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The legacy effect in early-stage diabetes: Don't stay by me, cardiovascular disease!

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The DIANA (DIAbetes and diffuse coronary Narrowing) study, performed in 2012, was new and prescient in terms of clarifying the cardiovascular outcome of improvement in glycemic status in early-stage diabetes with coronary artery disease (CAD).[1] At 1 year, patients with improved glycemic status showed less atherosclerotic progression regardless of the type of treatment: α-glucosidase inhibitor; glinide, or life-style intervention.[1] Now, with the 10-year follow-up report, we learn that the beneficial effect of the 1-year glycemic status reversion has sustained particularly in impaired glucose tolerance (IGT) patients converting to normal glycemic status, although this 10-year report did not show favorable cardiovascular outcome with respect to mortality, non-fatal myocardial infarction.[2] It is notable that only 1-year intervention can affect cardiovascular outcome in early-stage diabetes even with established CAD.[2] This 10-year results indicate a similar tendency for a late survival curve divergence beginning after 4–6 years as demonstrated by the seminal studies on frank diabetics including the DCCT/EDIC[3] and the Steno-2.[4]

Macrovascular diseases such as CAD initially occur during the period of early-stage diabetes or prediabetes. Prediabetes is generally defined by either an elevation in fasting or postprandial plasma glucose level. Prediabetes, including IGT, is a potential risk factor for cardiovascular disease (CVD). Despite the accumulating evidence, guidance for the management of prediabetes has not been established. IGT is still considered to be a mere risk factor for the future development of diabetes. This perception may result in a delay in early multidisciplinary intervention in individuals with IGT. The Funagata Diabetes Study demonstrated that the risk of death from CVD was significantly increased in patients with IGT and it was not different from that in patients with diabetes.[5] Tamita et al. reported the magnitude of CVD risk with IGT as compared to that with previously known diabetes in patients with acute MI undergoing reperfusion therapy.[6] They categorized IGT and newly diagnosed diabetes as abnormal glucose tolerance (AGT), and they showed equivalent 5-year CVD rates with previously known diabetes. The GAMI (Glucose Tolerance in Patients with AMI) study has shown that AGT determined by the presence of post-loaded glycemia was a risk factor for future CVD in patients with acute myocardial infarction.[7] Additionally, an observational study with a 10-year follow-up showed that IGT potentially results in worse future cardiovascular outcomes than in newly diagnosed diabetes.[8]

The majority of IGT patients do not convert to diabetes.[9] Nevertheless. diabetes-associated macrovascular diseases develop earlier than microvascular diseases when plasma glucose levels are in the prediabetic range.[10] Because IGT is an established risk for CVD, but plasma glucose levels are not as high as those in frank diabetes, macrovascular disease development seems to be associated with some factors other than hyperglycemia. The incidence of CVD in IGT increases steadily at a constant rate of 1.4 % per year according to the STOP-NIDDM trial.[11] Several studies have shown an increased risk of new-onset hypertension in IGT.[11,12] The potential association of metabolic syndrome (MetS) should also be considered. Most patients with prediabetes have hyperinsulinemia,[13] which potentially mediates all the metabolic risk factors of MetS including obesity, hypertension, and dyslipidemia. Hyperinsulinemia promotes atherosclerosis earlier before diabetes becomes clinically evident.[14] In the STOP-NIDDM trial, the treatment group

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receiving an alpha-glucosidase inhibitor (acarbose) was associated with significant reductions in the body weight, waist circumference, blood pressure, post-loaded plasma glucose level, and triglyceride level, whereas patients who developed CVD had a significantly larger waist circumference and higher blood pressure at baseline.[11] DIANA study showed that 22– 35 % of early-stage diabetic patients could be restored to normal glucose tolerance at 1-year with medical and non-medical intervention. The impact of reversion to normal glycemic profile is associated not only with the reduction of hyperglycemia itself, but also with the improvement of other risk factors including dyslipidemia through the regression of hyperinsulinemia as indicated in DIANA study.[1]

There are some obstacles that should be removed to optimize the management of prediabetes. First, practicing clinicians currently have very little guidance towards proper management of prediabetes. Physicians are in general less motivated to treat prediabetes as aggressively as diabetes and subsequently leading to a delay in risk factor modifications. Second, universal screening to detect prediabetes or early-stage diabetes could be desirable, but it may not be cost effective because glucose tolerance test would have to be generally implemented. Third, the optimal treatment strategy of IGT has not been established. Lifestyle modification over a period of time is effective in preventing diabetes in the future as DPP and DPPOS study shown.[15,16] A large body of evidence supports the effectiveness of lifestyle interventions, such as healthy diet, smoking cessation, and physical exercise in preventing IGT from progressing to diabetes as the first-line management.[17] In addition, a multidisciplinary approach to control the risk factors of CVD deserves consideration targeting hypertension, dyslipidemia, and pro-thrombotic factors. More aggressive administration of statins could be an effective intervention as shown in DIANA study.[1] An alpha-glucosidase inhibitor for patients with IGT is reportedly associated with a significant reduction in the incidence of CVD[11]. However, medication non-adherence is a concern because this drug needs to be taken thrice a day. More specific medications to treat IGT with preserved quality of life are anticipated. It would be also useful to further investigate the effectiveness of introducing sodium glucose cotransporter 2 inhibitors or glucose glucagon-like peptide-1 receptor agonists (GLP-1 RAs) from prediabetic stage, although another medical economic issues cannot be ignored.

The DIANA study first demonstrated that improvement in glycemic status is significantly associated with less atherosclerotic change.[1] Now, this 10-year post-trial follow-up study is further encouraging for clinicians, showing that intervention for as little as one year can improve long-term clinical outcomes for early-stage diabetic patients as UKPDS-80 provide data that confirm a so-called legacy effect associated with intensive glucose control in patients with type 2 diabetes, long after the cessation of randomized intervention.[18] New hopes are coming from the use of GLP-1 RAs and the most recent dual glucose-dependent insulinotropic peptide (GIP)/GLP-1 RAs in the treatment of non-diabetic obesity and pre-diabetes.[19] This is of particular importance in our current post-COVID era, since glycemic status and body weight have been deteriorated by the altered life-style and improper food consumption happened in the last three years.[20,21] It is our responsibility to translate the data we learn from clinical studies and trials into every day practice for a long healthier life of our patients.[22] If Paul Anka was still alive, he would have sung as follows: “Oh please *don't* stay by me, CVD.”

Author statement

This article has not been published previously and not under consideration for publication elsewhere. If accepted, it will not be published elsewhere in the same form including electronically without the written consent of the copy-right holder.

Declaration of competing interest

All authors disclose no financial and personal relationships with other people or organizations.

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