



Amylin, bariatric surgery, and type 2 diabetes mellitus

Wen-Ling Lee^{a,b,c}, Fa-Kung Lee^d, Peng-Hui Wang^{c,e,f,g,*}

^aDepartment of Medicine, Cheng-Hsin General Hospital, Taipei, Taiwan, ROC; ^bDepartment of Nursing, Oriental Institute of Technology, New Taipei City, Taiwan, ROC; ^cInstitute of Clinical Medicine, National Yang Ming Chiao Tung University, Taipei, Taiwan, ROC; ^dDepartment of Obstetrics and Gynecology, Cathy General Hospital, Taipei, Taiwan, ROC; ^eDepartment of Obstetrics and Gynecology, Taipei Veterans General Hospital, Taipei, Taiwan, ROC; ^fFemale Cancer Foundation, Taipei, Taiwan, ROC; ^gDepartment of Medical Research, China Medical University Hospital, Taichung, Taiwan, ROC

Type 2 diabetes mellitus (T2DM), a complex metabolic disease characterized by the presence of hyperglycemia and insulin resistance, leading to the development of microvascular and macrovascular complications, including retinopathy, neuropathy, nephropathy, coronary heart disease, peripheral vascular, and cerebrovascular diseases, exerts a major public-health toll worldwide, affecting more than 450 million people.¹⁻⁴ A unifying definition of T2DM in most people with overweight/obesity-associated metabolic disorders recognizes the importance of impaired glucose metabolism/insulin resistance and overweight/obesity, and highlights weight control and weight loss interventions – through behavioral and lifestyle modification, pharmacotherapy, and metabolic-bariatric surgery – as a cornerstone of lowering T2DM-related and/or non-T2DM-related disability and mortality.^{3,5-8} Among the aforementioned strategies, some of them are effective, but needing more efficacious and better tolerable treatment approaches, and by contrast, some of them are more effective, but costly, associated with a non-negligible risk of complications, and not all people are eligible for this strategy.^{3,5-10} Recently, bariatric surgery over the past 60 years has impressively attracted our attention not only in providing a means of achieving substantial weight loss but also in giving us many novel insights on the pathophysiology of obesity.¹¹ There are two main approaches currently performed widely as Roux-en-Y gastric bypass (RYGB) and vertical sleeve gastrectomy (VSG), and the former creates a small gastric pouch around 30 mL being anastomosed to the proximal jejunum with a transection at 30–75 cm from the ligament of Treitz to form the “alimentary limb” which further connects the excluded biliopancreatic limb approximately 75–150 cm distal to the gastrojejunostomy to restore the continuity of the small intestine, and the latter involves dividing the stomach along its vertical length to create a sleeve and removing three-quarters of gastric volume, in both of which decrease the absorption of food intake and result in weight loss due to

changes in the physiology of body weight regulation.¹¹ Therefore, we are happy to learn the article published in the current issue of the *Journal of the Chinese Medical Association* with a focus on bariatric surgery-related remission of T2DM.¹²

The authors retrospectively enrolled 20 patients (10 RYGB and 10 VSG) to compare the posttreatment plasma level of amylin in both groups and found that plasma amylin levels decreased after a 75-g oral glucose tolerance test (OGTT) significantly in the patients with remission of T2DM in both groups, although this change was detected at the different time point between two groups (60–90 min in the RYGB group and 30–60 min in the VSG group).¹² By contrast, in the partial remission (RYGB group) or non-remission (VSG group) of T2DM patients, although plasma amylin levels were also decreased, the time occurred at the 30–90 min in the RYGB group and 30–60 in the VSG group, respectively.¹² Then, the authors concluded that a post-75-g OGTT plasma amylin level can be used as one of the parameters to evaluate T2DM remission after bariatric surgery and this plasma biomarker is especially useful for patients undergoing VSG.¹² The current study is interesting and worthy of further discussion.

On the basis of the authors' study,¹² it is interesting to find that plasma amylin levels in the RYGB group were higher than those in the VSG group; however, all patients in the RYGB took advantage of their T2DM control since 50% had a complete remission and the remaining 50% had a partial remission. By contrast, although complete remission of T2DM was also found in 50% of patients undergoing VSG, one-half of patients did not get any remission of T2DM in the VSG group. If the above findings are true, is it supposed that T2DM patients with high plasma levels of amylin may have a better chance to take advantage of T2DM control after bariatric surgery? This hypothesis may be further supported by lower plasma levels of amylin in the patients with T2DM remission compared to those from either non-remission of T2DM in the VSG group or partial remission of T2DM in the RYGB group. However, the above-mentioned hypothesis may be overestimated by ourselves. In fact, the plasma levels of amylin varied greatly and overlapped significantly when we read Dr. Wang's article. Furthermore, the trend of alternation of plasma levels of amylin in patients after bariatric surgery was very similar, regardless of whether T2DM was remitted or non-remitted. Therefore, it is hard to convince us of the value of using plasma levels of amylin as shown by Dr. Wang's study for routine clinical practice.¹³

Although we argue the clinical value of using plasma levels of amylin as biomarkers for the detection of remission of T2DM, the role of amylin in T2DM is worthy of emphasis. Amylin, a

*Address correspondence. Dr. Peng-Hui Wang, Department of Obstetrics and Gynecology, Taipei Veterans General Hospital, 201, Section 2, Shi-Pai Road, Taipei 112, Taiwan, ROC. E-mail addresses: phwang@vghtpe.gov.tw; pongpongwang@gmail.com (P.-H. Wang).

Conflicts of interest: The authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

Journal of Chinese Medical Association. (2021) 84: 983-984.

Received August 31, 2021; accepted August 31, 2021.

doi: 10.1097/JCMA.0000000000000618.

Copyright © 2021, the Chinese Medical Association. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>)

37-amino acid neuroendocrine peptide of the calcitonin family of peptides, including calcitonin and calcitonin gene-related peptides (CGRPs), with insulin as a ratio of 1:10–100 from the pancreatic β -cell, acts the several isotypes of the functional amylin receptor (AMY-R), which shares the same core 7-transmembrane G protein-coupled receptor with the calcitonin receptor (CTR) by the interaction of a CTR mediated by one of three receptor activity-modifying proteins (RAMPs), showing pleiotropic effects like suppression of postprandial glucagon release, an increase of renin and aldosterone secretion, and the delay of gastric emptying with resulting in reducing energy intake being involved in the regulation of appetite and satiation and restoring responsiveness to leptin through activation of receptors located in the area postrema and nucleus of the solitary tract of the hindbrain.^{14,15} However, AMY-R are not selectively activated by amylin alone and interact indiscriminately with other hormones of similar structure, such as calcitonin, CGRP, and adrenomedullin, and additionally, amylin has an affinity for both CTR and AMY-R, contributing to the uncertainty of the real physiological and pathological interaction of amylin and AMY-R due to difficulty to establish the final action.⁸ That is why we concern the overstatement of the authors' conclusion to show post-OGTT amylin levels could be one of the parameters to evaluate T2DM remission after bariatric surgery.

Recently, a long-acting amylin analog (cagrilintide, AM833, or NNC0174-0833) with agonistic effects on both native AMY-R and CTR either using alone or using the combination of other agents has been applied into the clinical trials (phase 2 and phase 1b) for weight management.^{14,15} Cagrilintide not only decreases the bodyweight progressively and dose-dependently after 26 weeks by the range between 6.0% and 10.8%, but also continuously decreases body weight at the end of the trial.¹⁴ Additionally, subjects treated with cagrilintide reported to improve their emotional and cognitive control of eating, and of most importance, the adverse events are mild and most are related to gastrointestinal disorders.¹⁴ In the combination of cagrilintide and semaglutide (a glucagon-like peptide-1) clinical trial for weight management, the results also show the impressive finding, since the reduction of body weight was significantly regardless of which dose of cagrilintide was used, and similar to the safety of cagrilintide used alone, concomitant treatment with cagrilintide and semaglutide 2.4 mg was well tolerated with an acceptable safety profile, encouraging a larger and longer trials to fully assess the efficacy and safety of this treatment combination.¹⁵ Therefore, although the biomarker value of plasma levels of amylin for T2DM might be low, the hopes and anticipated successes of amylin analog for the treatment of T2DM might be predictable in the near future.

ACKNOWLEDGMENTS

This article was supported by grants from the Taiwan Ministry of Science and Technology, Executive Yuan, Taiwan (MOST 109-2314-B-075B-014-MY2 and MOST 110-2314-B-075-016-MY3), and Taipei Veterans General Hospital (V110C-082, and VGH109E-005-5). The authors appreciate the support from Female Cancer Foundation, Taipei, Taiwan.

REFERENCES

- Marx N, Davies MJ, Grant PJ, Mathieu C, Petrie JR, Cosentino F, et al. Guideline recommendations and the positioning of newer drugs in type 2 diabetes care. *Lancet Diabetes Endocrinol* 2021;9:46–52.
- Kalyani RR. Glucose-lowering drugs to reduce cardiovascular risk in type 2 diabetes. *N Engl J Med* 2021;384:1248–60.
- Syn NL, Cummings DE, Wang LZ, Lin DJ, Zhao JJ, Loh M, et al. Association of metabolic-bariatric surgery with long-term survival in adults with and without diabetes: a one-stage meta-analysis of matched cohort and prospective controlled studies with 174 772 participants. *Lancet* 2021;397:1830–41.
- Hwang DK, Chou YB, Lin TC, Yang HY, Kao ZK, Kao CL, et al. Optical coherence tomography-based diabetic macula edema screening with artificial intelligence. *J Chin Med Assoc* 2020;83:1034–8.
- Horng HC, Lee WL, Wang PH. Maternal weight gain and birth weight. *J Chin Med Assoc* 2021;84:741–2.
- Chiu HH, Wu SF, Wang PH. The experience of menopausal women participating in weight management program: a pilot study. *Taiwan J Obstet Gynecol* 2020;59:686–90.
- Seow KM, Chang YW, Chen KH, Juan CC, Huang CY, Lin LT, et al. Molecular mechanisms of laparoscopic ovarian drilling and its therapeutic effects in polycystic ovary syndrome. *Int J Mol Sci* 2020;21:E8147.
- Mathiesen DS, Lund A, Vilsbøll T, Knop FK, Bagger JI. Amylin and calcitonin: potential therapeutic strategies to reduce body weight and liver fat. *Front Endocrinol (Lausanne)* 2020;11:617400.
- Nauck MA, Wefers J, Meier JJ. Treatment of type 2 diabetes: challenges, hopes, and anticipated successes. *Lancet Diabetes Endocrinol* 2021;9:525–44.
- Lee WL, Chang WH, Wang PH. Simple and less cost but not effective. *J Chin Med Assoc* 2021;84:902–3.
- Akalestou E, Miras AD, Rutter GA, le Roux CW. Mechanisms of weight loss after obesity surgery. *Endocr Rev* 2021;bnab022.
- Wang JW, Chen PY, Huang HH, Yeh C, Chen SC, Lee WJ, et al. Change of plasma amylin after bariatric surgery challenged by oral glucose is associated with remission of type 2 diabetes mellitus. *J Chin Med Assoc* 2021;84:1001–6.
- Chang WH, Lee WL, Wang PH. Is one-minute difference in operation time meaningful? *J Chin Med Assoc* 2021;84:561–2.
- Finer N. Future directions in obesity pharmacotherapy [published online ahead of print May 20, 2021]. *Eur J Intern Med* 2021. Doi: 10.1016/j.ejim.2021.04.024.
- Enebo LB, Berthelsen KK, Kankam M, Lund MT, Rubino DM, Satylganova A, et al. Safety, tolerability, pharmacokinetics, and pharmacodynamics of concomitant administration of multiple doses of cagrilintide with semaglutide 2.4 mg for weight management: a randomised, controlled, phase 1b trial. *Lancet* 2021;397:1736–48.