Editorial

Javier Escalada San Martín

Prediabetes: what are we talking about?

Intermediate hyperglycemia (or prediabetic status) is an umbrella term for two entities: impaired fasting glucose (IFG) and glucose intolerance (GI). Different definitions have been proposed for these two overlapping conditions, according to the normal range of glycemia established. The American Diabetes Association (ADA), the World Health Organization (WHO), and the International Diabetes Federation (IDF) identify a category of hyperglycemic situations between normal glycemia and diagnosis of diabetes mellitus (DM) based on fasting glycemia in plasma or glycemia in venous plasma 2 h after 75 g OGTT (oral glucose tolerance test) [1]. More recently, it has been incorporated the possibility of diagnosis based on plasmatic HbA_{1c} levels. For IFG diagnosis, these organizations establish different ranges of fasting glycemia in plasma (100 vs. 110 mg/dL) and normal HbA_{1c} levels (5.7 vs. 6%). At present, the diagnostic criteria for prediabetes are well established (see Figure 1)

Why is diagnosis of these entities important?

The prevalence of prediabetes is not a minor issue. According to the most recent data published in Spain in the *di@bet.es* study [2], the prevalence of IFG and GI is 3.4 and 9.2%, respectively. In addition, these are situations at a high risk of developing diabetes and cardiovascular disease (CV). Thus, patients with IFG are five times more likely to develop DM [3] and the cardiovascular risk is higher (nonfatal acute myocardial infarction [AMI]) and cerebrovascular events (relative risk [RR]: 1.19), with higher mortality rates (RR: 1.28), as compared to nondiabetic population [3]. On the other hand, GI is associated with a

higher risk of developing diabetes, as compared to IFG. This risk is six-fold higher that in patients with normal glycemia (RR: 6.02 [95%CI: 4.66–7.38]), and up to 12 times higher in patients with both associated (RR: 12.21 [95% CI: 4.32–20.10]) [3]. GI is also associated with a higher risk of cardiovascular mortality (RR: 1.48) and general death (RR: 1.66) [3].

These data, however, is challenged by a recent cohort study [4] conducted in a sample of older adults (mean age 75.6 years) who, despite the high prevalence of prediabetes (diagnosis of IFG and/or HbA_{1c}), restoration of normal glycemia, or death were more frequent than progression to diabetes. These results suggest that prediabetes may not be a solid diagnostic entity in older adults. Further research is needed in this population.

What can we do?

A diversity of studies has been conducted to assess the effectiveness of different pharmacological and non-pharmacological interventions in the prevention of diabetes and its associated cardiovascular comorbidities in patients with prediabetes [5–14]. The clinical benefits of primary prevention interventions for DM2 have been demonstrated in patients with GI, but not with IFG alone or in patients diagnosed with prediabetes based on HbA_{1c} levels.

Lifestyle and some antidiabetic drugs are effective in the prevention of DM. An analysis of recent studies on the effectiveness of lifestyle changes and pharmacological interventions is detailed below.

One of the latest studies on lifestyle changes is the *European Diabetes Intervention Study* [15], which is an extension of the Finnish study published in 2001 [9] and carried out in three European countries (Finland, United Kingdom and the Netherlands) to validate the findings of an initial Finnish study. After a 3.1 year follow-up, the incidence of DM decreased by 57% in the intervention group, as compared to the control group (hazard ratio [HR]: 0.42 [95% CI: 0.29–0.60], p<0.001). The incidence of DM was 65% lower in the participants who experienced a weight loss ≥ 5% 1 year after the intervention (HR: 0.35 [95%CI: 0.22–0.56], p<0.001). The incidence of diabetes further decreased in

Javier Escalada San Martín, Director, Department of Endocrinology and Nutrition, Clínica Universidad de Navarra, Avenida Pío XII, 36, 31008, Pamplona, Spain; Chair, Spanish Society of Endocrinology and Nutrition, Center for Biomedical Research Network on the Physiopathology of Obesity and Nutrition (CIBEROBN), Madrid, Spain; and Navarra Institute for Health Research (IdiSNA), Pamplona, Spain, E-mail: fescalada@unav.es
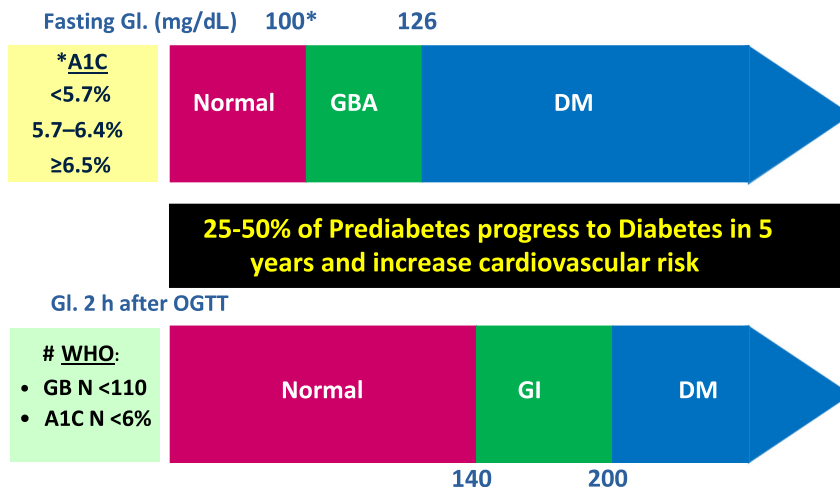
Figure 1: Diagnosis of preDM and DM (ADA* vs. WHO#).
ADA, American Diabetes Association; DM, diabetes mellitus; IFG, impaired fasting glucose; Gl, glycemia; GI, glucose intolerance; N, normal; WHO, World Health Organization; OGTT, oral glucose tolerance test.

patients who maintained a constant weight loss of ≥5% for 2 and 3 years (79 and 89% reduction, respectively) [15]. It is worth mentioning an intervention study on lifestyle habits undertaken by the DE-PLAN-CAT group in Spain, which revealed a 36.5% reduction in the incidence of diabetes after an average follow-up of 4 years [16].

In relation to pharmacological interventions for the prevention of diabetes, the highest reduction in progression to diabetes was obtained in the ACT-NOW study with pioglitazone [17], which achieved a 72% reduction in the treatment group, as compared to placebo, although it was accompanied with a weight gain of 3.9 vs. 0.8 kg (p<0.001) and an increase in the incidence of peripheral edema (12.9 vs. 6.4%; p=0.007). The *Diabetes Prevention Program* (DPP) study had previously demonstrated that metformin (850 mg/BID) was effective in reducing prediabetes progression to diabetes by 31%, as compared to placebo. Of note, a 51% reduction was achieved through lifestyle changes [10]. Finally, liraglutide (a GLP-1 receptor agonist) has also been proven to significantly reduce progression to DM2 (2% in the treatment group vs. 6% in the control group) in a 3-year follow-up study [18].

In patients with morbid obesity, the most effective approach was bariatric surgery (odds ratio 0.16 [95% CI: 0.11−0.24]) [17].

Conclusive data on its effect on cardiovascular morbidity and mortality has not been obtained due to the short duration of studies. Acarbose has demonstrated to be effective in reducing cardiovascular complications in the STOP-NIDDM study [12], but this finding is based on only 48 events, and its results should be interpreted with caution since assessing its effects on CV morbidity and mortality was not within the scope of this study.

A recent meta-analysis revealed that the use of lifestyle changes and medication in adult patients with prediabetes reduced the incidence of DM2 by 39 and 36%, respectively. Nevertheless, medication is less effective in the long-term (its effects are not maintained over time), whereas the effects of lifestyle changes are maintained after the intervention [19].

This study confirms previous results, as weight loss was found to be the primary factor associated with progression to DM2. The risk of progression to DM2 decreased by 7% per lost kilogram which, in clinical terms, is very relevant.

The accusation of "prediabetes business"

There is solid evidence about the beneficial effects of lifestyle interventions. However, the main limitation of these interventions is patient's difficulty in maintaining the recommended lifestyle changes; therefore, pharmacological prevention emerges as an alternative for some patients. Despite the data available on the effectiveness of pharmacological interventions in reducing the incidence of diabetes, the indication of hypoglycemic drugs for prediabetes has not yet been approved.

Some authors suggest that prediabetes is a diagnostic invention intended to make the population use medications unnecessarily [20]. This statement, however, is challenged by solid data. On the one hand, only ADA [21] clearly considers the possibility of using metformin in the prevention of DM2 in patients at a very high risk of developing diabetes, such as patients with GI (level of evidence A), IFG (E level), or HbA$_{1c}$ of 5.7−6.4% (E level), especially in the presence of a BMI >35 kg/m^2, age < 60 years (higher efficacy within this range of age demonstrated in the

DPP study) or in women with a previous diagnosis of gestational diabetes (A level of evidence). On the other hand, a study recently published in *Diabetes Care* revealed that the use of metformin in patients with prediabetes is <1%, which demonstrates that pharmacological interventions are not frequent in the prevention of DM2 [22].

Finally, after doubts were raised about the reality or relevance of prediabetes, research is increasingly focused on it as a real entity and its categorization into subtypes [23]. The different metabolic groups identified are associated with future complications associated with prediabetes, insulin resistance, future risk of DM2 and mortality. These subphenotypes might reflect key pathological features potentially associated with metabolic complications in the future. However, the purpose of phenotype identification is not to classify individual patients in clinical practice, but to provide guidance about the design of strategies for the prevention and management of cardiovascular and kidney diseases and DM2. We expect further news about this interesting condition to better understand prediabetes.

References

1. American Diabetes Association. Classification and diagnosis of diabetes: standards of medical care in diabetes—2021. Diabetes Care 2021;44(1 Suppl):S15-33.
2. Soriguer F, Goday A, Bosch-Comas A, Bordiú E, Calle-Pascual A, Carmena R, et al. Prevalence of diabetes mellitus and impaired glucose regulation in Spain: the Di@bet.es Study. Diabetologia 2012;55:88–93.
3. Santaguida PL, Balion C, Hunt D, Morrison K, Gerstein H, Raina P, et al. Diagnosis, prognosis, and treatment of impaired glucose tolerance and impaired fasting glucose. Evid Rep Technol Assess 2005;128:1–11.
4. Rooney MR, Rawlings AM, Pankow JS, Echouffo Tcheugui JB, Coresh J, Sharrett AR, et al. Risk of progression to diabetes among older adults with prediabetes. JAMA Intern Med 2021;181:511–9. e208774.
5. Soriguer F, Valdés S, Tapia MJ, Esteva I, Ruiz de Adana MS, Almaraz MC, et al. Validation of the FINDRISC (FINnish Diabetes RIsk SCore) for prediction of the risk of type 2 diabetes in a population of southern Spain. Pizarra Study. Med Clínica 2012;138:371–6.
6. Costa B, Barrio F, Piñol JL, Cabré JJ, Mundet X, Sagarra R, et al. Shifting from glucose diagnosis to the new HbA1c diagnosis reduces the capability of the Finnish Diabetes Risk Score (FINDRISC) to screen for glucose abnormalities within a real-life primary healthcare preventive strategy. BMC Med 2013;11:45.
7. Tuomilehto J, Lindstrom J, Eriksson JG, Valle TT, Hämäläinen H, Ilanne-Parikka P, et al. Finnish Diabetes Prevention Study Group. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. N Engl J Med 2001;344:1343–50.
8. Mata-Cases M, Artola S, Escalada J, Ezkurra-Loyola P, Ferrer-García JC, Fornos JA, et al. Consensus on the detection and management of prediabetes. Consensus and Clinical Guidelines Working Group of the Spanish Diabetes Society. Rev Clin Esp 2015;215:117–29.
9. Gerstein HC, Yusuf S, Bosch J, Pogue J, Sheridan P, Dinccag N, et al. Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomised controlled trial. Lancet 2006;368:1096–105.
10. Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, et al. Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 2002;346:393–403.
11. Pan XR, Li GW, Hu YH, Wang JX, Yang WY, An ZX, et al. Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance. The Da Qing IGT and Diabetes Study. Diabetes Care 1997;20:537–44.
12. Chiasson JL, Josse RG, Gomis R, Hanefeld M, Karasik A, Laakso M, et al. STOP-NIDDM Trail Research Group. STOP-NIDDM Trial Research Group. Acarbose for prevention of type 2 diabetes mellitus: the STOP-NIDDM randomised trial. Lancet 2002;359:2072–77.
13. Gillies CL, Abrams KR, Lambert PC, Cooper NJ, Sutton AJ, Hsu RT, et al. Pharmacological and lifestyle interventions to prevent or delay type 2 diabetes in people with impaired glucose tolerance: systematic review and meta-analysis. BMJ 2007;334:299.
14. Norris SL, Zhang X, Avenell A, Gregg E, Schmid CH, Lau J. Long-term non-pharmacological weight loss interventions for adults with prediabetes. Cochrane Database Syst Rev 2005;2:CD005270.
15. Penn L, White M, Lindström J, den Boer AT, Blaak E, Eriksso JG, et al. Importance of weight loss maintenance and risk prediction in the prevention of type 2 diabetes: analysis of European Diabetes Prevention Study RCT. PloS One 2013;8:e57143.
16. Costa B, Barrio F, Cabré JJ, Piñol JL, Cos X, Solé C, et al. Delaying progression to type 2 diabetes among high-risk Spanish individuals is feasible in real-life primary healthcare settings using intensive lifestyle intervention. Diabetologia 2012;55:1319–28.
17. DeFronzo RA, Tripathy D, Schwenke DC, Banerji M, Bray GA, Buchanan TA, et al. for the ACT NOW Study. Pioglitazone for diabetes prevention in impaired glucose tolerance. N Engl J Med 2011;364:1104–15.
18. le Roux CW, Astrup A, Fujioka K, Greenway F, Lau DCW, Van Gaal L, et al. SCALE Obesity Prediabetes NN8022-1839 Study Group. 3 years of liraglutide versus placebo for type 2 diabetes risk reduction and weight management in individuals with prediabetes: a randomised, double-blind trial. Lancet 2017;389:1399–409.
19. Haw JS, Galaviz K, Straus AN, Kowalski AJ, Magee MJ, Weber MB, et al. Long-term sustainability of diabetes prevention approaches: a systematic review and meta-analysis of randomized clinical trials. JAMA Intern Med 2017;177:1808–17.

20. Piller C. Dubious diagnosis. Science 2019;363:1026–31.
21. American Diabetes Association. Prevention or delay of type 2 diabetes: standards of medical care in diabetes-2021. Diabetes Care 2021;44(1 Suppl):S34-9.
22. Tseng E, Yeh HC, Maruthur N. Metformin use in prediabetes among U.S. Adults, 2005–2012. Diabetes Care 2017;40: 887–93.
23. Wagner R, Heni M, Tabák AG, Machann J, Schick F, Randrianarisoa E, et al. Pathophysiology-based subphenotyping of individuals at elevated risk for type 2 diabetes. Nat Med 2021;27:49–57.