The Role of Incretin on Diabetes Mellitus

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ABSTRACT

Beta cell dysfunction in type-2 diabetes mellitus holds an important role not just on its pathogenesis, but also on the progression of the disease. Until now, diabetes treatment cannot restore the reduced function of pancreatic \( \beta \) cell. McIntyre et al. stated that there is a factor from the intestine which stimulates insulin secretion as a response on glucose. This factor is known as incretin. It is a hormone which is released by the intestine due to ingested food especially those which contain carbohydrate and fat. Currently, there are 2 types of incretin hormones which have been identified, i.e. Glucose dependent insulinotropic polypeptide (GIP) and GLP-1 (Glucagon like peptide-1). These two hormones act by triggering insulin release immediately after food ingestion, inhibiting glucagon secretion, delaying stomach emptying, and suppressing hunger sensation. Several in vitro studies have demonstrated that these two incretin hormones may increase the proliferation of pancreatic \( \beta \) cell.

There is a decrease of GIP function and GLP-1 amount in type-2 diabetes mellitus; thus the attempt to increase both incretin hormones - in this case by using GLP-1 agonist and DPP-IV inhibitor - is one of treatment modalities to control the glucose blood level, either as a monotherapy or a combination therapy. Currently, there are two approaches of incretin utilization as one of type-2 diabetes mellitus treatment, which is the utilization of incretin mimetic/agonist and DPP-IV inhibitor.

Key words: incretin hormone, GIP GLP-1.

INTRODUCTION

The regulation of blood glucose level in normal individual is controlled by very strict limits. Immediately after food ingestion, the glucose level increases. This will trigger insulin secretion from pancreatic \( \beta \) cell and will lower the glucagon secretion from pancreatic \( \beta \) cell; and the contrariwise. Insulin will reduces the glucose level by lowering the glycogenolysis and gluconeogenesis in liver and increasing the glucose uptake in the peripheral tissue, as well as by lowering glucagon secretion in pancreas. This does not occur in diabetes mellitus, one of its causes is pancreatic \( \beta \) cell defect.\(^1\)

Beta cell dysfunction in type-2 diabetes mellitus holds an important role not only on its pathogenesis, but also on the progression of the disease. One of the targets of diabetes treatment is to lower the fasting and postprandial glucose level either by diets, exercises, oral anti diabetic agents, or insulin. Up to now, current diabetes treatment has not been able to restore the function of pancreatic \( \beta \) cell since the pharmacological treatment known so far is not able to inhibit and restore the \( \beta \)-cell damage.\(^2,3\)

The study conducted by McIntyre et al. demonstrated evidences that there is a higher increase of insulin level on oral glucose administration compared to intravenous administration, thus this opens a new viewpoint on the existence of a factor from intestine which may stimulates insulin secretion as a response to glucose. This study is known as the incretin effect. In normal condition, incretin hormone acts on the release of half the amount of insulin secreted in time of blood glucose level upsurge. On the contrary, in type 2 diabetes mellitus there is reduced incretin amount and function on insulin secretion. Currently, two polypeptides with incretin function have been found, which are the GIP (Gastric inhibitory peptide/glucose-dependent insulinotropic polypeptide) and GLP-1 (Glucagon like peptide – 1). Moreover, they develop as one of
pharmacological therapeutic modality for type-2 diabetes, in addition to the earlier established treatment.4,5

This paper will discuss about the history and physiology of incretin hormone, also its role in controlling blood glucose level in type-2 diabetes mellitus patients.

THE HISTORY OF INCRETIN HORMONE

The study by Bayliss and Starling found secretin in 1902. They stated that after food ingestion there is a signal originating from the intestine that affects insulin release. This finding is supported by Moore et al who indicated that duodenum produces a substance that can stimulate pancreas to release insulin, and they used it as diabetes treatment.5 Furthermore, in 1932, Le Berre et al gave a name incretin to the substance contained in duodenum, to represent the intestine humoral activity which can trigger the secretion of pancreatic endocrine hormones. The theory at first was controversial and did not develop significantly. As the science is getting more advanced and the method to detect insulin level in human plasma is found, thus in 1960-ies, Mc Intyre et al performed an experiment to evaluate the plasma insulin response towards oral and intravenous glucose. They concluded that there is a higher insulin level in oral glucose group.4,5 This mechanism which explains insulin increase on oral glucose administration was named as entero-insular-axis theory by Unger and Eisentraut in 1969. The theory was further explained by Creutzfeldt as an axis involving nutrition, neural, and hormonal signal from intestine to pancreas cell to produce insulin, glucagon, and other pancreatic polypeptides.5 In 1971, Brown et al isolated a polypeptide from cholecystokinin, which functions to inhibit the pepsin and gastric acid secretion, and named it as the gastric inhibitory peptide (GIP). Subsequently, Dupre et al demonstrated evidences that the GIP inhibitory effect on gastric acid secretion is weak, and its effect is primarily in triggering insulin secretion immediately after glucose ingestion; thus, this polypeptide is also called glucose-dependent insulinotropic polypeptide.4,6

The study by Ebert et al in 1983 demonstrated evidences that incretin effect still exists albeit separation of GIP hormone from intestine extract by immuno-absorption method.7 A decade later, owing to the invention of DNA coding process, Bell et al successfully identified the glucagon like peptide-1 (GLP-1), which also functions as incretin hormone.4,7,8

THE PHYSIOLOGY OF INCRETIN HORMONE

Glucose dependent insulitropic polypeptide (GIP) is one of incretin hormones which consists of 42 amino acids and is mostly produced by the K-enteroendocrine cells in duodenum and proximal jejunum.4,7

GIP is expressed from proGIP gene located on the long arm of chromosome 17 with 6 exons and 5 introns, which will be translated into 42 amino acids.9 (Figure 1) In fasting state, the circulated GIP level is very low and reaches its peak in 15-30 minutes after food ingestion, especially food which contains carbohydrate and fat. Subsequently, the GIP binds to its specific receptors in pancreatic b islet cell, adipocyte tissue and central nervous system.6,9 Glucagon like peptide-1 is an incretin hormone produced by L-enteroendocrine cell in distal ileum and colon. It is a member of glucagon hormone superfamily due to its 21-48% amino acids resemblance. GLP-1 is a post translation product of proglucagon gene which is cleaved by prohormone conververtase-1 into glycentin, oxyntomodulin, GLP-1, and GLP-2. GLP-1 consists of 30 amino acids which have active forms of GLP-1 (7-37) and GLP-1 amide (7-36).5,8,10 In normal condition, fasting plasma GLP- level is 1-2 pmol/L, and increases into 30 pmol/L during food ingestion, and reaches its peak plasma level in 15-30 minutes after food ingestion.11

The hormone will bind to GLP-1 receptors in pancreatic α and β cell, central and peripheral nervous system, heart, kidney, lung, and gastrointestinal tract.5

In pancreas, both incretins have an effect in triggering the insulin release, stimulate proliferation and slow down the β cell apoptotic process. The effect of increasing the insulin secretion from GIP and GLP-1 is mediated through their binding to specific receptor which is a type of G-protein coupled receptor class. If being activated, the binding will stimulate adenyl cyclase which then will increase the 3′5′-cyclic adenosine monophosphate (cAMP) level and subsequently will activate protein kinase A and the cAMP regulated
guanine nucleotide exchange (cAMP-GEFII). Moreover, both proteins will consequently increase intracellular calcium. The increased intracellular calcium in pancreatic islet cells will cause insulin exocytosis, which finally lead to increased insulin secretion.6,11,13 Other effects on pancreas are including triggering proliferation and neogenesis of islet cells, as well as suppressing the β-cell apoptosis. This fact was demonstrated by Trumper et al and Zhou et al studies, which concluded that both incretins can restore the damaged pancreatic β-cells so that the cells are able to synthesize and secrete insulin in the experimental animal model.14,15 Such facts are also supported by Farilla et al who conducted study on human islet cell in vivo.16 Buteau et al also demonstrated evidences that GLP-1 can protect pancreatic β-cell from glucolipotoxicity.17

GIP and GLP-1 are degraded by dipeptidyl peptidase-IV (DPP-IV), enzymes which cleave both hormones on its alanine amino acid site into their inactive forms. The DPP-IV enzyme is found in all organs including intestine capillary endothelial; thus majority of GIP and GLP-1 in portal circulation are in their inactive forms, with half life of 5-7 minutes for GIP and 1-2 minutes for GLP-1.19

**Figure 2.** The formation of GLP-1\(^1\)\(^2\)

**Figure 3.** The effects of incretin hormones on several organs\(^1\)\(^9\)

**INCRETIN HORMONE ON DIABETES MELLITUS**

In normal individual, oral glucose administration will increase insulin secretion twice of intravenous glucose administration. However, in diabetic patients the oral glucose administration will only cause 20% increase of insulin secretion due to several causes.20 Incretin hormones, the GIP and GLP-1, affect post-prandial insulin release of 60-70% considerably in normal individual and there is a reduced incretin effect in diabetic patients compared to normal individual.7 (Figure 4).

Reduced incretin effect in diabetic patients occurs because of reduced function and amount of incretin hormones. The GIP level in diabetic patients is normal or slightly increased, both in basal and post-prandial state. In contrast, the GLP-1 level decreases in type-2 diabetes mellitus and impaired glucose tolerance patients, compared to normal subjects. The mechanism of GLP-1 declination in these groups is still indefinite.21

In patients with type-2 diabetes mellitus, exogenous GIP and GLP-1 hormone administrations produce different effects. Nauck et al demonstrated that the administration of exogenous GIP and oral glucose in patients with type-2 diabetes mellitus patients apparently
does not yield the effect of insulin increase response as in normal individual. The mechanism that may probably explain this effect is the reduced GIP insulinoergic effect in diabetic patients. The opposite happens on administration of GLP-1 in patients with type 2 diabetes mellitus. GLP-1 administration will give insulinoergic, gluconeostatic, and gastric emptying delay effects in patients with type-2 diabetes mellitus. These facts support the utilization of GLP-1 as one of pharmacological diabetes treatment.3,8,20

Insulin secretion in normal individual occurs 10 minutes after intravenous glucose administration. This secretion response is called as phase I insulin response, which does not occur in diabetic patients. The absence of this particular response is an early defect of pancreatic ß cell in diabetic patients. Fehse et al stated that exogenous GLP-1 administration will improve phase I and II of insulin secretion in diabetic patients.22

Kolterman et al demonstrated evidences that exogenous GLP-1 administration in patients with type-2 diabetes mellitus will suppress glucagon production and it is not affected by gastric emptying delay factor.23

By such effects, consequently the agents which may increase the GLP-1 plasma level - the GLP-1 receptor agonist and drugs that can inhibit the degradation of both incretin hormones – can be utilized as one of pharmacological treatment modalities for type 2 diabetes mellitus, in addition to the earlier established treatment.8,20,24

Figure 4. The reduced incretin effect in patients with type-2 diabetes mellitus7

Figure 5. The effects of exogenous GLP-1 administration on insulin secretion in normal and type-2 diabetes mellitus subjects22

INCRETIN HORMONE AS A TREATMENT FOR DIABETES MELLITUS

Currently there are two approaches of incretin utilization as one of treatment for type-2 diabetes mellitus, i.e. the use of incretin mimetic/agonist and DPP-IV inhibitor.5

GLP-1 Receptor Agonist

Glucagon like peptide-1 is rapidly degraded by DPP-IV enzyme, thus continuous infusion is necessary to produce clinical effect in patients with type-2 diabetes mellitus. Drugs that are included in this group are exenatide and liraglutide.
Exenatide or exendin-4 is a receptor agonist for GLP-1 which is isolated from Gila Monster (Heloderma suspectum) saliva. Exenatide has 53% resemblance with human GLP-1 and is more resistant to DPP-IV, thus it has longer duration of action. This drug is administered through subcutaneous injection on thigh, abdomen and upper arm; administered twice a day, an hour before breakfast and dinner, with initial dose of 5 mcg and can be increased to 10 mcg after 1 month administration, depending on clinical response. After 10 mcg subcutaneous injection, this drug reaches its peak plasma level in 2.1 hour with concentration of 211 pg/mL.25,26 Exenatide is mainly eliminated through glomerular filtration, thus is not recommended for patients with chronic kidney disease. The side effects of this drug are nausea, vomiting, bloating, dizziness, headache, and hypoglycemia, particularly when it is combined with sulfonylurea group or if it is administered to patients with GFR less than 30 ml/hour.27

This drug is contraindicated for patients with end stage kidney failure, type-1 diabetes mellitus and diabetic patients with severe gastrointestinal disease. Until now, there has not been any clinical evidence of its administration in pregnant women and children. The drug primarily interacts with drugs that need immediate effect and absorption, such as paracetamol, digoxin, lovastatin, oral antibiotics, and oral contraceptives.25,28

De Fronzo et al, Buse et al, and Kendall et al - using HbA1C as a standard of their studies - indicated that in patients with type-2 diabetes mellitus whose glucose level is uncontrolled by the treatment of sulfonylurea, metformin, or combination of sulfonylurea-metformin; exenatide administration for 30 weeks significantly lowers A1C compared to placebo (Table 2).29-31

These three studies also found that there is a significant weight loss after 30 weeks of exenatide administration, particularly on 10 mcg dose (Table 3).29-31 On 82 weeks of 10 mcg exenatide administration, Kendall et al found significant weight loss with mean value of 4.5±0.5 kg.32

### Table 1. The Differences Between GIP and GLP-2

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>GLP-1</th>
<th>GIP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peptide</td>
<td>42 amino acids</td>
<td>30 amino acids</td>
</tr>
<tr>
<td>Normal t½</td>
<td>2 min</td>
<td>7 min</td>
</tr>
<tr>
<td>Promotes β-cell proliferation</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Produced in</td>
<td>Enterodendocrine cells of the colon and distal small bowel</td>
<td>Duodenal cell in proximal small bowel intestine</td>
</tr>
<tr>
<td>Inhibitory abilities</td>
<td>Gastric acid secretion, glucagon secretion, food intake, and libitum energy intake</td>
<td>Gastric acid secretion and fat metabolism in adipocytes</td>
</tr>
<tr>
<td>Secretion in type 2 DM</td>
<td>Normal</td>
<td>Reduced</td>
</tr>
<tr>
<td>Status of ability in type 2 DM</td>
<td>Preserved</td>
<td>Diminished</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>Enhances satiety, likely therapeutic target for type 2 diabetes</td>
<td>Unlikely therapeutic target for type 2 diabetes</td>
</tr>
</tbody>
</table>

### Table 2. HbA1c Alteration on Exenatide Administration as Type-2 Diabetes Mellitus Treatment

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mean baseline A1C (%)</th>
<th>A1C after 30 weeks</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin + placebo</td>
<td>8.2</td>
<td>8.3</td>
<td>.1</td>
</tr>
<tr>
<td>Metformin + 5mcg exenatide</td>
<td>8.3</td>
<td>7.9</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Metformin + 10mcg exenatide</td>
<td>8.2</td>
<td>7.4</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Sulfonylurea + placebo</td>
<td>8.7</td>
<td>8.8</td>
<td></td>
</tr>
<tr>
<td>Sulfonylurea + 5 mcg exenatide</td>
<td>8.5</td>
<td>8.0</td>
<td>&lt;.0002</td>
</tr>
<tr>
<td>Sulfonylurea + 10 mcg exenatide</td>
<td>8.6</td>
<td>7.7</td>
<td>&lt;.0002</td>
</tr>
<tr>
<td>Combination th + placebo</td>
<td>8.5</td>
<td>8.7</td>
<td></td>
</tr>
<tr>
<td>Combination th + 5 mcg exenatide</td>
<td>8.5</td>
<td>7.9</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Combination th + 10 mcg exenatide</td>
<td>8.5</td>
<td>7.7</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

### Table 3. The Altered Weight Loss on Exenatide Administration as Diabetes Mellitus Treatment

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mean baseline weight (kg)</th>
<th>Change after 30 weeks (kg)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin + placebo</td>
<td>100</td>
<td>-0.3</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Metformin + 5 mcg exenatide</td>
<td>100</td>
<td>-1.6</td>
<td></td>
</tr>
<tr>
<td>Metformin + 10 mcg exenatide</td>
<td>101</td>
<td>-2.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sulfonylurea + placebo</td>
<td>99</td>
<td>-0.6</td>
<td></td>
</tr>
<tr>
<td>Sulfonylurea + 5 mcg exenatide</td>
<td>95</td>
<td>-0.9</td>
<td>0.98</td>
</tr>
<tr>
<td>Sulfonylurea + 10 mcg exenatide</td>
<td>95</td>
<td>-1.6</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Combination th + placebo</td>
<td>99</td>
<td>-0.9</td>
<td></td>
</tr>
<tr>
<td>Combination th + 5 mcg exenatide</td>
<td>97</td>
<td>-1.6</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Combination th + 10 mcg exenatide</td>
<td>98</td>
<td>-1.6</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

In diabetic patients whose blood glucose level is not controlled by oral drugs, addition of exenatide or glargine insulin can cause similar decrease of A1C level, i.e. 1.1%
after 26 weeks of treatment. Exenatide causes significant decrease on post-prandial blood glucose level; while glargine insulin is more effective in lowering the fasting glucose level. The study also indicated that there is 2.3 kg weight loss in exenatide group; while in the glargine insuline group, there is 1.8 kg weight gain.33

Another GLP-1 analog, liraglutide, is still in clinical trial phase. Liraglutide has 97% resemblance with GLP-1 particularly regarding its binding with albumin, the half life is between 11 – 15 hours. It is administrated subcutaneously with once daily 10 µg/kgBW dose. Reported side effects include headache, nausea, vomiting, and diarrheaa.15 Degn et al demonstrated that once daily liraglutide injection in diabetic patients for 1 week period can lower the fasting and post prandial glucose level and can restore the function of pancreatic β cell.34 By using liraglutide administration as a monotherapy for diabetic patients, with dosage that varies between 0.045 – 0.75 mg/day for 12 weeks, Madsbad et al reported approximately 0.75% A1C decrease; reduced proinsulin/insulin ratio; and 1.2 kg weight loss.35 Similar outcomes are also achieved on liraglutide administration as a combination therapy for diabetic patients who had metformin therapy previously. Liraglutide-metformin combination yields better outcome compared to metformin-sulfonylurea.36

**DPP-IV Inhibitor**

Degradation inhibition by DPP-IV inhibitor enzymes is one of alternative treatment to prolong the effect of incretin hormones. Currently, there are 2 types of DPP-IV inhibitor, i.e. sitagliptin and vildagliptin. These DPP-IV inhibitors can be used as another oral treatment for patients with type-2 diabetes mellitus.15

Sitagliptin is one of DPP-IV selective inhibitors and it is administered orally with 100 mg/day dose. In patients with diabetes mellitus patients, the administration of this drug can cause dose-dependent inhibition of plasma DPP-IV, increased insulin and C-peptide level, increased plasma GIP and GLP-1 level, and also lower the glucagon level. As the aforementioned discussion, GLP-1 will only produce slight effect on insulin stimulation when the glucose level is normal; therefore, it provides less hypoglycemia effect.37 Reported side effects include headache and increased incidence of upper respiratory tract infection.24 The study conducted by Aschner et al used 100 and 200 mg sitagliptin as a 24-week—monotherapy in 229 and 238 diabetes mellitus patients with A1C level around 8 – 10%, and they found significant decrease of A1C, fasting blood glucose, and glucose level after glucose load. Therefore, it can be concluded that sitagliptin can be used as a monotherapy for diabetic patients.38 As combination therapy, Charbonnel et al demonstrated that in 701 patients whose blood glucose level cannot be controlled by metformin, addition of 100 mg sitagliptin for 24 weeks can lower A1C level as much as < 7% in 47% patients, compared to placebo, which was only 18% patients; there were also lowered fasting glucose level; increase fasting insulin level as well as increased HOMA-β.39 This fact is also supported by other study which combined 100 mg sitagliptin with pioglitazone for 24 weeks in diabetic patients whose blood glucose level uncontrolled by pioglitazone monotherapy.40

Vildagliptin, which is also a DPP-IV inhibitor, can be used either as monotherapy or as combination therapy in diabetic patients, with twice daily 50 – 100 mg dosage. Xavier et al indicated that administration of 50 – 100 mg vildagliptin for 12 weeks can lower A1C as much as 0.5 – 0.9 %. Reported side effects are headache, upper respiratory tract infection, and myalgia.41 When it was used in diabetic patients whose blood glucose level cannot be controlled by metformin, it is found that combination of metformin and vildagliptin for 24 weeks can significantly lower A1C level, lower fasting plasma glucose level and 2 hours after glucose load level.42 Similar study result is also demonstrated by Fonseca et al who administered vildagliptin on diabetes patients whose blood glucose cannot be controlled by insulin, decreased A1C level was demonstrated.43

**CONCLUSION**

Incretin hormone is a hormone which is released by the intestine triggered by food intake, especially food which contains carbohydrate and fat. Currently, there are 2 types of incretin hormones that have been found, i.e. GIP and GLP-1. Both hormones play a role on glucose homeostasis, especially post prandial glucose level.

In normal individual, GIP stimulates insulin secretion and affects the lipid metabolism; while GLP-1 stimulates pancreatic β cells to produce insulin, suppresses glucagon secretion, delays gastric emptying, produces hunger sensation, and weight loss effect. There is a decrease of GIP function and GLP-1 amount in type-2 diabetes mellitus; thus, the attempt to increase GLP-1 - in this case by using GLP-1 agonist and DPP-IV inhibitor- is one of treatment modalities to control blood glucose level, either as a monotherapy or a combination therapy.
REFERENCES


