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# In This Issue of *Diabetes Care*

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## PREDIMED-Plus: The Initial Results Are In

The first-year results of the ongoing PREDIMED-Plus (PREvención con Dieta MEDiterránea-Plus) trial as reported by Salas-Salvadó et al. (p. 777) suggest that intensive lifestyle interventions on top of an energy-reduced Mediterranean diet and physical activity promotion can result in weight loss and reductions in a series of cardiovascular risk factors. This was specifically the case for older adults who were overweight/obese with metabolic syndrome and also for individuals at risk of or with diabetes. The analysis covers just over 600 of the initial volunteers that are enrolled in the wider trial, which is a much larger (~6,900 participants) and longer study that will eventually evaluate the effects of the interventions on hard cardiovascular outcomes. Approximately half of the volunteers were enrolled in the intensive lifestyle interventions group with the rest, acting as control subjects, only advised to consume a noncaloric restricted Mediterranean diet. The authors found that the intensive lifestyle intervention on top of the diet did result in significantly greater weight loss at 12 months; the average loss was 3.2 kg, while the control group lost an average of 0.7 kg. A range of cardiovascular markers also improved in the intervention group, including waist circumference, fasting glucose, triglycerides, and HDL cholesterol. Other markers also improved with the intervention including insulin resistance, HbA<sub>1c</sub>, leptin, interleukin-18, and MCP-1, but did not improve in the control group. Individuals with prediabetes or diabetes and those in the intervention group also saw a number of metabolic improvements. On the basis of the results, the authors suggest/hypothesize that if long-term weight loss can be maintained with the intervention, this might translate into beneficial effects in terms of hard cardiovascular events—an outcome that will be reported once the trial finishes in 2020. Commenting further, author Jordi Salas-Salvadó told *Diabetes Care*: “No large randomized controlled trial has ever demonstrated that intentional weight loss will reduce the incidence of hard cardiovascular events in the long term. PREDIMED-Plus addresses the need for effective strategies to reduce the burden of obesity and its adverse health consequences.”

Salas-Salvadó et al. Effect of a lifestyle intervention program with energy-restricted Mediterranean diet and exercise on weight loss and cardiovascular risk factors: one-year results of the PREDIMED-Plus trial. *Diabetes Care* 2019;42:777–788

## HbA<sub>1c</sub>, Triglycerides, Blood Pressure: Factors Affecting Renal Disease in Type 1 Diabetes

Higher, long-term cumulative glycemic exposure is a strong independent factor associated with the development of kidney disease in type 1 diabetes, according to Perkins et al. (p. 883). Specifically, they report that glycemic exposure is linked to incidence of macroalbuminuria and also incidence of reduced estimated glomerular filtration rate (eGFR). The authors also identify a series of other factors linked to renal outcomes, although with lower magnitudes of association. As a result, they suggest that in line with cardiovascular and retinal complications, glycemia should be aggressively targeted to reduce later renal complications. The conclusions are based on further analysis of the Diabetes Control and Complications Trial (DCCT) cohort and its follow-up Epidemiology of Diabetes Intervention and Complications (EDIC) study. The authors used hazard models to assess the association of a series of glycemic and nonglycemic risk factors with incident macroalbuminuria and reduced eGFR over 27 years of follow-up in the studies. They found that higher mean HbA<sub>1c</sub> levels and male sex had the greatest associations with macroalbuminuria. Additional factors included higher mean triglycerides, higher blood pressure, diabetes duration, and weight, although the magnitude of association was weaker for these factors. HbA<sub>1c</sub> was also strongly associated with reduced eGFR along with higher triglycerides, older age, and blood pressure. Study authors Bruce A. Perkins, Ionut Bebu, and John M. Lachin said: “The analysis shows with clarity that exposure to higher levels of blood glucose is the fundamental determinant of someone’s risk to develop advanced stages of kidney disease in type 1 diabetes. Although other risk factors such as higher levels of lipids and blood pressure appear to play an important causal role—and must be addressed in clinical care—they likely cannot overcome the risk imposed by higher glycemic exposure. The results support the current model of clinical care in which aggressive glycemic management coupled with strong control of nonglycemic renal risk factors are indicated for those with type 1 diabetes.”

Perkins et al. Risk factors for kidney disease in type 1 diabetes. *Diabetes Care* 2019;42:883–890

## Retinopathy Risks in Type 1 Diabetes: Glycemia Is Confirmed but There Are Other Factors

A further analysis of the Diabetes Control and Complications Trial/Epidemiology of Diabetes Intervention and Complications (DCCT/EDIC) cohort at 30 years of follow-up confirms that mean HbA<sub>1c</sub> is a strong risk factor for the progression of retinopathy in type 1 diabetes, but that it is not the only one. As a result, the authors of the study, Hainsworth et al. (p. 875), conclude that while aggressive management of glycemia is important, combining it with the management of other modifiable factors (e.g., lipids and blood pressure) may result in reducing the burden of retinopathy in type 1 diabetes. The conclusions are the result of applying modeling approaches to estimate the likely association between a series of risk factors and various retinopathy outcomes. These included proliferative diabetic retinopathy, macular edema, and a composite measure of ocular surgery. They found that higher mean HbA<sub>1c</sub> over the follow-up period was the most significant risk factor, predicting all three retinopathy outcomes. In minimally adjusted models, accounting for age and mean HbA<sub>1c</sub>, raised blood pressure and pulse rate, raised lipids, and longer duration of diabetes, as well as many other factors, appeared to influence risk for individual retinopathy outcomes. The final multivariate models confirmed and, in some cases, refined the outcomes, confirming that glycemia was the overall major risk factor involved in retinopathy progression. According to authors Dean P. Hainsworth, Ionut Bebu, and John M. Lachin: “Standardized assessments of risk factors and retinopathy outcomes over 30 years of follow-up in the DCCT/EDIC study provide a unique opportunity to assess risk factors for advanced retinopathy complications in type 1 diabetes. Our analyses confirmed that total exposure to glycemia is the dominant risk factor for proliferative diabetic retinopathy, clinically significant macular edema, and ocular surgery. Aggressive glycemic management coupled with aggressive management of other nonglycemic risk factors are recommended to reduce the burden of retinopathy in individuals with type 1 diabetes.”

Hainsworth et al. Risk factors for retinopathy in type 1 diabetes: the DCCT/EDIC study. *Diabetes Care* 2019;42:875–882

## Seasonal Variations in the Achievement of Diabetes Treatment Targets

The rate that patients with type 2 diabetes achieve a series of treatment targets varies with the season, according to Sakamoto et al. (p. 816). Specifically, achievement of HbA<sub>1c</sub>, blood pressure, and LDL cholesterol targets were consistently lower in winter than in summer. Accordingly, they suggest that seasonal variations in achievements should be taken into account in clinical practice, and if treatment intensification is used during winter, reductions in cardiovascular events might result. The conclusions are the result of a retrospective analysis of just over 100,000 patients with type 2 diabetes in Japan. Individuals were then included in the study if they had 12 or more measures of HbA<sub>1c</sub>, blood pressure, and LDL cholesterol in the period January 2013 to December 2014. Achievement of each of the measures was then defined according to cut-off points. Additional clinical measures were also included in the analysis to identify potential factors that might explain any patterns. Out of the original population, the authors managed to identify 4,678 patients with the required number of measurements. They found that around 53% of patients achieved the HbA<sub>1c</sub> target of <7% in summer months but this dropped to 49% in winter. Achievement of LDL cholesterol <100 mg/dL was 51% in summer months and 47% in winter, while systolic blood pressure targets were achieved by 57% of participants in summer and 41% in winter. A combined measure of achievement (termed ABC in the article) indicated that around 16% of individuals met all the primary targets in summer, while approximately 10% achieved it in winter. The authors go on to look for factors that might explain the patterns, identifying age ≥65 years as independently related to systolic blood pressure, and high BMI and diabetes duration related to lower achievement of HbA<sub>1c</sub> target. They also identify insulin and sulfonylurea use as independently associated with overall achievement of targets.

Sakamoto et al. Seasonal variations in the achievement of guideline targets for HbA<sub>1c</sub>, blood pressure, and cholesterol among patients with type 2 diabetes: a nationwide population-based study (ABC Study: JDDM49). *Diabetes Care* 2019;42:816–823