Dipeptidyl peptidase-4 inhibitors and osteoporosis

Wen-Ling Lee[a,b,c], Fa-Kung Lee[d,e], Peng-Hui Wang[b,e,f,g,*]

[a]Department of Medicine, Cheng-Hsin General Hospital, Taipei, Taiwan, ROC; [b]Institute of Clinical Medicine, National Yang Ming Chiao Tung University, Taipei, Taiwan, ROC; [c]Department of Nursing, Oriental Institute of Technology, New Taipei City, Taiwan, ROC; [d]Department of Obstetrics and Gynecology, Cathay General Hospital, Taipei, Taiwan, ROC; [e]Female Cancer Foundation, Taipei, Taiwan, ROC; [f]Department of Obstetrics and Gynecology, Taipei Veterans General Hospital, Taipei, Taiwan, ROC; [g]Department of Medical Research, China Medical University Hospital, Taichung, Taiwan, ROC

Type 2 diabetes mellitus (T2DM), a noncommunicable epidemic and systemic metabolic disorder characterized by hyperglycemia due to progressive loss of adequate insulin secretion by pancreatic β cells and insulin resistance secondary to malfunction of insulin action mediated by insulin receptor, or a combination of both, is one of the biggest killers for humans due to following sequelae: mainly microvascular and/or macrovascular diseases, rising as a major health issue across the globe.[1–3] T2DM management includes lifestyle intervention, pharmacologic therapy, and routine blood glucose monitoring, and all efforts attempt to prevent or delay the progression of complications and improve quality of life (QoL).[4–7] Glucose-lowering agents (antidiabetic medications) currently approved and commonly used in pharmacologic therapy contain injectable—insulin (basal and bolus), amylin agonist, glucagon-like peptide (GLP)-1 receptor agonist; and oral glucose-lowering medications—sulfonylurea (glyburide, glipizide, glimepiride), biguanide (metformin), α-glucosidase inhibitors (acarbose, miglitol), meglitinides (repaglinide, nateglinide), thiazolidinediones (pioglitazone, rosiglitazone), dipeptidyl peptidase-4 (DPP-4) inhibitors (sitagliptin, saxagliptin, linagliptin, alogliptin), and sodium-glucose cotransporter type 2 (SGLT2) inhibitors (canagliflozin, empagliflozin, dapagliflozin, ertugliflozin).[4,5] Monotherapy or polypharmacy of glucose-lowering agents is based on the patient's age, patient's compliance, patient's general condition, disease course, drug efficacy, and drug-related side effects.[5] Therefore, the development of new T2DM drugs with better efficacy, fewer side effects, and potential repositioning for any new indications or concomitant benefits for health promotion is a problem that researchers have been actively addressing. Therefore, any research focusing on the antidiabetic medication and promoted health/or improved disease is welcome.[8] In the July issue of the *Journal of the Chinese Medical Association,* we are happy to learn about the research addressing this type of problem.[9] Dr. Chang and colleagues tried to investigate whether the use of DPP-4 inhibitors for the treatment of T2DM patients influences the development of osteoporosis.[9]

The authors used data from the National Health Insurance Research Database (NHIRD) of Taiwan, which was organized and managed by the NHIR in Taiwan and covered about 97% of the healthcare providers and 99% of Taiwan residents,[10,11] to determine the potential of DPP-4i in reducing the incidences of osteoporosis in patients with T2DM.[9] The authors found that the risk of all-cause osteoporosis was significantly lower in the DPP-4 inhibitors group than in the non–DPP-4 inhibitors group (adjusted hazard ratio, 0.616; 95% confidence interval, 0.358-0.961). Furthermore, the preventive effect on osteoporosis was positively correlated with the cumulative dose of DPP-4 inhibitors (log-rank, $p = 0.039$) with the class effect.[9] All suggest that the use of DPP-4 inhibitors as glucose-lowering agents for the treatment of T2DM Taiwanese patients at a higher risk of developing osteoporosis may be a better choice compared with the use of non-DPP-4 inhibitors. The current study is interesting and worthy of discussion.

First, because T2DM, one of the chronic multisystem diseases with extremely varied clinical manifestations and a pathogenesis which is a result of complex interactions between genetic, epigenetic, immunoregulatory, ethnic, hormonal, and environmental factors, shares very similar pathophysiological mechanisms as many other chronic and troublesome diseases, such as cancer, autoimmune diseases, neurodegenerative disease, cardiovascular disease, and more,[12] besides the role of antidiabetic potential, it is valuable to reestablish new indications for those. In Dr. Chang's study,[9] the authors really showed that one of antidiabetic agents (DPP-4 inhibitors) may provide additional benefits for T2DM patients, such as the decreased incidence of new development of osteoporosis, suggesting that DPP-4 inhibitors may be one of better choices in the management of T2DM patients when so many types of antidiabetic agents available in the market.

Second, it is well known that osteoporotic fracture is also one of the comorbidities of T2DM, and fracture risk is increased significantly even though normal bone mineral density (absence of osteoporosis) in T2DM patients, suggesting bone quality may be also worse in T2DM patients.[13] Therefore, it is very important to avoid an episode of hypoglycemia in T2DM patients taking any antidiabetic agent. As shown by authors,[9] the relative risk of hypoglycemia is lower in T2DM patients treated with DPP-4 inhibitors, since other antidiabetic agents, such as sulfonylureas (and meglitinides), are at higher risk to induce hypoglycemia,[4] which may be associated with falls/fractures. Based on Dr. Chang's study, the strength of DPP-4 inhibitors may be further supported for the treatment of T2DM.

Third, we know that fracture is the worst outcome in osteoporotic patients since it not only results in increased morbidity

*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: Dr. Peng-Hui Wang, an editorial board member at Journal of the Chinese Medical Association, had no role in the peer review process of or decision to publish this article. The other 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. (2022) 85: 889-890.

Received July 3, 2022; accepted July 5, 2022.

doi: 10.1097/JCMA.0000000000000775.

and mortality of patients but also contributes to a heavy socioeconomic burden.[14] However, as shown in the past section of this editorial comment, the risk of fracture is dependent not only on the diagnosis of osteoporosis, which can be measured as bone mineral density (BMD), but also on the quality of bone, which can be measured by trabecular bone score (TBS).[13] One study tried to determine the effect of glycemic compensation on BMD and TBS in T2DM patients, and the results showed that good glycemic compensation with glycated hemoglobin value <7.0 % did not lead to BMD changes but had significantly better TBS.[13] However, there was a negative correlation between TBS and HbA1C with glycemic fasting. All suggest that good glycemic control is required also for the reduction of the risk of osteoporosis and osteoporotic fractures, because of better bone quality. Moreover, in a Korean population study, data did not show a statistically significant difference in fracture risk between DPP-4 inhibitors users and DPP-4 inhibitors nonusers or controls after the adjustments.[15] However, Dr. Chang's study only focused on the risk of osteoporosis, and bone quality did not be tested. Therefore, it is necessary to test the quality of bone in T2DM patients treated with DPP-4 inhibitors to clarify the real role of DPP-4 on the bone health of T2DM patients.

In conclusion, due to the high prevalence of T2DM and the long history of using antidiabetic agents, the long-term benefits and risks (safety) of antidiabetic agents and improvement of patient's QoL are always in concern. Additionally, patient's compliance and adherence are of paramount importance.[16–18] All make the choice of the therapeutic agents in dilemma and more difficult for healthcare providers and patients. We welcome more and more studies, especially using a big data just like Dr. Chang's study or others,[9–11,17] to investigate the optimal therapeutic choice for patients complicated with chronic but troublesome diseases in the future.

ACKNOWLEDGMENTS

This article was supported by grants from the Taiwan Ministry of Science and Technology, Executive Yuan, Taiwan (MOST 110-2314-B-075-016-MY3 and MOST 111-2314-B-075-045), and Taipei Veterans General Hospital (V110C-082, and V111C-103). The authors appreciate the support from Female Cancer Foundation, Taipei, Taiwan.

REFERENCES

1. Adiga U, Banawalikar N, Menambath DT. Association of paraoxonase 1 activity and insulin resistance models in type 2 diabetes mellitus: cross-sectional study. *J Chin Med Assoc* 2022;**85**:77–80.
2. Lin CC, Wu MF, Chang YL, Sheu WH, Liou WS. Glycemic control was associated with nonprostate cancer and overall mortalities in diabetic patients with prostate cancer. *J Chin Med Assoc* 2022;**85**:331–40.
3. Chen YL, Chi NF, Chiou HY, Hu CJ, Jeng JS, Tang SC, et al; Formosa Stroke Genetic Consortium. Application of hyperglycemia/diabetes-derived polygenic risk scores on the risk of poor outcomes after an ischemic stroke. *J Chin Med Assoc* 2022;**85**:81–7.
4. Kalyani RR. Glucose-lowering drugs to reduce cardiovascular risk in type 2 diabetes. *N Engl J Med* 2021;**384**:1248–60.
5. Zhu S, Bai Q, Li L, Xu T. Drug repositioning in drug discovery of T2DM and repositioning potential of antidiabetic agents. *Comput Struct Biotechnol J* 2022;**20**:2839–47.
6. Kuo SC, Lee WL, Wang PH. The effects of maternal body weight and gestational diabetes mellitus on the risk of the delivery of large-for-gestational age babies: synergistic or additive? *Taiwan J Obstet Gynecol* 2022;**61**:413–4.
7. Lee WL, Lee FK, Wang PH. Pre-pregnancy body mass index is a determined risk factor for the development of gestational diabetes, regardless of singleton or twin pregnancy. *Taiwan J Obstet Gynecol* 2022;**61**:1–2.
8. Wu TH, Lee IT, Ho LT, Sheu WH, Hwu CM. Combined lipid goal attainment in patients with type 2 diabetes and dyslipidemia: a head-to-head comparative trial of statins. *J Chin Med Assoc*. 2022;**85**:832–9.
9. Chang CH, Lu CH, Chung CH, Su SC, Kuo FC, Liu JS, et al. Dipeptidyl peptidase-4 inhibitors attenuates osteoporosis in patients with diabetes: a nationwide, retrospective, matched-cohort study in Taiwan. *J Chin Med Assoc* 2022;**85**:747–53.
10. Chuang WC, Chu CH, Hsu YH, Yao CS. Effect of socioeconomic status on survival in patients on the Diabetes Shared Care Program: Finding from a Taiwan nationwide cohort. *J Chin Med Assoc* 2022;**85**:311–6.
11. Lin WC, Chang WH, Bai YM, Li CT, Chen MH, Su TP. The risk of insomnia after surgical operation: a longitudinal, population-based, case-crossover study. *J Chin Med Assoc* 2022;**85**:519–24.
12. Lee WL, Lee FK, Wang PH. Vitamin D and systemic lupus erythematous. *J Chin Med Assoc* 2022;**85**:811–2.
13. Jackuliak P, Kužma M, Killinger Z, Payer J. Good long-term glycemic compensation is associated with better trabecular bone score in postmenopausal women with type 2 diabetes. *Physiol Res* 2019;**68**(Suppl 2):149–56.
14. Chang YC, Yao YC, Lin HH, Wang ST, Chang MC, Chou PH. Predictability of the preoperative lateral fulcrum radiograph of success in one-level vertebroplasty to treat painful osteoporotic vertebral fracture. *J Chin Med Assoc* 2022;**85**:129–35.
15. Ustulin M, Park SY, Choi H, Chon S, Woo JT, Rhee SY. Effect of dipeptidyl peptidase-4 inhibitors on the risk of bone fractures in a Korean population. *J Korean Med Sci* 2019;**34**:e224.
16. Tsai MS, Chen HC, Liu SY, Lee LA, Lin CY, Chang GH, et al. Holistic care for obstructive sleep apnea (OSA) with an emphasis on restoring nasal breathing: a review and perspective. *J Chin Med Assoc* 2022;**85**:672–8.
17. Tseng SY, Huang YS, Chang TE, Perng CL, Huang YH. Hepatotoxicity, efficacy and completion rate between 3 months of isoniazid plus rifapentine and 9 months of isoniazid in treating latent tuberculosis infection: a systematic review and meta-analysis. *J Chin Med Assoc* 2021;**84**:993–1000.
18. Yang YL, Leu HB, Yin WH, Tseng WK, Wu YW, Lin TH, et al. Adherence to healthy lifestyle improved clinical outcomes in coronary artery disease patients after coronary intervention. *J Chin Med Assoc* 2021;**84**:596–605.