Glucagon-like peptide 1 and dysglycemia: Conflict in incretin science

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ABSTRACT

Although GLP-1 (glucagon like peptide-1) based therapies (GLP-1 agonists and dipeptidyl peptidase-4 inhibitors) is currently playing a cornerstone role in the treatment of type 2 diabetes, dilemma does exist about some of its basic physiology. So far, we know that GLP-1 is secreted by the direct actions of luminal contents on the L cells in distal jejunum and proximal ileum. However, there is growing evidence now, which suggest that other mechanism via "neural" or "upper gut" signals may be playing a second fiddle and could stimulate GLP-1 secretion even before the luminal contents have reached into the proximities of L cells. Therefore, the contribution of direct and indirect mechanism to GLP-1 secretion remains elusive. Furthermore, no clear consensus exists about the pattern of GLP-1 secretion, although many believe it is monophasic. One of the most exciting issues in incretin science is GLP-1 level and GLP-1 responsiveness. It is not exactly known as to what happens to endogenous GLP-1 with progressive worsening of dysglycemia from normal glucose tolerance to impaired glucose to frank diabetes and furthermore with increasing duration of diabetes. Although, conventional wisdom suggests that there may be a decrease in endogenous GLP-1 level with the worsening of dysglycemia, literature showed discordant results. Furthermore, there is emerging evidence to suggest that GLP-1 response can vary with ethnicity. This mini review is an attempt to put a brief perspective on all these issues.

Key words: Dipeptidyl peptidase-4 inhibitors, glucagon-like peptide-1 agonist, glucagon like peptide-1 level, impaired fasting glucose, impaired glucose tolerance, type 2 diabetes

Introduction

Glucagon-like peptide-1 (GLP-1) is the incretin hormone secreted from intestinal L cell in two major forms: GLP-1 (7-36) and GLP-1 (7-37 amide) often termed "active" GLP-1. The main biological action of GLP-1 depends on their two N-terminal amino acid. This two N-terminal amino acid is primarily removed by an enzyme dipeptidyl peptidase-4 (DPP-4) to truncated "inactive" GLP-1 (9-36, 9-37 amide). Active GLP-1 is responsible for glucose-dependent insulin secretion, suppression of glucagon secretion and delayed gastric emptying. Both glucose-dependent intestinal polypeptide (GIP) and GLP-1 are together termed "incretins" and account for approximately 70% of beta cell insulin secretion. It is now increasingly clear that both peptides are necessary for normal glucose tolerance (NGT). However, ubiquitous distribution of enzyme DPP-4 in human bodies quickly metabolizes active GLP-1 that results in its half-life of only approximately 1 min in the circulation.[1] To exploit this gluco-metabolic benefit of GLP-1, two approaches were considered. The first approach included the development of GLP-1 receptor agonist (GLP-1RA) with closest possible homology to native GLP-1 structure, but resistant to DPP-4 and therefore capable of binding and stimulating GLP-1 receptor for a longer time. Second approach included the development of a molecule that can inhibit DPP-4 and thereby increases endogenous GLP-1 in circulation for a longer time.[2]

Consequently, it is obvious that GLP-1RA will be an effective agent irrespective of endogenous GLP-1 levels whereas DPP-4 inhibitors will depend upon endogenous GLP-1.

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Therefore, it is necessary to ascertain the effectiveness of DPP-4 inhibitors with the changes in endogenous GLP-1. It is generally perceived that DPP-4 inhibitors would be more effective during the early stages of diabetes considering the progressive GLP-1 decline; however, DPP-4 inhibitors have been found be effective even in later stage. Interestingly, it is not yet clear as to what happens to GLP-1 level with increasing duration of diabetes. This mini review is an endeavor to search the existing literature, to clarify primarily as to what happens to endogenous GLP-1 levels with worsening degree of glycaemia.

Glucagon like peptide-1 secretion

Controversies exist about the pattern of GLP-1 secretion. The temporal pattern of GLP-1 following oral administration of nutrients (carbohydrates and lipids in particular) seems to begin with a rather early rise starting approximately 10-15 min after eating, peaks during the 2nd h and then slowly declines to baseline over several hours.[3] Subsequently, few other studies in humans also describe "monophasic" secretory responses.[4-6] However, some studies suggested a classical "biphasic" pattern, with an early peak followed by a nadir and a second rise in GLP-1 concentration.[7-9] This biphasic pattern consist of the first or early phase which takes place within a few minutes after nutrient load and is supposed to lasts for approximately 30-60 min, whereas the second or delayed phase continues for approximately 60-180 min.[7-9] Therefore, further studies are required to conclude anything concrete regarding GLP-1 pattern of secretion.

Mechanism of glucagon like peptide-1 secretion

Currently, conflicting evidence exist about the mechanisms of GLP-1 early phase release. It is assumed that GLP-1 has a prior stimulatory effect on insulin secretion as an intestinal signal, even when nutrients are far away and have not yet reached to duodenum (K cell) or jejunum (L cell). This phase of GLP-1 release is presumably mediated by "upper gut signals" either via GIP or gastrin-releasing peptide or neural signals.[4,5] The second phase or delayed phase of GLP-1 secretion takes place due to direct actions of luminal contents on L cells in distal jejunum and proximal ileum.[4,5] A study by Schirra and Miholic *et al.* suggested an existence of L cell in the proximal duodenum. Possibly, direct stimulation of these proximal L-cells of duodenum may be accounted for early or first phase GLP-1 secretion.[10,11] Therefore, relative contributions of direct and indirect mechanisms prompting the biphasic secretion of GLP-1 in humans still remain to be fully elucidated.

Glucagon like peptide-1 level in dysglycemia

There is no substantial clarity yet, as to what happens to GLP-1 level on varying degree of dysglycemia [Table 1]. Literature also varies a lot on this issue. One of the earliest and the largest cross-sectional study by Toft-Nielsen *et al.* demonstrated that the postprandial GLP-1 levels, the area under the curve (AUC) and the GLP-1 increments, following a 4-h mixed meal tolerance tests were significantly lower in type 2 diabetes, when compared to impaired glucose tolerance (IGT) or NGT groups. Although, fasting GLP-1 were normal in all groups including type 2 diabetes.[7] This study suggested a highly significant (53%) reduction in incremental GLP-1 concentrations and overall (19%) reduction in the AUC in type 2 diabetes compared to healthy controls.[7] Subsequently, several other investigators also supported this finding and suggested a progressive decrease in GLP-1 level and GLP-1 responsiveness with the worsening degree of hyperglycemia starting from NGT to IGT to frank type 2 diabetes.[8,12-16,39] However, some recent studies challenge those findings and point to no changes in GLP-1 levels in either IGT or type 2 diabetes.[9,17-19] Furthermore, two meta-analysis currently available also suggested no changes in GLP-1 level.[19,20] Therefore, any conclusion regarding GLP-1 level on varying degree of worsening the glycaemia, remains elusive.

Table 1: GLP-1 levels in dysglycaemia

Author	Stimuli	IFG	IGT	IFG+IGT	T2DM	References
Toft-Nielsen *et al.* 2001	Mixed meal	ND	Normal to slight decrease	No change	Decreased	[4]
Vilsbøll *et al.* 2001	Mixed meal	ND	ND	ND	Decreased	[5]
Lugari *et al.* 2002	Mixed meal	ND	ND	ND	Decreased	[12]
Rask *et al.* 2004	OGTT	ND	Decreased	ND	ND	[13]
Laakso *et al.* 2008 (EUGENE 2 study)	OGTT	Decreased	Decreased	Decreased	ND	[14]
Muscelli *et al.* 2008	OGTT	ND	No change	ND	Decreased	[15]
Vollmer *et al.* 2008	OGTT/mixed meal	ND	No change	ND	No change	[6]
Lee *et al.* 2010	OGTT/mixed meal	ND	No change	ND	No change	[17]
Kozawa *et al.* 2010	Mixed meal	ND	ND	ND	No change	[18]
Pala *et al.* 2010	OGTT	ND	Decreased	ND	Decreased	[39]
Zhang *et al.* 2012	Fasting/OGTT	No change	No change	Decreased	Decreased	[16]
Hussein *et al.* 2014	OGTT	No change	ND	No change	ND	
Meta-analysis						
Nauck *et al.* 2011	OGTT/mixed meal	ND	ND	ND	No change	[19]
Calanna *et al.* 2013	OGTT/mix meal	ND	ND	ND	No change	[20]

GLP-1: Glucagon like peptide-1, IFG: Impaired fasting glucose, IGT: Impaired glucose tolerance, OGTT: Oral glucose tolerance test, T2DM: Type 2 diabetes, ND: Not determined

Although the mechanism for these discrepancies is far from clear, following factors are suggested to be responsible for giving diverging results:

Diagnostic criteria of pre-diabetes or diabetes across the studies

Criteria to define impaired fasting glucose (IFG), IGT and diabetes, vary in different studies. Earlier studies included IFG plus IGT under IGT groups, whereas newer study followed current ADA definition laid down in 2006 and had separate group for IFG, IGT, and both.

Course of disease

Different stages of glucose-metabolic disorders can complicate the impact of GLP-1 secretion.

Sample size

Previous study had very small patient number ($n < 50$) and not all of them took all three subgroups of pre-diabetes (IFG, IGT, IFG plus IGT) and type 2 diabetes in to the consideration.

Treatments influence

In most of the previous studies, the subjects could have taken the hypoglycemic therapies, which can influence GLP-1 release. Recent studies have shown that metformin and alpha-glucosidase inhibitor increases GLP-1 level.

Sampling time

Possible variations in duration of GLP-1 second phase release and timing of GLP-1 measurement following glucose load or mixed meal could be responsible.

Detection methods

On secretion, GLP-1 and GIP undergo rapid processing catalyzed by DPP-4 and lose their ability to stimulate insulin secretion. It is therefore of great importance to measure not only intact but also a total (i.e. intact plus DPP-4-processed) forms of incretin hormones to study their secretion and processing *in vivo*. Although, assay for intact GLP-1 and GIP require specific antibodies that have not been widely available. These differences in the methodology and sensitivity of techniques used over time in measuring total GLP-1 or intact GLP-1 concentrations can sometimes produce divergent results.

Racial differences

Variance may be attributed to a significant difference in fasting and glucose-stimulated GLP-1 levels among different races.[17,21]

Other factors determining glucagon like peptide-1 response

A univariate and multivariate regression analysis suggested that age, body weight, non-esterified fatty acid (NEFA) and glucagon level can influence the GLP-1 secretion. While increasing age and higher NEFA can increase GLP-1, higher BMI and high glucagon suppresses GLP-1.[19]

Glucagon like peptide-1 levels in Asians

From Asians perspective, data are even more conflicting as diverging results in total GLP-1, intact GLP-1 and GIP have been observed:

1. "Total" GLP-1 level in Asian studies varied from low to normal.[16-18,22] A study by Yabe *et al.* showed negligible GLP-1 response after meal ingestion despite robust GIP response in both healthy and diabetic Japanese subjects.[22] The reason for this reduced GLP-1 response is not exactly clear but could be explained by meal size and meal composition (nutrient-induced), sometimes critically responsible for GLP-1 response.[23-26] South-Asians may be different from Japanese in their GLP-1 response. Study by Sleddering *et al.* suggested higher GLP-1 and higher insulin level after a glucose load in young healthy South-Asians living in UK, compared to Caucasian counterparts.[27] However, it remains to be elucidated whether higher GLP-1 response in South-Asians was due to a compensatory increased secretion or due to GLP-1 resistant state.[27] This study also suggested that the peak GLP-1 levels preceded the peak insulin response and paralleled with insulinogenic index, thereby suggesting a direct relation between the increased GLP-1 response and the insulin secretion by the β-cell.[27] These finding stimulates further research to ascertain the intra-ethnic difference among East-Asians versus South-Asians
2. "Intact" GLP-1 level was found to be considerably low in both Japanese type 2 diabetes and healthy controls, compared to Caucasians.[22,28,29] The very low levels of intact GLP-1 can occur due to either impaired secretion from the gut or accelerated metabolism by DPP-4, or both. Logically, any finding of low "intact" GLP-1 despite a significant peak of "total" GLP-1 following a glucose load would hint towards a possible enhanced GLP-1 metabolism mediated by DPP-4. Interestingly, the study by Yabe *et al.* also showed a higher "intact" GIP: "total" GIP ratio compared to GLP-1, thereby implying that enhanced DPP-4 activity was selective to GLP-1. Although, it appears that GLP-1 is more liable to DPP-4 processing compared to GIP, further studies are really required to understand the basis of the selective reduction of intact GLP-1 in Japanese.[30] Moreover, these findings must be interpreted with caution in the light of different assay and methodology used to measure "total" GLP-1 or "intact" GLP-1 in these studies[31]
3. "Total" GIP level following a glucose load or mixed meal were higher in Japanese but levels of "intact"

GIP were similar compared to Caucasians.[8,22,28,29] This might suggest a possible increase in processing of GIP by DPP-4 in Japanese. It should be noted that although the GIP response are enhanced in both Caucasians and Japanese type 2 diabetes (compared to healthy controls), the GLP-1 response in Japanese Type 2 diabetes is significantly reduced. The reason for perceived enhanced GIP response in diabetic patients is not fully clear currently.

In summary, as there is no significant difference in either GLP-1 or GIP levels between T2DM and healthy control, incretin deficiency does not seem to be accountable for the reduced insulin response in Japanese. However, findings of low "intact" GLP-1 levels and low GLP-1 response after meal might have special implications for reduced insulin secretory capacity and exaggerated response to incretin-based therapy in the Asians in particular with East-Asians diabetic cohorts.[32-34]

Some data does exist in the literature that suggests differential incretin response in different ethnic groups. A randomized, double-blind, placebo-controlled, 18-week trial (n = 530) conducted by Mohan *et al.*, evaluating efficacy and safety of Sitagliptin among Asian population (Korea, China and India) revealed significant glucose lowering (placebo-subtracted, −1.0%; $P < 0.001$) with Sitagliptin. Although, similar HbA1c reduction were noted in all three subpopulation relative to baseline, Indians and Koreans exhibited better HbA1c lowering (−1.4% each) compared with Chinese (−0.7%) against placebo.[35] However, this seems to have occurred primarily due to increase HbA1c in placebo arm of Indians (+0.7%) and Koreans (+0.6%) patients and decrease HbA1c in placebo arm of Chinese (−0.2%) patients. Few other individual studies and a meta-analysis primarily conducted in Asian subjects also hinted at better HbA1c reduction with incretin-based therapies, when indirectly compared with the results from phase 3 global trials primarily done in Caucasian, African-American and Hispanic populations.[36]

A 24-week, real-life observational study (n = 14) conducted by Kesavadev *et al.* evaluating efficacy and safety of liraglutide in Indian patients showed remarkable lowering of HbA1c (−2.26%, $P < 0.001$), which looked quite higher from what had been observed in six phase 3 global randomized liraglutide effect and action in diabetes study (maximum − 1.5% in LEAD-4 study).[37] However, these results should be interpreted in the light of the biases associated with any smaller, observational studies. In contrast, a 16-week double blind randomized study (n = 929) by Yang *et al.* suggested a similar glucose-lowering with liraglutide among all Asians (Chinese, Koreans and Indians).[38]

Finally, a meta-analysis done from 62 randomized controlled trial by Park *et al.* suggested a significant better glucose lowering effect of DPP-4 inhibitor in Asians compared to non-Asians (Asians: −1.67%; 95%CI, −1.89 to − 1.44 vs. nonAsians: −0.65%; 95% CI, −0.71 to − 0.60; $P < 0.05$).[32] Another recent meta-analysis done by Kim *et al.* also suggested significantly exaggerated incretin response in Asians. Asian-dominant studies (studies with ≥ 50% Asians participants) clearly showed a greater HbA1c lowering than non-Asian dominant studies (between-group difference for DPP-4 inhibitors: −0.18%, $P = 0.006$; between-group difference for GLP-1 agonist: −0.32%, $P = 0.04$).[33,34]

It should be noted however that, Asian studies included in these meta-analysis mainly consisted of East-Asians. Whether, these results can be extrapolated to South-Asians is a subject of speculation in the light of significantly different etio-patho-physiological features between South-Asians versus East-Asians.

Conclusion

Although conventional wisdom suggests that the GLP-1 level progressively decreases with increasing duration of dysglycemia, meta-analysis of various studies suggests no significant changes in GLP-1 level. Nevertheless, the final conclusion can only be derived from prospective or longitudinal studies, which will measure GLP-1 level along the entire course of diabetes starting from normoglycemia to IGT to frank diabetes and its further course over the years.

Possible ethnic differences in GLP-1 level and GLP-1 responsiveness after meal challenge might also exist among East-Asians, in particular in Japanese and Koreans. However, this cannot be generalized to South-Asians. South-Asians found to have higher GLP-1 and higher insulin levels, and they could be completely divergent from East-Asians counterparts. Consequently, further data would be required to understand the difference in GLP-1 response among East-Asians versus South-Asians. Nevertheless, it is likely that these differences in GLP-1 response may impact the effectiveness of incretin-based therapies among certain ethnic groups. As, beta cell secretory dysfunctions and poor GLP-1 reserve are two main primary defects observed in East-Asians, they may perhaps respond better with incretin-based therapies.

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