

# Metformin in type 1 diabetes mellitus?

## Revisiting treatment dogmas in diabetes

Tomasz Klupa<sup>1,2</sup>

<sup>1</sup> Unit on Advanced Technologies in Diabetes, Jagiellonian University Medical College, Kraków, Poland

<sup>2</sup> Department of Metabolic Diseases, University Hospital in Krakow, Kraków, Poland

Type 1 diabetes mellitus results from autodestruction of pancreatic  $\beta$ -cells and is characterized by absolute insulin deficiency. Thus, the therapy of type 1 diabetes must be based on insulin replacement. However, despite the development of more physiological strategies of exogenous insulin delivery, including the use of advanced technologies such as insulin pumps or systems of continuous glucose monitoring, the treatment of type 1 diabetes remains an ongoing challenge. Even when the glycemic goals are reached, the life expectancy among type 1 diabetes patients is shorter than that in age-matched healthy individuals.<sup>1</sup>

There is no doubt that the risk of cardiovascular disease in type 1 diabetes is significantly increased.<sup>1,2</sup> There may be many reasons for this, including hyperglycemia per se,<sup>2</sup> hypoglycemic episodes,<sup>3</sup> nonphysiological insulin delivery,<sup>4</sup> while the role of blood glucose variability is less established.<sup>3</sup> The alarming data have come from pediatric populations. It was shown that despite short disease duration, intensive insulin treatment, fair glycemic control, and no signs of microvascular complications, children and adolescents with type 1 diabetes had slightly increased carotid artery intima-media thickness (IMT) compared with healthy control subjects.<sup>5</sup>

Recently, the interest in the role of insulin resistance (IR) in type 1 diabetes has grown. IR is often observed in patients with type 1 diabetes during the natural history of adolescence and puberty and during intercurrent illness; however, it is now well established that diminished sensitivity to insulin may be a common feature of type 1 diabetes irrespectively of patients' age or current health status.<sup>6</sup> One of the first data showing that increased IR is typical not only for type 2 diabetes but also for type 1 diabetes patients were reported by DeFronzo et al<sup>7</sup> more than 30 years ago, confirmed by many other groups later on. IR in type 1 diabetes may also be worsened by weight gain. Unfortunately, obesity is increasing in type

1 diabetes overall; probably, at least to some degree, it is iatrogenic and due to overinsulinization, hypoglycemia generation, or lack of proper education. The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study (DCCT/EDIC)<sup>8</sup> has shown that excess weight gain in DCCT was associated with sustained increases in central obesity, IR, dyslipidemia, and blood pressure, as well as more extensive atherosclerosis during EDICT.<sup>8</sup> Other factors that may influence IR in type 1 diabetes patients include a family history of type 2 diabetes, chronic hyperglycemia (glucotoxicity), age, ethnicity, physical activity, and drug use.<sup>9</sup> The presence of different degree of IR as part of clinical picture of latent autoimmune diabetes in adults is one of the arguments to postulate reclassification of diabetes.

However, the problem of IR in type 1 diabetes requires further investigation including studies on a relative distribution of the resistance to insulin among different organs and tissues. It was recently shown, for example, that in patients with type 1 diabetes who naturally lack the portal/peripheral insulin gradient, insulin stimulation of hepatic lipogenesis may be diminished. That would protect type 1 diabetes individuals against the development of nonalcoholic fatty liver disease and hepatic IR.<sup>10</sup>

IR is a well-established risk factor for cardiovascular disease.<sup>11,12</sup> It has been suggested that for type 1 diabetes individuals, IR-related factors, not the glycemic control, may be crucial in the development of cardiovascular events.<sup>11,12</sup> Furthermore, it has been shown that in patients with type 1 diabetes, sex differences in IR-associated fat deposition and distribution of high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol may explain why diabetes increases coronary calcification in women relatively more than in men.<sup>12</sup>

### Correspondence to:

Prof. Tomasz Klupa, MD, PhD,  
Pracownia Zaawansowanych  
Technologii Diabetologicznych,  
Katedra i Klinika Chorób  
Metabolicznych, Uniwersytet  
Jagielloński, Collegium Medicum,  
ul. Kopernika 15, 31-501 Kraków,  
Poland, phone: +48 12 424 83 00,  
e-mail: tomasz.klupa@uj.edu.pl  
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Thus, the question arises as to whether IR is present in type 1 diabetes patients (or at least in some subgroups) and whether it is a key factor increasing the risk of cardiovascular events. Can we treat IR in type 1 diabetes patients in the same way as we do it in those with type 2 diabetes? Can metformin be effective and safe in patients with type 1 diabetes? If so, what is the mechanism of metformin-related cardiovascular protection in type 1 diabetes patients?

Some of these issues have already been addressed. It has been shown in a well-designed randomized study that metformin improves endothelial function in patients with type 1 diabetes.<sup>13</sup> A meta-analysis published recently has shown that when used in type 1 diabetes patients, metformin was associated with a reduction in daily insulin dosage, body weight, and total cholesterol, LDL cholesterol, and HDL cholesterol levels. Of note, no significant difference was found between the metformin and placebo groups in the risk of severe hypoglycemia or diabetic ketoacidosis.<sup>14</sup>

Burchardt et al<sup>15</sup> studied the relationship between the metformin usage and lipid profile and assessed the influence of metformin therapy on carotid IMT in type 1 diabetes patients with excess body fat.<sup>15</sup> Of note, in their analysis, they included the measurement of the activity of 2 enzymes involved in LDL oxidization, lipoprotein-associated phospholipase A<sub>2</sub> (Lp-PLA<sub>2</sub>), and cholesterol ester lipase.

The authors have found that the use of metformin resulted in significant reductions in IMT of the carotid artery and glycated LDL. Of interest, glycated LDL inversely correlated with the Lp-PLA<sub>2</sub> concentration in patients receiving metformin. These findings require further investigation but they may contribute to the explanation of antiatherosclerotic properties of metformin.

The study contributes to the discussion concerning the need of taking under consideration the complex phenotype of type 1 diabetes when choosing optimal treatment strategies for patients. This discussion may be relevant also for other types of diabetes, traditionally seen as arising from pancreatic  $\beta$ -cell failure only. We have shown the presence of IR features in Permanent Neonatal Diabetes Mellitus (PNDM), in individuals with mutations in genes encoding the subunits of pancreatic  $\beta$ -cell ATP-dependent potassium channel (ABCC8 and KCNJ11).<sup>16,17</sup>

To conclude, we are probably in the advent of revisiting treatment dogmas in diabetes. The need for IR treatment may be much more common than we used to believe, and metformin should be considered as adjunctive therapy in many more so far “not obvious” clinical situations in diabetes. However, the longitudinal studies are needed to elucidate the potential relationship between metformin use and protection from vascular damage in diabetes resulting primarily from pancreatic  $\beta$ -cell failure.

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