ARTIKEL ASLI

Print ISSN: 2580-2925
Online ISSN: 2580-2933

Jurnal Penyakit Dalam Udayana
Udayana Journal of Internal Medicine
Volume 4, No 1: 2020 ; 14-18

Correlation between glomerular filtration rate, fasting glucagon like peptide 1, and response after 75 gram oral glucose loading in type 2 diabetes mellitus

Ni Made Dwi Adnyani[1], Ida Bagus Aditya Nugraha[1], I Gde Raka Widiana[2], Made Ratna Saraswati[3*]

[1]Resident of Internal Medicine, Faculty of Medicine Udayana University, Sanglah Hospital Denpasar
[2]Nephrology Division, Department of Internal Medicine, Faculty of Medicine Udayana University, Sanglah Hospital, Denpasar
[3]Endocrinology and Metabolism Division, Department of Internal Medicine, Faculty of Medicine Udayana University, Sanglah Hospital, Denpasar

[*]Korespondensi:
Made Ratna Saraswati; Endocrinology and Metabolism Division, Department of Internal Medicine, Faculty of Medicine Udayana University, Sanglah Hospital, Denpasar;
ratnasaraswati@unud.ac.id

Tanggal diterima : 12 Maret 2020
Tanggal Disetujui : 17 April 2020
Tanggal Diterbitkan : 20 Juni 2020

DOI : 10.36216/jpd.v4i1.128

***Background*:** Glucagon like peptide 1 (GLP1) is incretin hormone which possess biological effect on the kidneys. In conditions where the estimated glomerular filtration rate (eGFR) decreases or in the condition of chronic kidney disease (CKD), there is an increase in the inactive GLP1 or metabolites levels.
***Objective*:** To prove the relationship between eGFR with fasting and response of GLP1 after oral glucose loading in type 2 diabetes mellitus (T2DM) patients.
***Methods*:** An analytic cross sectional study on fasting and response of GLP1 after glucose loading in 60 subject with T2DM, age 35-65 years, was conducted. Each subject was obtained for fasting GLP1 and 30 minutes after 75 gram oral glucose loading. Subject were grouped based on eLFG into <60 ml/mnt/1.73m^2 and ≥60 ml/mnt/1.73 m^2.
***Result*:** In the group of T2DM with eGFR <60 ml/mnt/1.73m^2, median fasting GLP1 was 1.43 (0.38-8.50) ng/mL, in the group of eGFR ≥60 ml/mnt/1.73 m^2 was 1.57 (0.46-3.69) ng/mL (p=0.124). In the group of eGFR <60 ml/mnt/1.73 m^2, median GLP1 after 30 minutes was increasing to 1.78 (1.12-8.35) ng/mL, as well as in group of eGFR ≥60 ml/mnt/1.73 m^2 1.79 (0.65-4.22) ng/mL (p=0.250). There were no correlation between fasting and 30 minutes after oral glucose load GLP1 with eGFR (p=0.510).
***Conclusion*:** There were no correlation between eGFR and GLP1, both fasting and 30 minutes after 75 gram oral glucose loading in T2DM. Level of GLP1 was increasing after oral glucose load in T2DM patients but not affected by stage of chronic kidney disease based on eGFR.

***Keywords*:** T2DM, GLP1, eGFR, fasting glucose

INTRODUCTION

Epidemiological research shows a rising trend of type 2 diabetes (T2DM) incidence in the world. The World Health Organization (WHO) predicts an increasing in the number of people with T2DM in Indonesia from 8.4 million in 2000 to around 21.3 million in 2030, a two to threefold increase in the number of people with T2DM in 2035.[1] Type 2 diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia due to absolute deficiency of insulin secretion or reduced biological effectiveness of insulin, or both. In T2DM there are kidney disorders such as urinary tract stones, urinary tract infections, acute and chronic pyelonephritis, and glomerulonephritis called *non diabetic renal disease* (NDRD) or non diabetic kidney disease in diabetic patients. Diabetic nephropathy is the most common kidney disorder in T2DM.[2]

Glucagon like peptide 1 (GLP1) is one of the incretin hormone produced by gastrointestinal tract and its release depends on nutrient intake.[3] The total of GLP1 concentration between 5 to 15 pmol/L in basal conditions will increase to 20 to 60 pmol/L after giving oral glucose.[4] GLP1 plasma levels increase within 10-15 minutes after food intake and reach its peak with levels of 15-50 pmol/L in 40 minutes.[5]

Research shows that GLP1 has a biological effect on the kidneys. The GLP1 hormone increases natriuresis by inhibiting *sodium-hydrogen ion exchanger isoform* 3 (NHE3) in the proximal tubule.[6] In conditions where the estimated glomerular filtration rate (eGFR) decreases or in the condition of chronic kidney disease (CKD), there is an increase in the levels of inactive GLP1 or metabolites, but the ability of DPP IV to degrade the active form of GLP1 is maintained so that the levels of active or intact GLP1 do not get a difference with the population of normal people.[7]

Some studies that support the biological effects of GLP1 on the kidneys are mostly done with experimental animals, and research in humas is still limited. This study aimed to determine the relationship between GLP1 (fasting and response after 75 gram oral glucose loading) and eGFR in subject with T2DM.

Jurnal Penyakit Dalam Udayana
Udayana Journal of Internal Medicine
Volume 4, No 1: 2020 ; 14-18

Print ISSN: 2580-2925
Online ISSN: 2580-2933

MATERIAL AND METHODS

Research design

Research with an analytic cross-sectional observational design involving 60 subjects with T2DM patients was conducted in April - June 2018 at the Diabetic Centre Outpatient Clinic Department of Internal Medicine, Sanglah Hospital, Denpasar. Subjects were collected by consecutive sampling until 60 subjects had met the inclusion criteria. This study was approved by the Ethical Committee of the Faculty of Medicine, Udayana University and Sanglah Hospital (No. 2472 / UN.14.2 / KEP / 2017), and it was authorized by the Director of Sanglah Hospital (No. LB.02.01 / XIV.2.2.1 / 39962 /2017). All subjects were given information regarding this study and signed the informed consent. This study was conducted in accordance with the Declaration of Helsinki. Formulation to calculate eGFR use CKD-EPI as follow : eGFR (ml/min) = 141 × min (S_{cr} /κ, 1)$^{\alpha}$ × max(S_{cr} /κ, 1)$^{-1,209}$ × 0,993^{Age} × 1,018. Subject were divided into 2 groups based on eGFR, <60ml/mnt/1.73m^2 and ≥60 ml/mnt/1.73 m^2.

Statistical methods

Descriptive analysis has done as a basis for statistical analysis (hypothesis testing) to determine the characteristics of the data held. Descriptive analysis was carried out with the SPSS program. The selection of data presentation and hypothesis testing depends on whether the data distribution was normal or not. The normality test was carried out by the Komolgorov-Smirnov test.

Bivariate analysis has done to determine differences in fasting GLP1 and 75 gram oral glucose loading GLP1 levels. Data of both GLP1 levels was normally distributed two of variables are numerical so the analysis of mean difference using an unpaired T test.

Multivariate analysis to determine the difference between fasting GLP1 and post-loading of 75 gram glucose GLP1 between the eGFR <60 ml/min/1.73 m^2 group compared to the eGFR ≥ 60 ml/min/1.73 m^2 using the *general linear repeated measurement model* test.

RESULTS

In the 60 study subjects, 2 measurements were carried out, fasting GLP1 and 30th minute after 75 gram oral glucose loading GLP1. The characteristic of the study subjects described in Table 1. There was an increase in 30th minute post-loading of glucose GLP1 levels in thein both groups (p = 0.000) (Figure 1). The mean fasting GLP1 level was 1.87 ± 1.48 ng/mL, and the mean of 30th minute post-loading of 75 grams glucose GLP1 was 2.30 ± 1.51 ng/mL.

The differences in GLP1 levels, either fasting or 30 minutes after 75 gram oral glucose loading, and based on eGFR was measured (Figure 2). No differences of fasting GLP1 (Table 1) and 30 minutes after 75 gram oral glucose loading GLP1 (Table 2) was found between eGFR< 60 ml/min/1,73 m^2 group and eGFR ≥ 60 ml/min/1.73 m^2 group.

There was no correlation between the increase in 30 minutes after 75 gram oral glucose loading GLP1 compared to fasting GLP1 and CKD categories (eGFR <60 ml/min/ 1.73 m^2 and eGFR ≥ 60 ml/min/ 1.73 m^2 (p = 0.510).

Table 1. Characteristics of research subjects

Variable (unit)	n	Median	Range	Mean ± SD	Test of abnormality (p)
Gender	60 (100%)				
Male	40 (66.67%)				
Female	20 (33.33%)				
Age (years)		58	35 – 65	56.51 ± 6.97	0.002
Fasting GLP1 (ng/mL)		1.47	0.38 – 8.50	1.87 ± 1.48	0.000
30 minutes GLP1 (ng/mL)		1.79	0.65-8.35	2.30 ± 1.51	0.000
DM Span (year)		5	1- 25	6.55 ± 4.80	0.000
eGFR ml/min/1.73m²		44	7-120	49.10 ± 28.76	0.200
CKD stage 1	7 (11.7%)				0.427
CKD stage 2	12 (20%)				0.626
CKD stage 3A	11 (18.3%)				
CKD stage 3B	13 (21.7%)				
CKD stage 4	9 (15%)				
CKD stage 5	8 (13.3%)				

Abbreviations: *GLP1, glucagon like peptide 1; n, number of samples; DM, Diabetes mellitus; SD, standard deviation. CKD, chronic kidney disease, e-GFR, estimated glomerular filtration rate.*

ARTIKEL ASLI
Print ISSN: 2580-2925
Online ISSN: 2580-2933
Jurnal Penyakit Dalam Udayana
Udayana Journal of Internal Medicine
Volume 4, No 1: 2020 ; 14-18

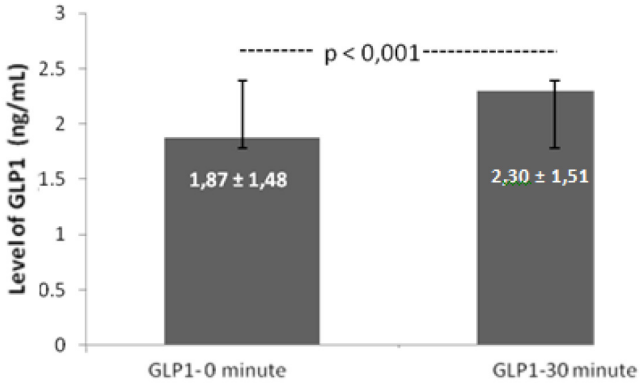

Figure 1. Fasting GLP1 levels (GLP1-0) and 30th minute post loading of glucose (GLP1-30)

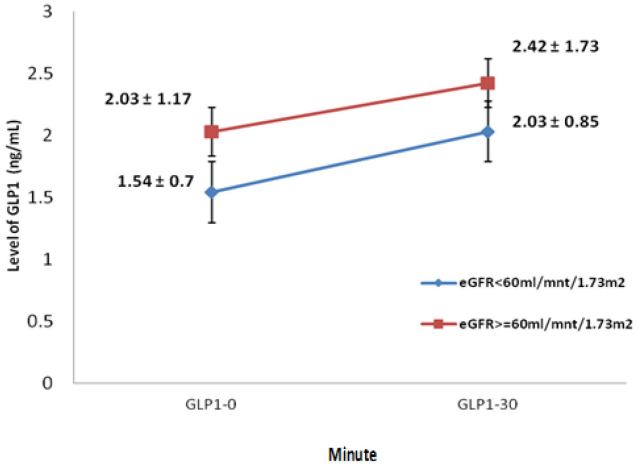

Figure 2. Fasting GLP1 levels (GLP1-0) and 30th minute post loading of glucose (GLP1-30) in eGFR groups

DISCUSSION

This study found several results. First, no differences of fasting GLP1 (Table 1) and 30 minutes after 75 gram oral glucose loading GLP1 (Table 2) was found between eGFR< 60 ml/min/1,73 m^2 group and eGFR ≥ 60 ml/min/1.73 m^2 group. Second, no correlation between the increase in 30 minutes after 75 gram oral glucose loading GLP1 compared to fasting GLP1 and CKD categories.

The total GLP1 concentration between 5 to 15 pmol/L in basal conditions increase to 20 to 60 pmol/L after giving oral glucose.[4] Plasma GLP1 levels increase within 10-15 minutes after food intake and reach its peak with levels of 15-50 pmol/L in 40 minutes. In this first phase of GLP1 secretion, it is assumed that the nutrient detector found in the upper gastrointestinal tract plays a role in controlling GLP1 secretion, which is called the *proximal-distal loop* phenomenon. The second phase of GLP1 secretion lasts 1-3 hours because of direct interaction between food ingredients and L cells in the small intestine.[8] In the research conducted stated in units of ng/mL and measured several types of GLP1 which are detected and it is not exactly known what proportion of GLP1 is measured (GLP1 7-36 / GLP1 9-36, GLP1 1-36) so that it is difficult for us to convert to pmol/L units. Unlike the case with Nauck's research by only measuring GLP1 7-36, so pmol/L was used.

GLP1 secretion during food absorption slightly decreases in patients with T2DM. The sensitivity of β cells to GLP1 also decreases in individuals with diabetes compared to without diabetes. GLP1 improves hyperglycemia in diabetic patients, where continuous giving of GLP1 intravenously in hyperglycemia patients with slightly controlled and uncontrolled T2DM can reduce fasting hyperglycemia close to normal levels within 3-4 hours. Visboll research in

Table 2. Differences in fasting GLP1 levels between eGFR groups <60 ml/min/1.73m² and ≥60 ml/min/1.73m²

Variable	n	Mean ± standard deviation	Mean Difference (CI 95%)	p
Fasting GLP1 eGFR< 60 ml/min/1,73 m^2	41	2.03 ± 1.17	-0.48(-0.13-1.1)	0.124
Fasting GLP1 eGFR ≥ 60 ml/min/1.73 m^2	19	1.54 ± 0.70		

Abbreviations: GLP1, glucagon like peptide 1; n, number of samples; eGFR, estimated glomerular filtration rate; CI, confidence interval.

Table 3. Differences in 30th minute GLP1 levels between eGFR groups <60 ml/min/1.73m² and ≥60 ml/min/1.73m²

Variable	n	Mean ± Standard Deviation	Mean Difference (CI 95%)	p
30th minute GLP1 eGFR< 60 ml/min/1.73 m^2	41	2.42 ± 1,73	-0.38(-0.28-1.05)	0.250
30th minute GLP1 eGFR ≥ 60 ml/mnt/1.73 m^2	19	2.03 ± 0,85		

Abbreviations: GLP1, glucagon like peptide 1; n, number of samples; eGFR, estimated glomerular filtration rate; CI, confidence interval.

Jurnal Penyakit Dalam Udayana
Udayana Journal of Internal Medicine
Volume 4, No 1: 2020 ; 14-18

Print ISSN: 2580-2925
Online ISSN: 2580-2933

2001 showed that the mean level of fasting GLP1 in T2DM population was 10.7 mmol/L (8.0 - 14.8 mmol/L) compared with healthy population of 5.7 mmol/L (5.0 – 6.2 mmol/L).[9] Nugraha et al research in 2018 showed that the patterns of GLP-1 levels post glucose loading were similar in obese and non-obese subjects, and there was a tendency of lower GLP-1 levels in fasting state and post-glucose loading in obese subjects compared to non-obese subjects.[10] In this study, in addition to assessing the response of giving 75 gram oral glucose loading to an increase in 30th minute GLP1 levels in a population of diabetic subjects, it also investigated the relationship between glomerular filtration rate and GLP1 levels both fasting and post-loading of glucose. Basically, the secreted GLP1 hormone is immediately eliminated from circulation in less than five minutes, therefore the half-life of GLP1 in circulation is only about one to two minutes. The elimination process occurs through three channels. The first pathway through the enzymatic process by the enzyme dipeptidyl peptidase (DPP) IV which is found in intestinal lumen endothelial cells. The second pathway is excretion through the process of glomerular filtration and catabolism in the renal tubules of the kidney. The third pathway is its binding directly to the GLP1 receptor.[11] Generally these receptors are not found in the distal tubule, but several studies have found GLP1 in the proximal tubule and in the glomerulus in mRNA.[12] In humans using autoradiography, GLP1 receptor is found in large and medium-sized renal arteries, but is not found in tubules or glomerulus. These different findings may be partly explained by the presence of different species.[13]

In this study, there was a tendency of increasing fasting GLP1 levels and the 30th minute post-loading of glucose in the group of eGFR <60 ml/minute/ 1.73 m^2. This may due to the decrease in GLP1 elimination so that the levels of inactivated GLP1 increase. In T2DM, decreased of GLP1 secretion is obtained. Inflammatory cytokines known to be involved in kidney injury in the setting of diabetes, and the longer duration of diabetes, GLP1 will be lower, however lower eGFR will lower the elimination, so that GLP1 levels will be detected not different from the normal population.[11,14]

There was no correlation between the increase in 30 minutes after 75 gram oral glucose loading GLP1 compared to fasting GLP1 and CKD categories (eGFR <60 ml/min/ 1.73 m^2 and eGFR ≥ 60 ml/min/ 1.73 m^2 (p = 0.510). This corresponds to theory in the publication by Ahren that in the process of degradation and elimination of GLP1, the active form or intact GLP1 (7-36) amide will experience cutting N-terminal dipeptide chains by DPP IV enzymes into inactive forms or GLP1 (9-36) amide metabolites. The final elimination process occurs through glomerular filtration and catabolism in the renal tubules of the kidney.[11] In conditions where the renal filtration rate decreases there is an increase in inactivated GLP1 levels or metabolites, but the ability of DPP IV to degrade the active form of GLP1 is maintained so that active or intact GLP1 levels are not found to differ from populations without impaired renal function.[7] In this study, the measured GLP1 levels were total so that they could not assess active or inactive GLP1 levels.

CONCLUSION

There was an increase in 30th minute post-loading of glucose in T2DM patients. There is no relationship between glomerular filtration rate and fasting GLP1 levels and 30th minute after 75 gram oral glucose loading in T2DM patients. Further research needs to be done regarding the levels of active GLP1 in the T2DM population with impaired renal function in order to further emphasize the relationship of the degree of impaired kidney function to fasting GLP1 levels and 30th minute after 75 gram oral glucose loading. Further research is needed to prove whether T2DM span affects fasting GLP1 levels and GLP1 response after 75 gram oral glucose loading.

AUTHORS' CONTRIBUTIONS

NMDA design the study and performed data analysis, interpreted the data, and drafted the manuscript. MRS, GRW, IBAN participated in the design of the study and helped revise the final manuscript. All authors read and approved the final manuscript.

ACKNOWLEDGMENTS

The authors thank Prodia Laboratory for laboratory technical assistance and all of the participant subjects who support this study.

DISCLOSURE

The authors reports no conflicts of interest in this work.

REFERENCES

1. Perkumpulan Endokrinologi Indonesia (Perkeni). Konsensus Pengendalian dan Pencegahan Diabetes Melitus Tipe 2 di Indonesia. PB Perkeni. 2015; Jakarta; p.1-11.
2. Ghost S, Collier A. Chronic Complication. *Churchill's Pocketbook of Diabetes*. 2nd. Ed. London: Elsevier. 2012, p:165-226.
3. Gautier JF, Choukem SP, Girard. Physiology of incretins (GIP and GLP-1) and abnormalitas in type 2 diabetes. *Diabetes and Metabolism*. 2008;34:s65-s72.
4. Nauck MA, Vardarli I, Daecon CF, Holst JJ. Secretion of glucagon-like peptide-1 in type 2 diabetes: what is up, what is down?. *Diabetologia*. 2011;54:10-18.
5. Holst JJ. The Physiology of glucagon-like peptide-1. *Physiol Rev*. 2007;87:1409-1439.

Print ISSN: 2580-2925
Online ISSN: 2580-2933

Jurnal Penyakit Dalam Udayana
Udayana Journal of Internal Medicine
Volume 4, No 1: 2020 ; 14-18

6. Skov, J. Effects of GLP-1 In The Kidney. *Rev Endocr Metab Disord.* 2014;1-13. DOI: 10.1007/s11154-014-9287-7.
7. Idorn T, Knop FK, Jorgensen MB, dkk. Elimination and degradation of glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide in patients with end-stage renal disease. *J Clin Endocrinol Metab*, 2014;10:2013-2019.
8. DeLeon DD, Crutchlow MF, Ham JY, dkk. Role of glucagon-like peptide-1 in the pathogenesis and treatment of diabetes mellitus. *Int. J. Biochem. Cell Biology.* 2006;38(5-6):845–859.
9. Vilsboll T, Krarup T, Deacon CF, dkk. Reduced postprandial concentrations of intact biologically active glucagon-like peptide 1 in type 2 diabetic patients. *Diabetes.* 2001;50:609–613.
10. Nugraha IBA, Saraswati MR, Suastika K. The Pattern of Fasting and Post 75 G Glucose Loading of Glucagon-Like Peptide 1 Levels in Obese and Non-Obese Subjects. *Open Access Maced J Med Sci.* 2019;7(3):358-362.
11. Ahren B. Glucagon-like peptide-1 (GLP-1): a gut hormone of potential interest in the treatment of diabetes. *Bio Essay.* 1998;20:642-651.
12. Schlatter P, Beglinger C, Drewe J, dkk. Glucagon-like peptide1 receptor expression in primary porcine proximal tubular cells. *Regul Pept.* 2007;141(1–3):120–128.
13. Pyke C, Knudsen LB. The Glucagon-Like Peptide-1 Receptor-or Not?. *Endocrinology.* 2013;154(1):4–8.
14. Sindhughosa,DA, Pranamartha AAGMK. The involvement of proinflammatory cytokines in diabetic nephropathy: Focus on interleukin 1 (IL-1), interleukin 6 (IL-6), and tumor necrosis factor-alpha (TNF-α) signaling mechanism. Bali Medical Journal. 2017;6(1):44-51.