Blood Glucose and Glucagon-Like Peptide 1 Level Comparison in Obese Versus Non-Obese Patients

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Abstract

Obesity, a major health concern worldwide, has a pathophysiology related to energy imbalance in the body. Glucagon-like peptide 1 (GLP-1), secreted by L cells of the intestine, acts as a signal for energy balance. GLP-1 is a satiation signal that can promote satiety and reduce food intake. Its secretion is thought to be impaired in obese individuals, causing reduced satiety and hyperphagia.

This study was conducted as a clinical trial to determine the effect of breakfast with a balanced macronutrient composition (68.2% carbohydrates, 22.6% lipids, and 12.4% protein) on GLP-1 levels in 22 obese versus 21 non-obese subjects.

Blood glucose levels were also evaluated Subjects were provided breakfast, followed by measurement of blood glucose and GLP-1 levels at 0, 15, 60, 120, and 180 minutes after intervention. We found that there are no significant differences between blood glucose levels in obese versus non-obese subjects before or after having breakfast with a balanced macronutrient composition ($p > 0.05$).

There was a significant difference between GLP-1 levels in obese and non-obese subjects at 15 and 60 minutes following intervention ($p = 0.042$ and $p = 0.037$, respectively). This finding suggests that there is impairment in postprandial GLP-1 secretion in obese subjects.

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Introduction

Obesity and its comorbidities are a major health concern globally. In 2014, there were 1.9 billion (39%) overweight and 600 million (13%) obese adults.[1] Meanwhile, in Indonesia, in 2013, the prevalence of overweight or obese adults was 13.5% and 15.4% of the general population, respectively.[2] The World Health Organization has estimated that 44% of global diabetes, 23% of ischaemic disease, and 7%–41% of specific cancers' global burdens are related to obesity.[3] Obesity also has psychological impact related to social stigma and discrimination, which impairs the quality of life and increases depression rates.[4,5]

Obesity can occur when there is an imbalance between energy intake and energy expenditure. Higher energy intake compared to expenditure results in increased energy storage in the form of triglycerides in adipose tissues. Amount of food intake and energy balance is regulated by a complex biological system, which also influences the senses of hunger and satiety. This system involves interactions between peripheral endocrine, nutritional, as well as neural signals, which act on the arcuate nucleus of the hypothalamus.[6-8] Peripheral endocrines in the system can be involved as long- or short-acting signals. Long-acting signals monitor energy stores to help the brain adjust food intake and energy expenditure to maintain body weight. Examples of long-acting signal molecules include leptin and insulin. Meanwhile, short-acting signals are modulated by situational and meal-related factors, such as glucagon-like peptide 1 (GLP-1).[9,10]

GLP-1 is a 31 amino acid polypeptide synthesized by L cells of the terminal ileum. It is a potent incretin, functioning to increase insulin levels following meals.[11] GLP-1 is a cleavage

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product of the preproglucagon gene, and is also synthesized by the nucleus of the solitary tract in the brainstem. GLP-1 is a satiation signal produced by gastric mechanoreceptors when the stomach is distended by food, and works in delaying gastric emptying and motility. Interventricular injections of GLP-1 have been found to inhibit food intake, independent of the presence of food in the stomach. GLP-1 analogues are currently used for treatment of type 2 diabetes, and could reduce food intake, appetite, and hunger, while promoting fullness and satiety, resulting in weight loss.[12]

GLP-1 is thought to be impaired in obese people. Most obesity today can be referred to as polygenic obesity, in which some inherited genes make certain individuals more susceptible to obesity.[13,14] One such gene is PCSK1 encoding the enzyme PC1/3, which is involved in the proteolytic processing of proglucagon yielding GLP-1 as one of the peptides. *In vitro* studies suggest that the enzyme variant in obese people may not be as active as its common form, resulting in partial deficiency of the enzyme. Decreased GLP-1 synthesis promotes increased gastric motility and gastric emptying, causing reduced satiety and hyperphagia in obese people.[15-19] We conducted this study to evaluate the levels of GLP-1 and blood glucose in obese and non-obese patients following consumption of a breakfast containing balanced macronutrient composition.

Methods

Study design. This clinical trial is part of larger study evaluating the effects of consuming breakfast with different protein compositions on several gut endocrines as well as the level of satiety in obese patients. There are two intervention groups, obese and non-obese patients. Both groups were given breakfast with a balanced macronutrient composition. Two preliminary studies were done prior to the primary study for taste testing of the milk formula and to determine sample size. This study has been approved by Health Research Ethical Committee of the Faculty of Medicine Universitas Indonesia – Cipto Mangunkusumo Hospital, with the letter approval number 307/PT02.FK/ETIK/2010.

Participants. Participants of this study included women aged 20–40 years old with a body mass index of 18.5–23 (non-obese) or 25–30 (obese), stable body weight within the last 6 months (body weight change < 4 kg), with normal blood glucose levels. The exclusion criteria encompassed patients who never ate breakfast, those in a weight loss program, patients consuming lipid absorption inhibitors or appetite-suppressing drugs, and individuals having undergone gastrointestinal tract resection.

Interventions. There were 22 obese and 21 non-obese participants. Before intervention, participants were interviewed to obtain demographic data and food intake analysis, and were given counseling in healthy dietary habits. The day of intervention, participants were required to fast for 10 hours, with an allowance of mineral water up to 2 hours before intervention. The breakfast administered was a milk-based formula which was required to be consumed within 15 minutes, and subjects could only consume 600 mL of mineral water within subsequent 4 hours after intervention. Participants' blood was taken prior to, and 15, 60, 120, and 180 minutes after intervention, then tested for blood glucose and GLP-1 levels.

The breakfast administered was adjusted to the participants' energy requirements, which was calculated by adding basal metabolic rate (BMR) with additional energy from physical activity around 40%. BMR was calculated by the Cunningham equation. Breakfast was given as chocolate milk-based formula with a volume 200 mL. Composition of the formula is shown in Table 1.

Statistical analysis. Statistical analysis was conducted using SPSS software version 20. Data distribution was calculated by the Shapiro-Wilk test. Data analysis was conducted using independent t-test and Mann–Whitney U test, depending on the data distribution of each group, where blood glucose and GLP-1 levels from obese and non-obese participants were compared at each point in time (prior to, and 15, 60, 120, and 180 minutes after intervention). P values < 0.05 are considered to be significant.

Breakfast	Balanced composition breakfast	%
Calorie	200.85	
Protein (g)	6.25	12.4
Carbohydrates (g)	34.27	68.2
Lipid (g)	5.06	22.6
Fiber (g)	2.25	
Form	Liquid	
Volume	200 mL	
Density	1 kcal/1 mL	
Taste	Chocolate	

Table 1. Composition of macronutrients in breakfast formula

Results

Initially 51 subjects underwent screening, with 22 obese and 21 non-obese subjects completing the study. Sociodemographic characteristics of the subjects are shown below in Table 2.

Blood glucose and GLP-1 levels at 0, 15, 60, 120, and 180 minutes following intervention are shown in Figure 1 and Figure 2. Table 3 compares GLP-1 levels in obese versus non-obese patients following intervention with a breakfast composed of balanced macronutrients. Table 4 shows the comparison between blood glucose levels in obese and non-obese patients after intervention.

Mean GLP-1 levels in obese subjects was lower than that of non-obese subjects. GLP-1 levels increased with fluctuations after eating breakfast in both obese and non-obese subjects. Before consumption of the meal (at minute 0), there is no significant difference between GLP-1 levels in obese and non-obese subjects. However, there was a significant difference between GLP-1 levels of obese and non-obese subjects at 15 and 60 minutes after the meal.

Previous clinical studies have evaluated GLP-1 secretion in obese and non-obese subjects. In several studies, GLP-1 secretion following an oral glucose tolerance test consistently demonstrated a reduction in obese subjects.[20] Meanwhile, postprandial GLP-1 responses showed conflicting results. Faerch et al. and other groups showed similar results as our study, in which there is lower level of postprandial GLP-1 - secretion in obese

Characteristics	Obese (n = 22)	Non-obese (n = 21)	p-value
Age	31.55 ± 5.34	28.90 ± 5.53	0.119[TT]
Education (n, %)			1.000[MW]
Low	0 (0)	0 (0)	
High	22 (100)	21 (100)	
Body mass index	28.68 ± 2.34	21.21 ± 1.12	0.000[TT]
Income (n, %)			0.464[F]
Below UMP	0 (0)	1(4.8)	
Equal or more than UMP	22 (100)	21(95.2)	
Teenage nutritional status (n, %)			
Thin			0.002[MW]
Normal	2 (9.1)	9 (42.9)	
Overweight	15 (68.2)	12 (57.1)	
	5 (22.7)	0 (0)	

Notes [C]: Chi-Square test, [M]: Mann–Whitney test, UMP: Upah Minimum Propinsi (provincial minimum wage)

Table 2. Sociodemographic characteristics of obese and non-obese subjects

GLP-1 level (pmol/L)	Obese	Non-obese	p-value
Time after intervention (minutes)			
0	0.165 (1.41)	0.320 (0.82)	0.082[M]
15	0.245 (1.90)	0.500 (1.20)	0.042[M]
60	0.205 (1.85)	0.490 (1.11)	0.037[M]
120	0.250 (2.42)	0.470 (1.05)	0.106[M]
180	0.220 (2.14)	0.500 (1.18)	0.061[M]

Notes [M]: Mann–Whitney test

Table 3. Comparison between GLP-1 levels in obese and non-obese subjects

Blood glucose level (mg/dL)	Obese	Non-obese	p-value
Time after intervention (minutes)			
0	87.23 ± 6.43	87.05 ± 6.87	0.930[TT]
15	112.00 (75.00)	109.00 (71.00)	0.465[M]
60	103.09 ± 25.80	99.52 ± 19.06	0.610[TT]
120	80.59 ± 8.88	79.09 ± 10.41	0.614[TT]
180	82.00 (45.00)	80.00 (40.00)	0.592[M]

Notes [M]: Mann–Whitney test, [TT]: Independent T-test

Table 4. Comparison between blood glucose levels in obese and non-obese subjects

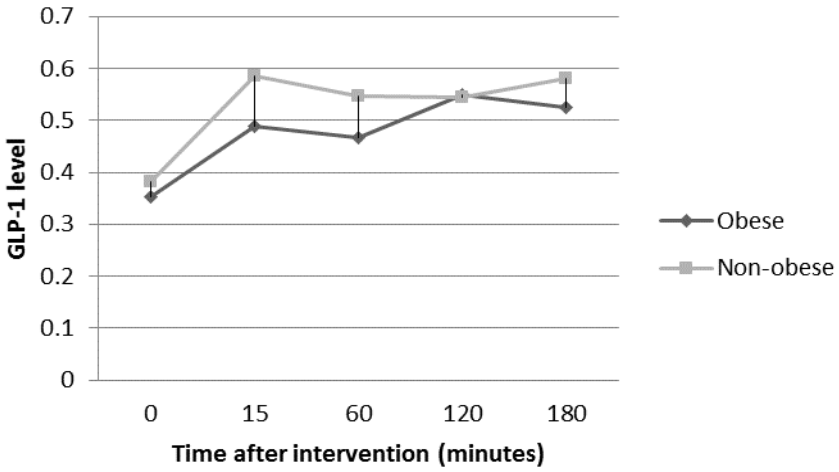

Figure 1. Mean GLP-1 levels in obese and non-obese subjects following intervention

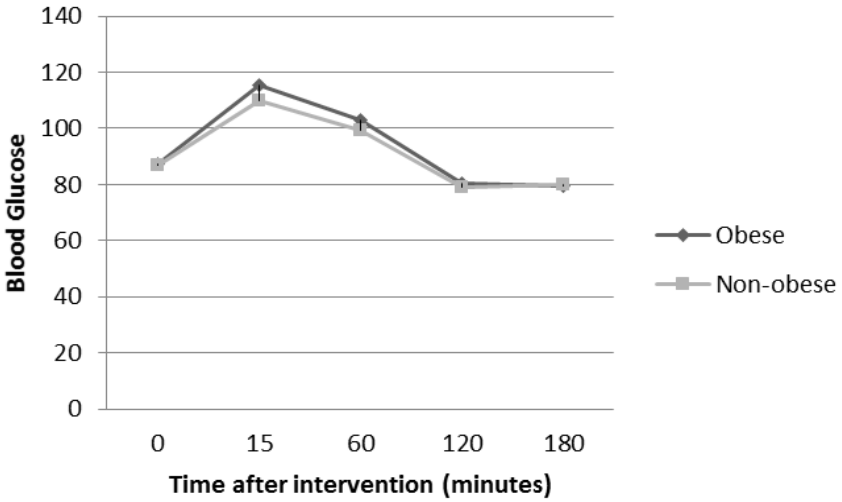

Figure 2. Mean blood glucose levels in obese and non-obese subjects following intervention.

compared to non-obese subjects.[21-24] Meanwhile, earlier studies found that there was no significant difference in postprandial GLP-1 secretion in obese versus non-obese subjects.[25] Another report demonstrated that GLP-1 increases after a meal only correlate positively with satiety in non-obese subjects, which might provide an alternate hypothesis in the role of GLP-1 in obesity.[20] Evidences from clinical studies suggest that weight gain induces alteration in functional GLP-1 signaling. Though the mechanism remains to be defined, several satiety signals - such as insulin, leptin, and ghrelin - are thought to participate in GLP-1 impairment. Increased BMI is associated with hyperinsulinemia, and increasing glucose intolerance could impair GLP-1 secretion. Chronic hyperinsulinemia in obese people might act as a negative feedback signal inhibiting postprandial GLP-1 release.[21-23] Meanwhile, leptin resistance associated with obesity is also associated with decreased postprandial GLP-1 secretion.[20] Physiological ghrelin signaling has been shown to enhance postprandial GLP-1 release, and a reduction in fasting ghrelin levels in obese individuals might account for decreased postprandial GLP-1 release.[20]

As can be seen in Figure 2, mean blood glucose levels within obese subjects were slightly higher than within non-obese subjects. Blood glucose levels in both groups rose from 0 to 15 minutes after intervention, and then declined. However, this study found that there was no significant difference in blood glucose levels between obese and non-obese subjects at any point of time following intervention. Previous studies show that obese people have higher blood glucose levels and lower glycaemic control. A study in overweight/obese girls also showed a

positive association between BMI and fasting blood glucose.[26] However, subjects with abnormal blood glucose levels have been excluded from this study, and this exclusion might be a contributing factor to the nonsignificant results found in this study.

Conclusions

This study found that there is no significant difference between blood glucose levels in obese versus non-obese subjects following consumption of breakfast with a balanced macronutrient composition. We did find that there is a significant difference in GLP-1 levels between obese and non-obese subjects at 15 and 60 minutes following this intervention. Therefore, we can conclude that following the same meal composition, postprandial GLP-1 release is lower in obese compared to non-obese subjects. This finding also supports the theory that there is an impairment of GLP-1 release and signaling in obese subjects.

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Declaration of Interest

The authors report no conflict of interest.

References

1. World Health Organisation. Obesity: Situation and Trends. Available at: “http://www.who.int/gho/ncd/risk_factors/obesity_text/en/.” Accessed July 29, 2018.
2. Center for Health Research and Development of The Indonesian Ministry of Health. Household Health Survey. Jakarta: Indonesia Ministry of Health; 2013.
3. Guh DP, Zhang W, Bansback N, Amarsi Z, Birmingham CL, Anis AH. The Incidence of Comorbidities Related to Obesity and Overweight: A Systematic Review and Meta-Analysis. BMC Public Health. 2009;9:88.
4. Puhl RM, Heuer CA. Obesity Stigma: Important Considerations for Public Health. Am J Public Health. 2010;100(6):1019-28.
5. Luppino FS, de Wit LM, Bouvy PF, et al. Overweight, Obesity, and Depression: A Systematic Review and Meta-Analysis of Longitudinal Studies. Arch Gen Psychiatry. 2010;67(3):220-9.
6. Woods SC, D’Alessio DA. Central Control of Body Weight and Appetite. J Clin Endocrinol Metab. 2008;93(11 Suppl 1):37-50.
7. Berthoud HR. Metabolic and Hedonic Drives in the Neural Control of Appetite: Who is the Boss? Curr Opin Neurobiol. 2011;21:888-96.
8. Williams DL. Neural Integration of Satiation and Food Reward: Role of GLP-1 and Orexin Pathways. Physiol Behav. 2014;136:194-9.
9. Gao Q, Horvath TL. Neurobiology of Feeding and Energy Expenditure. Annu Rev Neurosci. 2007;30:367-98.
10. Volkow ND, Wang GJ, Baler RD. Reward, Dopamine and the Control of Food Intake: Implications for Obesity. Trends Cogn Sci. 2011;15(1):37-46.
11. Anandhakrishnan A, Korbonits M. Glucagon-Like Peptide 1 in the Pathophysiology and Pharmacotherapy of Clinical Obesity. World J Diabetes. 2016;7(20):572-98.
12. Shah M, Vella A. Effects of GLP-1 on Appetite and Weight. Rev Endocr Metab Disord. 2014;15(3):181-7.
13. Locke AE, Kahali B, Berndt SI, et al. Genetic Studies of Body Mass Index Yield New Insights for Obesity Biology. Nature. 2015;518(7538):197-206.
14. Choquet H, Meyre D. Genetics of Obesity: What Have We Learned? Curr Genomics. 2011;12(3):167-79.
15. Benzinou M, Creemers JW, Choquet H, et al. Common Nonsynonymous Variants in PCSK1 Confer Risk of Obesity. Nat Genet. 2008;40(8):943-5.
16. Choquet H, Kasberger J, Hamidovic A, Jorgenson E. Contribution of Common PCSK1 Genetic Variants to Obesity in 8,359 Subjects from Multi-Ethnic American Population. PLoS One. 2013;8(2):e57857.
17. Kilpelainen TO, Bingham SA, Khaw KT, Wareham NJ, Loos RJ. Association of Variants in PCSK1 Gene with Obesity in the EPIC-Norfolk Study. Hum Mol Genet. 2009;18(18):3496-501.
18. Qi Q, Li H, Loos RJ, et al. Association of PCSK1 rs6234 with Obesity and Related Traits in A Chinese Han Population. PLoS One. 2010;5(5):e10590.
19. Chang YC, Chiu YF, Shih KC, et al. Common PCSK1 Haplotypes are Associated with Obesity in the Chinese Population. Obesity (Silver Spring). 2010;18(7):1404-9.
20. Adam TC, Westerterp-Plantenga MS. Glucagon-Like Peptide 1 Release and Satiety After A Nutrient Challenge in Normal-Weight and Obese Subjects. Br J Nutr. 2005;93(6):845-51.
21. Faerch K. Torekov SS, Vistisen D, et al. GLP-1 Response to Oral Glucose is Reduced in Prediabetes, Screen-Detected Type 2 Diabetes, and Obesity and Influenced by Sex. The ADDICTION-PRO Study. Diabetes. 2015;64(7):2513-25.
22. Hussein MS, Abushady MM, Refaat S, Ibrahim R. Plasma Level of Glucagon-Like Peptide 1 in Obese Egyptians with Normal and Impaired Glucose Tolerance. Arch Med Res. 2014;45(1):58-62.
23. Muscelli E, Mari A, Casolaro A, et al. Separate Impact of Obesity and Glucose Tolerance on the Incretin Effect in Normal Subjects and Type 2 Diabetic Patients. Diabetes. 2008;57(5):1340-8.
24. Svendsen PF, Jensen FK, Holst JJ, Haugaard SB, Nilas L, Madsbad S. The Effect of A Very Low Calorie Diet on Insulin Sensitivity, Beta Cell Function, Insulin Clearance, Incretin Hormone Secretion, Androgen Levels and Body Composition in Obese Young Women. Scand J Clin Lab Invest. 2012;72(5):410-9.
25. Carroll JF, Kaiser KA, Franks SF, Deere C, Caffrey JL. Influence of BMI and Gender on Postprandial Hormone Responses. Obesity (Silver Spring). 2007;15(12):2974-83.
26. Mehdad S, Hamrani A, El Kari K, et al. Body Mass Index, Waist Circumference, Body Fat, Fasting Blood Glucose in A Sample of Moroccan Adolescents. J Nutr Metab. 2012;510458:1-7.