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Pioglitazone/Metformin
A Viewpoint by Guntram Schernthaner

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Insulin resistance is common in patients with type 2 diabetes mellitus, contributing not only to disturbed glucose metabolism in these patients, but also to dyslipidaemia, hypertension, endothelial dysfunction, prethrombotic state and chronic vascular inflammation.[1] Thus, isolated lowering of hyperglycaemia is not sufficient to reduce the high risk of cardiovascular morbidity and mortality in type 2 diabetic patients, most of whom present with several components of the insulin resistance syndrome.

Although the glucose lowering effects of pioglitazone and metformin are very similar, as demonstrated in a large, head-to-head, prospective, randomised trial,[2] these drugs act through different mechanisms. Pioglitazone improves insulin sensitivity in peripheral tissue, whereas metformin acts mainly on the liver. These two drugs also differ in their effects on diabetic dyslipidaemia, with pioglitazone exhibiting pronounced effects on high-density lipoprotein (HDL)-cholesterol and very low-density lipoprotein (LDL)-triglycerides, and metformin affecting total and LDL-cholesterol.[2] Pioglitazone can reduce visceral adipose tissue by 25%, but increases weight by approximately 3–4kg owing to an increase of 42% in subcutaneous adipose tissue and the water retention effect. In contrast, metformin is the only antidiabetic drug associated with weight loss or less weight gain because of its anorectic effect. Based on the different mechanisms of pioglitazone and metformin, the two compounds in combination may have the best relative effects on improving all components of the insulin resistance syndrome: lowering glycosylated haemoglobin, fasting and postprandial glucose and triglycerides levels, increasing HDL-cholesterol levels and improving vascular inflammation and the atherothrombotic state.

Of particular relevance is the fact that promising results were reported for both drugs in reducing severe cardiovascular complications (myocardial infarction and stroke): primary prevention in the case of metformin (UKPDS; UK Prospective Diabetes Study) and secondary prevention in the case of pioglitazone (PROactive; PROspective pioglitAzone Clinical Trial In macroVascular Events). The availability of a combination therapy with both drugs contained in one tablet may increase the compliance of patients and offer an optimal anti-insulin-resistance drug with beneficial effects on the high cardiovascular risk of type 2 diabetes. ▲

References

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