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A Novel Attribute of Insulin Secretion via Incretin Axis by Metformin

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Dear Editor,

Metformin, a diabetes drug, has been used to control hyperglycemia in patients with type 2 diabetes for more than 50 years. Metformin exerts its antidiabetic activity by counteracting insulin resistance to hepatic glucose production and/or increasing the insulin-stimulated glucose uptake in muscle and fat. In addition to controlling blood glucose levels, it has also been shown to reduce the long-term complications of diabetes, including micro- and macrovascular diseases (1). Metformin has also been reported to reduce the incidence of type 2 diabetes in high-risk individuals with impaired glucose tolerance (2). Although lactic acidosis has been reported in patients treated with metformin, the drug is considered as the safest hypoglycemic agent to date. In contrast to treatment with other oral drugs and insulin, metformin monotherapy is not associated with the risk of hypoglycemia, nor does it cause weight gain (3). Moreover, recent studies have shown that metformin reduces the risks of developing solid organ cancer (4) and osteoporosis (5). Thus, the drug has been recently recognized as the first-line oral agent for the treatment of type 2 diabetes, particularly in overweight patients.

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In type 2 diabetes, the gradual deterioration in glycemic control over time can be attributed to the progressive loss of pancreatic β-cell mass and function. Therefore, it is important to maintain and improve the residual insulin secretion capacity in pancreas. Although metformin was considered to be an insulin-sensitizing drug, recent evidence indicates that metformin is also involved in insulin secretion from pancreatic β-cells. Metformin is increasingly being used in combination with incretin-based therapies such as treatment with glucagon-like peptide 1 (GLP-1) analogs and dipeptidyl peptidase-4 (DPP-4) inhibitors (6), both of which enhance the function of pancreatic β-cells. It has been reported that metformin interacts with the incretin axis. Metformin treatment increases plasma levels of GLP-1 in rodents (7, 8). It also inhibits DPP-4 activity, resulting in an increase in the GLP-1 levels in circulation (9). Further, metformin stimulates the expression of the genes encoding a GLP-1 receptor in mouse islets cells and increases the effects of GLP-1 on insulin secretion from β-cells (7). Thus, metformin stimulates the function of GLP-1 on β-cells by increasing plasma levels of GLP-1 and the expression of its receptor, resulting in increased insulin secretion.

In a recently published study in the International Journal of Endocrinology and Metabolism (10), Hashemitaber et al. investigated the effects of metformin on insulin gene expression in mouse embryonic and neonatal pancreas. Although metformin did not show a significant effect on the insulin gene expression in embryonic

and neonatal pancreases, the expression levels of the insulin gene in neonatal mice treated with metformin were significantly higher than those in the embryonic treatment groups. In addition, metformin induced a significant and dose-dependent increase in the expression of pancreatic duodenum homeobox-1 (Pdx-1) gene, which encodes a transcription factor necessary for pancreatic development and β-cell maturation in neonatal pancreas. Taken together, these findings suggest that metformin regulates insulin expression and secretion in pancreatic β-cells after birth by stimulating Pdx-1 expression. In contrast, in this study, metformin did not affect the expressions of Pdx-1 and insulin in embryonic pancreas. The authors suggested that the insensitivity of the embryonic pancreas to metformin was because of the lack of functional maturity. However, the exact mechanisms of the effect of metformin on embryonic and neonatal pancreases have not been examined so far. Further, although metformin stimulated GLP-1 signaling and increased insulin expression, the lower glucose levels achieved with metformin treatment were not associated with the increased insulin levels. Therefore, the clinical significance of metformin's effect on insulin secretion needs to be evaluated. Thus, further longitudinal studies are necessary to investigate the effect of metformin and/or combination therapy of metformin and incretin-based drugs on residual insulin secretory capacity in type 1 and type 2 diabetes.

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References

1. UK Prospective Diabetes Study Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet*. 1998;**352**(9131):854-65.
2. Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med*. 2002;**346**(6):393-403.
3. Bolen S, Feldman L, Vassy J, Wilson L, Yeh HC, Marinopoulos S, et al. Systematic review: comparative effectiveness and safety of oral medications for type 2 diabetes mellitus. *Ann Intern Med*. 2007;**147**(6):386-99.
4. Currie CJ, Poole CD, Gale EA. The influence of glucose-lowering therapies on cancer risk in type 2 diabetes. *Diabetologia*. 2009;**52**(9):1766-77.
5. Kanazawa I, Yamaguchi T, Yano S, Yamauchi M, Sugimoto T. Metformin enhances the differentiation and mineralization of osteoblastic MC3T3-E1 cells via AMP kinase activation as well as eNOS and BMP-2 expression. *Biochem Biophys Res Commun*. 2008;**375**(3):414-9.
6. Phung OJ, Scholle JM, Talwar M, Coleman CI. Effect of noninsulin antidiabetic drugs added to metformin therapy on glycemic control, weight gain, and hypoglycemia in type 2 diabetes. *JAMA*. 2010;**303**(14):1410-8.
7. Maida A, Lamont BJ, Cao X, Drucker DJ. Metformin regulates the incretin receptor axis via a pathway dependent on peroxisome proliferator-activated receptor-alpha in mice. *Diabetologia*. 2011;**54**(2):339-49.
8. Yasuda N, Inoue T, Nagakura T, Yamazaki K, Kira K, Saeki T, et al. Enhanced secretion of glucagon-like peptide 1 by biguanide compounds. *Biochem Biophys Res Commun*. 2002;**298**(5):779-84.
9. Lenhard JM, Croom DK, Minnick DT. Reduced serum dipeptidyl peptidase-IV after metformin and pioglitazone treatments. *Biochem Biophys Res Commun*. 2004;**324**(1):92-7.
10. Hashemitabar M, Soleimani Mehranjani M, Momeni H, Bahramzadeh S, Negad Dehbashi F, Khorsandi L. The effects of metformin on Pdx-1 and insulin gene expression in mouse embryonic and neonatal pancreas. *Int J Endocrinol Metab*. 2010;**8**(4):211-14.