Biomedical Research 2017; 28 (10): 4460-4465 *ISSN 0970-938X*
www.biomedres.info

To evaluate the efficacy of GLP-1 analogues on the blood sugar levels, insulin resistance, islet β-cell function and pre-diabetes of the children.

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Abstract

Background: To evaluate the clinical efficacy of Glucagon-Like Peptide-1 (GLP-1) analogues on the blood sugar levels, insulin resistance, islet β-cell function and pre-diabetes of the children.
Methods: Prospective and randomized controlled clinical trial was done on 82 cases of newly diagnosed pre-diabetes in children. First group was comprised of 41 subjects of lifestyle intervention group i.e. control group and the second group were comprised of 41 subject of lifestyle intervention+GLP-1 analogs liraglutide group i.e. observation group. Interventions were done lasted for 3 months. Review of intervention was done at 1 month and at after the 3 months. We carried out the medical examinations at the time when the patient had been diagnosed with prediabetes and after the intervention of 3 months. The medical test examinations includes the Fasting Blood Glucose (FPG), 2 h Postprandial Blood Glucose (2hPG), detection of glycated haemoglobin (HbA1C), Total Cholesterol (TC), Triglyceride (TG), Low Density Lipoprotein Cholesterol (LDL-C), High Density Lipoprotein Cholesterol (HDL-C), BMI, insulin resistance and the islet cell functions.
Results: After the 1 month of intervention, the observation group showed a better control on FPG and 2hPG compared with the control group (P<0.05). The levels of HbA1C, TC, TG, LDL-C, HDL-C, and BMI of the observation group were statistically better controlled, when compared with the control group after the intervention of 3 months. The insulin resistance index of the observation group was significantly decreased than that of the control group (P<0.05) and the islet function index of the β cell of the observation group showed statistically higher values than that of the control group (P<0.05).
Conclusions: GLP-1 analogs could be a better controller of blood sugar levels, effectively improve lipid profile, body mass, insulin resistance and islet β-cell function. Furthermore, GLP-1 analogs open up a new way to intervene pre-diabetes in children.

Keywords: GLP-1 analogues, Pre-diabetes, Liraglutide.

Accepted on February 25, 2017

Introduction

Prediabetes ("intermediate hyperglycaemia"), based on glycaemic parameters above normal but below diabetes thresholds is a high risk state for diabetes with an annualized conversion rate of 5%-10%; with similar proportion converting back to normoglycaemia [1]. Multifactorial risk scores could optimize the estimation of diabetes risk using non-invasive parameters and blood-based metabolic traits in addition to glycaemic values. For prediabetic individuals, lifestyle modification is the cornerstone of diabetes prevention. At present, the prevalence of DM and T2DM in children has been significantly increasing in umber [2]. Currently, there are very less research reports on the early intervention for children with DM and also very less literature based on pre diabetic children intervention in lifestyle.

Glucagon-Like Peptide-1 (GLP-1) is an endogenous incretin hormone that is released from the intestine in response to food intake. Effects of GLP-1, including increased insulin secretion, decreased glucagon secretion, slowed gastric emptying, and maintenance of blood glucose levels [3]. In patients with T2DM, continuous intravenous infusion and intermittent subcutaneous administration of GLP-1 lowered Fasting Plasma Glucose (FPG) and increased insulin and C-peptide levels, but after normal FPG levels were reached, insulin and C-peptide levels decreased, resulting in stable blood glucose levels. These findings indicated a glucose-dependent response and a reduced risk for hypoglycemia. The duration of effect and clinical usefulness of GLP-1 were limited because of the rapid degradation of GLP-1 by dipeptidyl peptidase-IV (DPP-IV), which occurs within minutes of GLP-1 release [3].

This limitation has been overcome by the discovery of molecules with DPP-IV resistance. Exenatide and liraglutide are DPP-IV-resistant GLP-1 agonists and were marketed for the treatment of T2DM in 2005 and 2010, respectively. Though these agents have shown benefit in the management of T2DM, they require once- or twice- daily administration [3].

Liraglutide has 97% homology to native GLP-1 and exhibits greater similarity than exenatide. Liraglutide's prolonged half-life of 13.1 h is due to delayed absorption and considerable resistance against DPP-4 degradation. This is primarily a result of a fatty acid substitution in the structure that results in albumin bonding, which extends the duration of action. Therefore, liraglutide is suitable for once-daily administration without regards to meals. After injection, liraglutide binds to the GLP-1 receptor and results in increases in insulin secretion and reductions in postprandial glucagon. Liraglutide should be initiated at a dose of 0.6 mg once daily for 1 week and then titrated to 1.2 mg daily. If the 1.2 mg dose does not achieve glycemic goals, the dose can be further increased to 1.8 mg daily [4].

So with this thing in mind, we proposed a research study with the aim to evaluate the effect of GLP-1 analogues for reversal of normal blood glucose in patients with prediabetes.

Materials and Methods

Total sample size was comprised of 82 children having the diagnosis of prediabetes visited in the outpatient department of Endocrinology of our hospital. All the samples were selected from the period of 2012 to 2015 with age between 6-18 years. Out of 82 children, 49 subjects were male and 33 subjects were female. Ethical clearance of the study were taken from the institutional ethical board before starting the study as well as the informed patient consent regarding the study were also collected from all the subjects.

Exclusion criteria

People with genetic metabolism, endocrine disease, kidney disease high blood pressure and high blood lipid profile were excluded from the study.

General information of both groups of patients was enlisted in Table 1 and the diagnostic criteria for the early stage of diabetes mellitus and dyslipidemia were enlisted in the Table 2.

The children were randomly divided into two groups; one is the intervention group i.e. control group and second is the lifestyle intervention+GLP-1 analogs liraglutide group injection group i.e. observation group.

In the lifestyle intervention group, all the children followed the unified diet exercise prescription with regular telephonic conversation, outpatient follow-up, and education of the parents and children at the same time.

Liraglutide injection (18 mg/piece, Novo Nordisk, Copenhagen, Denmark) treatment was given. The initial dose was 0.6 mg/d subcutaneous injection, q.d. After 1 week it was adjusted to 1.2 mg/d subcutaneous injection, q.d. After 1.2 mg/d maintenance therapy upto 3 months.

Determination of fasting height and weight of children was taken by hand. After 10 hours of fasting, in the next morning venous blood indexes including FPG, HbA1C, TC, TG, LDL-C, HDL-C, insulin (FINS), 2hPG were measured and OGTT were taken as diagnostic test for DM. After 10 h of fasting, oral glucose was taken as 1.75 g/kg, ≤ 75 g/time. All other diagnostic methods of DM like TC, TC, Enzymatic measurement, LDL-C, HDL-C, direct method of measurement, FPG, measurement by the sugar kinase method, Body mass index, insulin β cell secretion index (HOMA-β) and insulin resistance index (HOMA-IR) were calculated.

BMI was calculated as Weight Kg/height m^2. HOMA-β was calculated as =20 × FINS/(FPG-3.5). Insulin resistance was calculated by Homeostais Model Assessment (HOMA). HOMA is calculated as HOMA-IR=(FPG mmol/l × FINS mU/L/22.5. If the HOMA-IR value<4, then it showed prompted high insulin sensitivity and if the HOMA-IR value>4, then it showed prompted low insulin sensitivity and high insulin resistance [5,6].

Statistical methods

SPSS18.0 software (SPSS Inc., Chicago, IL, USA) was applied for statistics and analysis of data. Data of normal distribution were recorded by x ± s. HOMA-β was transformed into normal data for analysis. Measurement data between the two groups was tested by t-test. The analysis before and after treatment was done by using paired t-test was used. P<0.05 indicated that the difference was statistically significant.

Results

Analysis of blood glucose metabolism of two groups before and after the intervention

Fasting blood glucose level of the both the groups were compared before the intervention and after the 1 month and 3rd month of the intervention. After 1 month of intervention, the fasting blood glucose in the observation group was 6.11 ± 0.78 mmol/l, which is lower than that in the control group (6.21 ± 1.21) mmol/l (P<0.05). After 3 months of intervention, the fasting blood glucose (0.01 ± 0.66) mmol/l in the observation group was significantly lower than that in the control group (6.12 ± 1.08) with the statistical significant P value of less than 0.01.

After the 2 h of Glucose loading: We compared the blood glucose levels after 2 h of glucose loading between both the groups. After 1 month of intervention with 2 h of glucose loading, the blood glucose (7.22 ± 2.01) mmol/l in the observation group was lower than that in the control group (7.89 ± 1.97) mmol/l with the non-significant P<0.05.After 3 months of intervention with after 2 h of glucose loading, the blood glucose (6.15 ± 1.67) mmol/l in the observation group was significantly lower than that of the control group (7.63 ± 1.82) mmol/l with the significant P<0.01.

Levels of HbA1C between the both groups: When enrolment HbA1C in the observation group was 5.87 ± 1.35% and in the control group was 5.85 ± 1.33%. It showed no significant difference in HbA1C levels between the two groups with non-significant p value>0.05. After 3 months of intervention, the HbA1C in the observation group was 5.23 ± 1.01%, which was

significantly lower than that in the control group 5.56 ± 1.14 with significant P<0.01.

Serum lipid profile and BMI levels were analysed in both the groups before and after the intervention. BMI, TC, TG, LDL-C, HDL-C, FINS of the observation group were revealed statistically significant results, when compared with the control group (P<0.05). Referring to the Chinese BMI criteria (7-18 years old) and CDC 2000 criteria of the United States (6 years old), children in the group were mostly overweight and having obesity, with the cumulative incidence up to 83.33% (Table 3).

Comparison of the level of HOMA-IR and HOMA-β: The levels of HOMA-IR and HOMA-β were analysed before and after intervention in the both the groups. The decreased insulin resistance index of the observation group was higher than that of the control group, and the difference was statistically significant (P<0.05). Islet function index of the β cell of the observation group was significantly higher than that of the control group, and the difference was statistically significant with p value of <0.05 (Table 4).

Table 1. *General information of both the groups of patients.*

Group	Number (case)	Gender		Age	BMI (kg/m2)	HbA1c (%)
		Male (case)	Female (case)			
control group	41	25	16	11.12 ± 2.10	30.89 ± 5.02	5.85 ± 1.33
Observation group	41	24	17	11.19 ± 2.27	30.98 ± 4.97	5.87 ± 1.35

Note: Gender, age, BMI and HbA1c were compared in two groups of children, and P>0.05 indicated that they were comparable.

Table 2. *Diagnostic criteria of DM in the early stage and dyslipidemia.*

DM and DM pre diagnostic criteria (mmol/l)			Diagnostic criteria for dyslipidemia (mmol/l)		
IFG	IGT	DM	High TG	High TC	Low HDL-C
FPG: (5.6-6.9), while OGTT2h blood glucose<7.8	OGTT2h blood glucose (7.8-11.0), while FPG<5.6	FPG ≥ 7.0 or OGTT2h blood glucose>11.1	≥ 1.7	≥ 5.2	≤ 1.03

Table 3. *Blood lipids and fasting insulin were compared between the two groups.*

Index	control group		observation group	
	Enrolment	Intervention for 3 months	Enrolment	Intervention for 3 months
BMI (kg/m^2)	30.89 ± 5.02	29.88 ± 5.32^{A}	30.98 ± 4.97	28.68 ± 5.19^{AB}
FINS (μU/ml)	31.21 ± 8.01	28.82 ± 9.64^{A}	31.19 ± 8.11	26.79 ± 9.69^{AB}
TG (mmol/l)	1.13 ± 0.72	1.10 ± 0.39	1.14 ± 0.62	1.04 ± 0.37^{AB}
TC (mmol/l)	4.19 ± 1.26	3.95 ± 1.03 ^{A}	4.17 ± 1.27	3.80 ± 1.01^{AB}
HDL (mmol/l)	1.18 ± 0.31	1.20 ± 0.19	1.19 ± 0.24	1.33 ± 0.25^{AB}
LDL (mmol/l)	2.45 ± 1.00	2.39 ± 0.66	2.47 ± 0.96	2.21 ± 0.88^{AB}

Note: The blood lipid profile of two groups of children were compared when enrolment, P>0.05, with comparability. Compared with before intervention. ^{A}P<0.05; The observation group was compared with the control group, ^{B}P<0.05.

Table 4. *Comparison of the changes of HOMA-IR and HOMA-β in two groups after 3 months of intervention.*

Index	The number of cases	Control group	Observation group
HOMA-IR of enrolment	41	7.04 ± 2.73	7.06 ± 2.68
HOMA-IR after 3 months	41	6.52 ± 3.51A	6.02 ± 3.11^{AB}
HOMA-βof enrolment	41	2.64 ± 0.38	2.65 ± 0.32
HOMA-IR after 3 months	41	2.56 ± 0.37	2.46 ± 0.31^{AB}

Note: HOMA-IR and HOMA-β of two groups of children were compared when enrolment, P> 0.05, with comparability. Compared with before intervention, ^{A}P<0.05; The observation group was compared with the control group, ^{B}P<0.05.

Discussion

The study has found that the obese and overweight children were totally up to 83.33% in the early stage of DM. As with the changes of lifestyle, reduced physical activity and unhealthy eating habits caused obesity incidence gradually

increased and further, showed that about 110 million of the world's children was overweight or obese [7]. Related studies also showed that compared with normal children, overweight and obese children had higher average blood glucose levels, blood glucose abnormalities, IGT and diabetes incidence [8]. Studies have indicated that BMI in children with T2DM were elevated, while BMI and Insulin Resistance (IR) in childhood appeared simultaneously [9-11]. The sensitivity of insulin was negatively correlated with BMI and obesity. Children with increased BMI revealed decrease insulin sensitivity and increased blood glucose level that further, resulted in impaired glucose metabolism. As according to Santos et al. study demonstrated high prevalence of insulin resistance and impaired glucose tolerance associated with body trunk fat, among obese non-diabetic adolescents. Nakahara et al. also concluded that both obestatin and ghrelin are increased in anorexic and decreased in obesity. We suggest that obestatin is a nutritional marker reflecting body adiposity and insulin resistance [12].

Period of Normal Glucose Tolerance (NGT) and hyperlipidemia are considered to be the early stage of DM [13]. There are the 3 phases of the glucose metabolism in children and adolescents Mention 3 stages first. The early stage of diabetes refers to the impaired glucose regulation between normal glucose metabolism and DM, including three types: IFG, IGT, and IFG/IGT both coexist. According to current research report, in our country, in the early stage of diabetes there are 148 million people which further increased the incidence rate up to 15.5% [14,15]. About 70% of the patients of the early stage of diabetes will eventually progress into diabetes, which is a serious harm issue for the population. Overweight, obesity and decreased physical activity in children with diabetes are at greater risk in the developing diabetes. Over the past 40 years, there have been 8 large-scale clinical trials showing that 25%-60% of pre diabetes patients can prevent the development of diabetes by just lifestyle intervention. In order to prevent the development of obesity in children, the key is how to prevent the development of obesity by early control. By changing the lifestyle like proper diet plan and adequate exercise therapy, can prevent the conversion of pre-diabetes into the diabetes. Change of lifestyle considered to be the cornerstone in the treatment of the pre-diabetes. Tuso et al. concluded that the primary aim of lifestyle interventions is to prevent diabetes and its complications by targeting obesity and physical inactivity. Patients not responding to lifestyle interventions may be considered for pharmacologic interventions or surgery. The goal for prediabetes treatment should be to normalize blood glucose levels. Strategies targeting interventions aimed at the entire population at risk of pre-diabetes can make health care more affordable, prevent a preventable disease, and save lives [16].

Knowler et al. hypothesized that lifestyle intervention would prevent or delay the development of diabetes [17].

Perreault et al. [18] reported that patients with prediabetes that did not progress to diabetes after they completed an intensive lifestyle intervention were still at high risk for the development of diabetes. They also discovered that reversion to normal glucose levels, even transiently, was associated with a 56% reduced risk of future diabetes [18].

Schellenberg et al. compared the effectiveness of lifestyle interventions to standard care on minimizing progression of prediabetes to diabetes or reducing all-cause mortality in diabetes. This meta-analysis study identified 9 randomized, controlled trials with prediabetic patients who were at risk of diabetes and 11 randomized, controlled trials with patients who had diabetes. Seven of the 9 studies looking at patients who were at risk of diabetes reported that lifestyle interventions decreased the risk of diabetes up to 10 years after a lifestyle intervention [19].

But it is generally believed that the long-term effectiveness of lifestyle intervention is not good, and it is easy to rebound. Even if the body mass reduces, there are still 40%-50% chances that the IGT damages causing type 2 diabetes. Therefore, lifestyle intervention alone cannot completely prevent the occurrence and development of the diabetes. There are very few reports about the long term effectiveness of only lifestyle intervention for the obese children. The practicability of the simple lifestyle intervention is poor, which is widely questioned by the doctors and the patients. In view of the particularity of school age children, due to the lack of self-discipline in children, the simple lifestyle intervention may be difficult to achieve the individual weight loss because of its inability to achieve the amount of physical activity. On the other hand, considering the children's stage, calorie restricted intake will affect their growth and development, which will further lead to the fact that the only simple life style intervention cannot be implemented to reduce the obesity. That's why Early drug intervention programmes becoming more popular in these days.

According to McLellan et al. concluded that T2DM can be prevented in high-risk individuals through lifestyle modification, pharmacologic interventions, and bariatric surgery. However, the translation of this research to a population level, especially finding the most effective methods of preventing T2DM in various societies and cultural settings is challenging, but is a crucial priority [20].

Glucagon-like peptide 1, GLP-1 belongs to the gut peptide hormone secreted by intestinal epithelial cells. GLP-1, the incretin hormone works in regulating appetite, delaying gastric emptying, stimulating islet beta cell proliferation, suppressing apoptosis, promoting insulin secretion, improving insulin sensitivity, fat mobilization, and restoring the function of islet beta cell [20-22]. Because of its main role in so many metabolic activities, GLP - 1 peptide has become a hot topic in the study of obesity and diabetes prevention. Natural GLP-1 has a half-life of only 1 to 2 minutes and can be rapidly degraded by DPP-4 *in vivo*. After the degradation it becomes into inactive form that further hinders its clinical application. The representative drugs of GLP-1 peptide are exenatide and liraglutide. The peptide is the first GLP-1 analogue for the treatment of T2DM. The research studies reveals that the daily twice dose of exenatide subcutaneous injection and daily one

dose of liraglutide subcutaneous injection, plays a good role in the regulation of blood sugar, reduction in weight, protection of islet beta cells and the prevention of cardiovascular disease [22-26]. LEAD results showed that liraglutide administered alone or in combination with other antidiabetic drugs, could effectively improve the blood glucose level, controls the pancreatic beta cell function, weight loss with less risk of hypoglycemia [27-32]. When the glucose concentration is lower than about 4.5 mmol/l, GLP-1 loses its hypoglycemic effect [33].

Reddy et al. concluded that the GLP-1 receptor agonists are effective agents for the treatment of type 2 diabetes, offering many advantages over other agents, including weight loss, potential beta-cell protection, and low risks of hypoglycemia. They also have positive benefits on cardiovascular parameters, including reductions in blood pressure, lipids, and weight, although the clinical relevance of this remains to be determined. Though long-term safety data is unavailable due to the short duration of time that these agents have been on the market, future studies will provide guidance to practitioners on the appropriate choice of agents to mitigate risk, including cardiovascular risk. Overall, GLP-1 receptor agonists are effective and innovative agents for patients with type 2 diabetes and other chronic conditions, who are either uncontrolled or intolerant to first-line metformin therapy.

Because the early application of GLP-1 analogues may reverse the early development of diabetes, this study used a prospective randomized controlled trial to compare the blood glucose, lipid profile, body weight, insulin resistance and beta cell function of pre diabetic children after the intervention of 3 months in simple lifestyle intervention group (control group) and lifestyle intervention+GLP-1 analogue liraglutide treatment (observation group). After 1 month of intervention, 2hPG and FPG in the observation group were lower than those in the control group ($P<0.05$). After 3 months, FPG and 2hPG of the observation group were significantly lower than those of the control group ($P<0.01$). After the 3 months of intervention, HbA1C, TC, TG, LDL-C, HDL-C, BMI of the observation group were statistically different compared with the control group ($P<0.05$). The decreased insulin resistance index of the observation group was significantly higher than that of the control group ($P<0.05$). The islet function index of the β cell of the observation group was significantly higher than that of the control group ($P<0.05$). GLP-1 analogues can control FPG, 2hPG blood glucose in early stages, improve blood lipid profile, improves body mass index, insulin resistance and improves the function of islet beta cell and further explores new ways of early childhood intervention. In view of the current domestic and international use of GLP-1 powder injection of long-acting analogue of chemical synthesis, with complex production process, high cost, expensive market price, the storage and transportation difficulties, inconvenience of subcutaneous administration, so the clinical feasibility is not ideal. Therefore, we need to improve the production mode of GLP-1 similar peptide, change the way of using GLP-1 similar peptide, and develop GLP-1 similar peptide of high efficiency, low price and easy to use, in order to obtain good social benefits.

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