monotherapy of metformin or other OHD; i.e., 16 were treated with metformin, 4 were treated with sulfonylurea (SU) and 2 were treated with an α-glucosidase inhibitor (α-GI). Four received insulin. At the time of the study, metformin alone or in combination with an additional medication was frequently prescribed; i.e., 6 patients were treated with metformin alone, and 9 were treated with metformin and an additional OHD such as an α-GI, the SU glimepiride, the thiazolidinedione (TZD) pioglitazone, a dipeptidyl peptidase-4 (DPP-4) inhibitor or a glucagon-like peptide-1 (GLP-1) receptor agonist. Only 2 patients were administered glimepiride alone. Nine patients received insulin therapy, 4 using metformin with basal insulin (glargine) support and 5 using biphasic premix insulin or multiple injections of insulin. Most patients treated with insulin had a long history of diabetes and had ultimately shown impaired endogenous insulin release during the course of diabetes. The mean value of HbA1c in the obese patients with pharmacologic therapies was 6.8 ± 0.7% (NGSP).

Pharmacologic therapies in children with nonobese T2DM

On the other hand, the majority of the 23 nonobese patients were initially treated with SU alone or insulin; i.e., 8 patients were treated with SU alone, and 9 received insulin therapy. Five patients, who had recently been diagnosed with T2DM, were initially prescribed new antidiabetic drugs, DPP4 inhibitors and GLP-1 receptor agonists. At the time of this study, patients were frequently treated with

Table 3 Antidiabetic medications in 23 nonobese children with T2DM

Regimens	N	Female	HbA1c (%)
Insulin alone	8	8	7.6 ± 0.7
Insulin + Metformin	1	0	8.2
Insulin + SU	1	1	7.8
SU	3	2	6.9 ± 0.6
SU + Metformin	2	1	7.0 ± 0.1
SU + α-GI	2	1	6.3 ± 0.6
DPP-4 inhibitor + SU	2	1	6.3 ± 0.7
GLP-1 agonist alone	3	3	7.1 ± 0.7
GLP-1 agonist + Metformin	1	1	7

insulin alone or in combination with additional medications followed by SUs; i.e., 11 patients received insulin alone or with an additional OHD such as metformin or glimepiride, and 9 were treated with glimepiride alone or in combination with another OHD. As for insulin therapy, most patients initially did not require intensive insulin therapy as prescribed for type 1 diabetes, though some eventually needed multiple injections of insulin during the course of diabetes. A DPP4 inhibitor and GLP-1 receptor agonist alone or in addition to metformin exerted positive effects on glycemic control without inducing hypoglycemic episodes in the 6 patients with residual ß-cell function within a relatively short period after the diagnosis (Table 3). The mean value of HbA1c in the nonobese patients with pharmacologic therapies was 7.2 ± 0.7% (NGSP). The nonobese patients had a significantly higher mean value of HbA1c than the obese patients ($p<0.0001$).

In the present study, we found that nonobese patients tended to require pharmacologic therapy, in particular insulin, at an earlier stage of diabetes as compared with obese patients. The mean interval to the start of pharmacologic treatment was 3.1 ± 2.3 yr, (2.2 ± 2.1 yr, for OHD, and 4.8 ± 2.9 yr, for insulin therapy, $p=0.0195$).

Adverse events associated with pharmacologic therapies

Both obese and nonobese patients using insulin occasionally experienced mild hypoglycemic episodes, but there were neither serious nor persistent adverse events with any of the anti-diabetic medications used in this study.

Discussion

Because the pathophysiology of T2DM in children appears to be similar to that in adults, it is reasonable to assume that OHDs as well as insulin would be effective in children with T2DM who fail to improve glycemic control through diet and exercise regimens. The International Society for Pediatric and Adolescent Diabetes (ISPAD) has recommended metformin as a first-choice drug for pharmacologic treatment of childhood T2DM (4). Metformin acts mainly on the liver, and suppresses hepatic glucose production by decreasing gluconeogenesis, and also increases insulin-stimulated glucose uptake in peripheral muscle and fat. This drug has the advantage over SU of similar reductions in HbA1c values without the risk of hypoglycemia. Furthermore, weight either decreases or remains stable, and serum lipid levels decrease during treatment. We recognized that metformin would be effective for most children with T2DM because more than 80% of cases with childhood T2DM are obese and exhibit insulin resistance with hyperinsulinemia (7, 8). Failure of monotherapy with metformin over 3 months indicates the need to add SU, TZD, or insulin, either alone or in combination with other types of anti-diabetic medications

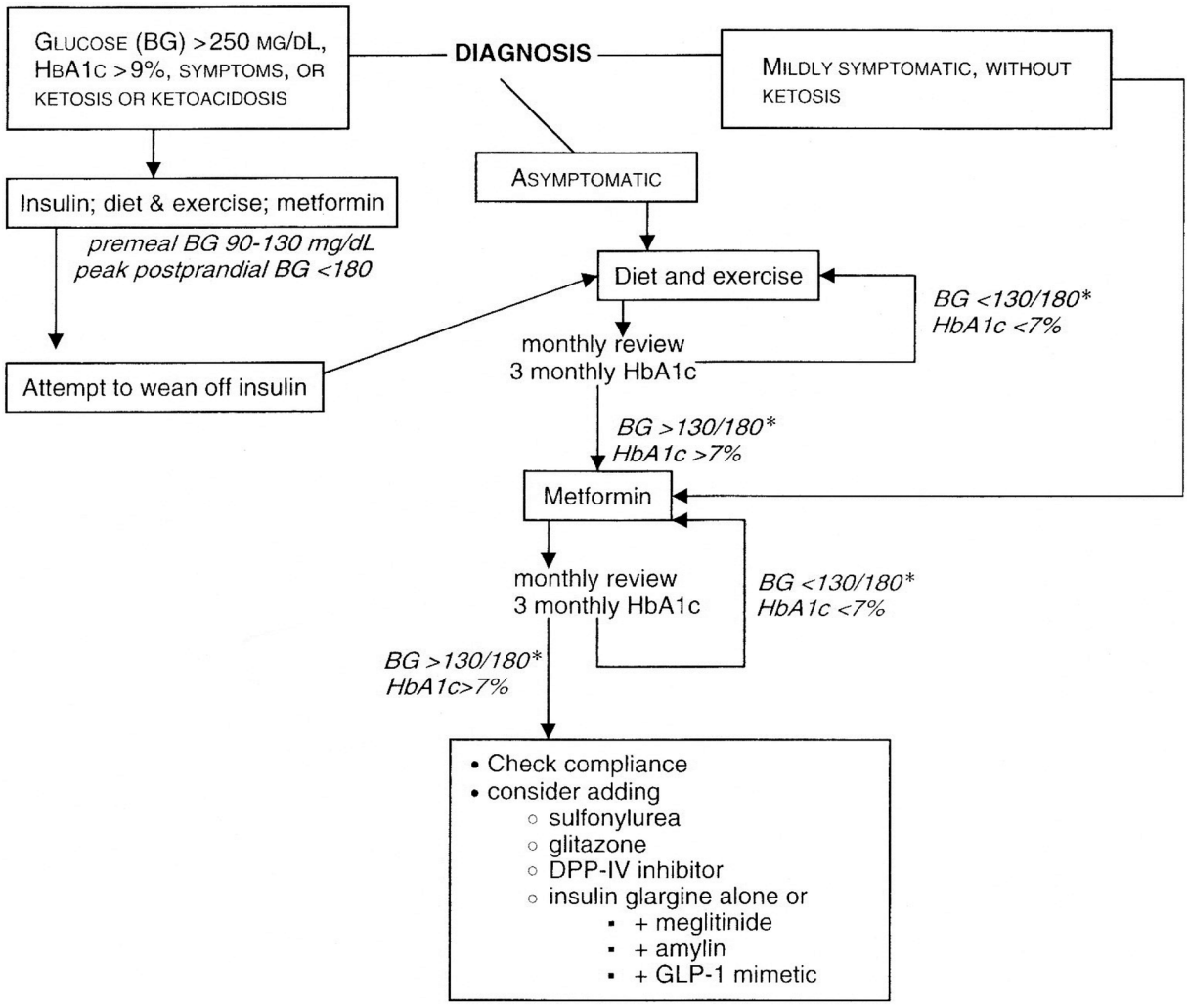

Fig. 1 Treatment decision according to the ISPAD guidelines 2009.

including DPP4-I and GLP-1 receptor agonist (Fig. 1).

In regards to SU, glibenclamide has been widely used not only in adults but also in children and adolescents with T2DM as a first OAD. However, glibenclamide markedly simulates insulin secretion from ß-cells and may accelerate ß-cell apoptosis due to oxidative stress (10). This drug also carries a high risk of hypoglycemia and accelerated weight gain. On the other hand, while having a lower capacity to bind SU receptors on K_{ATP} channels, glimepiride exerts extrapancreatic effects such as decreased glucose output from the liver and enhanced sensitivity of peripheral tissues to insulin (11).

In 2004, The Japanese Society for Pediatric Endocrinology (JSPE) conducted a survey on the present use of antidiabetic medications and their efficacy and safety in Japanese children and adolescents with T2DM (9). The JSPE surveyed 259 children with T2DM, all less than 18 yr, of age and treated at 42 medical centers in 2003, and examined how antidiabetic drugs were used at the time of diagnosis and survey. Eighty-seven (34%) of the 259 patients were initially treated without medication and were managed only by modifying their dietary intakes and physical activities. One hundred

and seventy-two patients (66%) were treated using OHDs. α-GI was used most frequently, being the most commonly prescribed drug at that time for Japanese children with T2DM, followed by insulin, metformin, SU, nateglinide, and a combination of α-GI and metformin. The mean percentage overweight was lower and the HbA1c level was higher in medicated patients than in non-medicated patients at the time of diagnosis. Many patients who were initially treated with a single drug eventually required insulin alone or in combination with an additional medication, suggesting that their glycemic control had deteriorated during the course of treatment. The HbA1c level of the 14 subjects who received only metformin decreased without severe adverse events. This result suggests that metformin is safe and effective for treating obese children and adolescents with T2DM. On the other hand, nonobese patients tended to use SU or insulin. SU seemed to be useful for nonobese T2DM patients with sustained residual ß-cell function.

We demonstrated that various pharmacologic therapies would currently be available even for children and adolescents with T2DM, and that the efficacies of these regimens apparently differ between obese and nonobese cases. As recommended in the ISPAD Clinical Practice Consensus Guidelines 2009 (4), the first treatment for obese children with T2DM should be metformin monotherapy. Most obese patients, at the early stage of diabetes, achieve adequate glycemic control using metformin alone, with some subsequently needing additional medications including an α-GI, SU and TZD. Patients with increasingly impaired ß-cell function as the disease progresses ultimately require insulin therapy. However, most obese patients do not need intensive insulin therapy using multiple daily injections, instead being managed with basal insulin support therapy in addition to an OHD or biphasic premix insulin. On the other hand, for nonobese patients, we prefer glibenclamide as the SU because it reportedly improves glycemic control to a degree similar to that of metformin in pediatric patients with T2DM (12). It is also recognized as being safe with a low risk of hypoglycemia and less weight gain than other SUs (13). Glimepiride, but not glibenclamide, also has extrapancreatic effects that might protect ß-cells from apoptosis through, at least in part, the antioxidant properties of the molecule (14).

We have reported that nonobese children with T2DM exhibit mild insulin resistance and gradually reduced endogenous insulin secretion as diabetes progresses. The nonobese patients were basically negative for any diabetes-related autoantibodies. Thus, genetic factors not associated with autoimmunity may play a role in the deterioration of ß-cell function in nonobese children with T2DM (unpublished data). In the present study, we demonstrated that insulin therapy was introduced earlier for nonobese patients with shorter diabetes durations than for obese patients. This observation also indicates that endogenous insulin secretion is reduced earlier in nonobese than in obese children with T2DM.

Drugs targeting the incretin system, i.e., DPP-4 inhibitors and GLP-1 receptor agonists, have recently been introduced (15–17). Although the efficacy and safety of these new drugs are well documented in adults, studies in the pediatric population are lacking. In the present study, we found positive effects on glycemic control in some patients regardless of obesity. Stimulating endogenous insulin secretion in a glucose-dependent fashion and suppressing pancreatic glucagon output have major effects on lowering blood glucose. We recognized that both obese and nonobese children could obtain adequate blood glucose levels and preserve substantial residual ß-cell function by using DPP-4 inhibitors or GLP-1 agonists, although the efficacy seemed to be greater with the GLP-1 agonists. For the obese patients, decreased appetite and slower gastric emptying leading to weight loss, which was modest in some patients but significant in others, was the main advantage of GLP-1

agonists. Furthermore, for the nonobese patients, GLP-1 agonists might protect against ongoing deterioration of ß-cell function by suppressing apoptosis and promoting regeneration (18). On the other hand, the maintenance dose for GLP-1 agonists is generally set at 0.9 mg daily (19), though some children achieved optimal glycemic control with a lower dose of 0.3–0.6 mg daily. The optimal dosage of GLP-1 agonists for maintenance therapy in children with T2DM should be examined in further studies. In addition, the efficacy and safety of incretin- related drugs should be studied in a large pediatric population.

In conclusion, we identified differences in pharmacologic therapies between obese and nonobese children with T2DM. New antidiabetic drugs, incretin mimetics and enhancers, appeared to be effective for some young patients, similar to the situation in adults with T2DM. These results suggest that pharmacologic regimens for childhood T2DM should be tailored to individual patient characteristics.

References

1. Bloomgarden ZT. Type 2 diabetes in the young. The evolving epidemic. Diabetes Care 2004;27:998–1010. [Medline] [CrossRef]
2. Shaw J. Epidemiology of childhood type 2 diabetes and obesity. Pediatr Diabetes 2007;8:7–15. [Medline] [CrossRef]
3. Rosenbloom AL, Silverstein JH, Amemiya S, Zeiter P, Klingensmith GJ. ISPAD Clinical Practice Consensus Guidelines 2009 compendium. Type 2 diabetes in children and adolescents. Pediatr Diabetes 2009;10:17–32. [CrossRef]
4. Urakami T. How should we treat type 2 diabetes in youth? Pediatr Endocrinol Rev 2005;3:33–9. [Medline]
5. Urakami T. Treatment for childhood type 2 diabetes. Clin Pediatr Endocrinol 2005;14:1–9. [CrossRef]
6. Asayama K, Ozeki T, Sugihara S, Ito K, Okada T, Tamai H, *et al*. Criteria for medical intervention in obese children: a new definition of obesity disease in Japanese children. Pediatr Int 2003;45:642–6. [Medline] [CrossRef]
7. Urakami T, Kubota S, Nitadori Y, Harada K, Owada M, Kitagawa T. Annual incidence and clinical characteristics of type 2 diabetes in children as detected by urine glucose screening in the Tokyo metropolitan area. Diabetes Care 2005;28:1876–81. [Medline] [CrossRef]
8. Urakami T, Morimoto S, Nitadori Y, Harada K, Owada M, Kitagawa T. Glucose screening program at schools in Japan to detect children with diabetes and its outcome-Incidence and clinical characteristics of childhood type 2 diabetes in Japan. Pediatr Res 2007;61:141–5. [Medline] [CrossRef]
9. Sugihara S, Sasaki N, Kohno H, Amemiya S, Tanaka T, Matsuura N. The Committee for the Medical Treatment of Childhood-Onset Type 2 Diabetes, The Japanese Society for Pediatric Endocrinology. Survey of current medical treatment for childhood-onset type 2 diabetes mellitus in Japan. Clin Pediatr Endocrinol 2005;14:65–75. [CrossRef]
10. Ogihara T, Mirmira RG. 2010 An islet in distress: ß cell failure in type 2 diabetes. J. Diabet Invest 2010;1:123–33.
11. Campbell RK. Glimepiride: role of a new sulfonylurea in the treatment of type 2 diabetes mellitus. Ann Pharmacother 1998;32:1044–52. [Medline] [CrossRef]
12. Gottschalk M, Danne T, Vlajnic A, Cara JF. Glimepiride versus metformin as monotherapy in pediatric patients with type 2 diabetes. A randomized, single-blind comparative study. Diabetes Care 2007;30:790–4. [Medline] [CrossRef]
13. Weitgasser R, Lechleitner M, Luger A, Klinger A. Effect of glimepiride on HbA1c and body weight in type 2 diabetes: results of a 1.5-year follow-up study. Diabetes Res Clin Pract 2003;61:13–9. [Medline] [CrossRef]
14. Del Guerra S, Grupillo M, Masini M, Lupi R, Bugliani M, Torri S, *et al*. Gliclazide protects human islet beta-cells from apoptosis induced by intermittent high glucose. Diabetes Metab Res Rev 2007;23:234–8. [Medline] [CrossRef]
15. Amori RE, Lau J, Pittas AG. Efficacy and safety

of incretin therapy in type 2 diabetes: systemic review and meta-analysis. JAMA 2007;298:194–206. [Medline] [CrossRef]
16. Drucker DJ, Buse JB, Taylor K, Kendall DM, Trautmann M, Zhuang D, *et al*. DURATION-1 Study Group Exenatide once weekly versus twice daily for the treatment of type 2 diabetes: a randomized open-label, non-inferiority study. Lancet 2008;372:1240–50. [Medline] [CrossRef]
17. Seino Y, Rasmussen MF, Zdravkovic M, Kaku K. Dose-dependent improvement in glycemia with once-daily liraglutide without hypoglycemia or weight gain: A double-blind, randomized, controlled trial in Japanese patients with type 2 diabetes. Diabetes Res Clin Pract 2008;81:161–8. [Medline] [CrossRef]
18. Zhang J, Tokui Y, Yamagata K, Kozawa J, Sayama K, Iwahashi H, *et al*. Continuous stimulation of human-glucagon-like peptide 1 (7-36) amide in a mouse model (NOD) delays onset of autoimmune type 1 diabetes. Diabetologia 2007;50:1900–9. [CrossRef]
19. Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, *et al*. Management of hyperglycemia in tyupe 2 diabetes: A patient-centered approach. Position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 2012;35:1364–79. [Medline] [CrossRef]