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PERSPECTIVES

The STOP DIABETES study: when prevention works

Aldo Bonaventura[1,2] · **Fabrizio Montecucco**[3,4]

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Abstract
Although many drugs are now available, a large effort is still needed to prevent diabetes. The STOP DIABETES study evaluated individuals at risk for type 2 diabetes (T2D) by a 2-h 75-g oral glucose tolerance test (OGTT). Based on the three main defective physiological responses, subjects were stratified as at low, intermediate, or high risk, and treated accordingly with lifestyle modifications and drugs. Participants at intermediate and high risk experienced the greatest reduction of T2D conversion. Interestingly, a group of individuals developing T2D presented a normal glucose tolerance at baseline, but a 1-h plasma glucose concentration > 155 mg/dL. These results are critical as prediabetes can increase the incidence of cardiovascular disease. Considering the timeframe between the first defects in glucose metabolism and the manifestation of diabetes complications, the effort to tackle the glycemic impairment as soon as possible represents an outstanding task to reduce the incidence of diabetes. Ideally, the earlier glycemic alterations are recognized, the lesser armamentarium needs to be used, and the lower is the expense in terms of drugs, complications, and related events and costs. Finally, a wealth of studies clearly demonstrated the importance of 1-h plasma glucose concentration, which has been proposed as an adjunctive diagnostic tool to detect prediabetes earlier. In conclusion, by an OGTT, a lot of individuals at risk for T2D may be detected when the central role for the 1-h plasma glucose concentration is also considered. Consequently, these subjects would be treated early and with less drugs and delay T2D complications.

Keywords Diabetes · Prediabetes · 1-h post-load plasma glucose · OGTT · Prevention

Since diabetes incidence is continuously growing [1], great efforts are needed to cope with this pandemic. To date, a large number of new anti-diabetic drugs are marketed, which would be able to target not only glycemic fluctuations, but also the higher cardiovascular risk shared by patients with type 2 diabetes (T2D) [2].

The recently published Successful Treatment of Prediabetes (STOP DIABETES) study [3] poses the attention on the issue of diabetes prevention, suggesting that a pathophysiological approach to T2D can represent a winning strategy. STOP DIABETES is a retrospective, observational study among people at increased risk to develop T2D from a community practice in southern California (USA). After individuals at intermediate or high risk for T2D have been identified based on risk factors, they have performed a 2-h 75-g oral glucose tolerance test (OGTT) to determine plasma glycemia, insulin, and C-peptide concentrations every 30 min. From the determination of the three physiological responses—glycemic response (considering both normal glucose tolerance after 2 h and 1-h plasma glucose concentration < 155 mg/dL), insulin sensitivity, and β-cell response, the severity of abnormalities has been considered mild, moderate, or severe, and consequently individuals stratified as at low, intermediate, or high risk. Based on risk stratification, subjects have been recommended no treatment

Managed by Massimo Federici.

✉ Aldo Bonaventura
aldo.bonaventura@edu.unige.it;
aldo.bonaventura@vcuhealth.org

[1] First Clinic of Internal Medicine, Department of Internal Medicine, University of Genoa, 6 viale Benedetto XV, 16132 Genoa, Italy

[2] Division of Cardiology, Department of Internal Medicine, Pauley Heart Center, Virginia Commonwealth University, Richmond, VA, USA

[3] First Clinic of Internal Medicine, Department of Internal Medicine and Centre of Excellence for Biomedical Research (CEBR), University of Genoa, 6 viale Benedetto XV, 16132 Genoa, Italy

[4] IRCCS Ospedale Policlinico San Martino-Italian Cardiovascular Network, 10 Largo Benzi, 16132 Genoa, Italy

(low risk), metformin 850 mg/daily + pioglitazone 15 mg/daily + lifestyle modifications (intermediate risk), and metformin 850 mg/daily + pioglitazone 15 mg/daily + glucagon-like peptide-1 receptor agonist (GLP-1RA) based on insurance coverage (exenatide 10 μg twice daily, liraglutide 1.2 mg daily, exenatide extended release 2 mg weekly, or dulaglutide 1.5 mg weekly) + lifestyle modifications (high risk). During the follow-up period (mean 32.09 months), 28 participants developed T2D based on American Diabetes Association (ADA) criteria, with an annual incidence progressively decreasing with the increase in risk and no participant at high risk converting to T2D [3]. Moreover, the risk for progression to T2D reduced by 71% and 88% for participants at intermediate and high risk, respectively. Similarly, normal glucose tolerance has been restored in parallel with the increased risk as well as insulin sensitivity and β-cell function have been significantly improved in those participants receiving pharmacological treatment.

The first aspect to underpin is represented by the importance of the OGTT in showing pathophysiological disturbances preceding the overt manifestation of T2D. In particular, the "ominous octet" as depicted by DeFronzo [4] is needed to be kept in mind when dealing with patients at risk for developing T2D. In addition, when an impaired glucose tolerance is discovered, subjects have lost more than 80% of their β-cell function [4] corresponding to a large derangement of the pancreas in controlling glycemic fluctuations both in the fasting state and especially after meals. It is evident that, at this time, a much greater effort is requested to manage T2D, which can be frustrating for the patients asked for a stricter glycemic control and a higher number of drugs. Moreover, a poor glycemic control can also pave the way to complications [5], which, in turn, would constitute a further burden for the patients and their families. For these reasons, the only way to get as more information as possible from a single test still remains the OGTT, which also represents a fast, cheap, and efficient way to understand at which step the disease has come. In fact, in the natural history of diabetes, defects impairing the pancreatic β-cell start at least 10 years before T2D is diagnosed. In addition, OGTT represents the only way to diagnose an impaired glucose tolerance during the T2D screening, as witnessed by trials aiming at T2D prevention [6, 7], considering that the standardization of OGTT has reduced the variability previously acknowledged as a partial limitation of this diagnostic tool [8]. Finally, following the data about the regression from prediabetes to normal glucose tolerance of the Diabetes Prevention Program [9], it appears clear that only the OGTT can address the effective clinical weight of preventive strategies. Moreover, as prediabetes is associated with an increased cardiovascular risk, OGTT may have a pivotal role in this task [10], although Huang et al. [11] and Ford et al. [12] reported partially controversial conclusions. On the contrary, glycated hemoglobin (HbA1c) just allows to know how the glycemic trend was in the last 3 months, but fails to provide substantial information on pancreatic β-cell impairment, especially for HbA1c values < 7% [13].

Another interesting issue arising from the STOP DIABETES study is the coordinated pharmacological treatment directly targeting T2D defects, thus resulting in a marked reduction of progression to overt T2D. Getting back in touch with what oft-reported, the modern model for the management of T2D should include an intensive treatment at the earliest stages of the disease by tackling the peculiar defects of T2D. DeFronzo and colleagues already tested this hypothesis in the Efficacy and Durability of Initial Combination Therapy for Type 2 Diabetes (EDICT) study, demonstrating that a combination of metformin, pioglitazone, and exenatide reduced HbA1c in a greater manner compared to a traditional approach sequentially including metformin, sulfonylureas, and insulin [14]. The novelty of the STOP DIABETES study resides in the application of the pathophysiological-based therapeutic approach in a real-world context to prevent the development of T2D in subjects at high risk. This kind of approach was effective in that the risk for progression to T2D reduced by 71% and 88% for participants at intermediate and high risk, respectively, while no participant at high risk converted to T2D [3]. This strategy proved to be feasible in term of costs giving that all drugs were cheap and provided to the lower dosage. Moreover, considering that the time for generic GLP-1RAs approaches, their cost will decrease considerably in the next years. Finally, "the more we do, the best is" is likely to be not true for T2D prevention, considering that low drug dosages were chosen resulting effective in any case.

An item that deserves to be discussed deals with the 1-h plasma glucose concentration (1-h PG) during the OGTT. Considering that prospective epidemiological studies demonstrated that nearly 40% of participants developing T2D presented a normal glucose tolerance at baseline [15], great attention must be paid to subjects with 1-h PG > 155 mg/dL as they share a high risk to convert to T2D with those with impaired glucose tolerance [16, 17]. In the STOP DIABETES study, about a quarter of participants presented a normal glucose tolerance, but a 1-h PG > 155 mg/dL. As a further proof of it, these individuals showed a higher annual incidence of T2D compared to those with impaired fasting glucose or impaired glucose tolerance or both [3]. Although the 1-h PG is not currently recommended by the ADA to recognize high-risk individuals, a large number of studies clearly suggests its usefulness in recognizing subjects with normal glucose tolerance at increased risk for developing T2D [18, 19]. Alyass et al. described in nearly 5000 subjects from the Botnia and the Malmö Prevention Project (MPP) cohorts that the 1-h PG was a reliable tool to detect individuals at risk for developing T2D [20]. Interestingly, the 1-h PG

outperformed age, sex, body mass index, and family history of T2D in the Malmö Prevention Project cohort and HbA1c in the Botnia cohort in the prediction of T2D [20]. With regard to the latter, Abdul-Ghani et al. confirmed that HbA1c alone was a weaker predictor of future T2D risk compared to 1-h PG [21]. In addition, subjects with 1-h PG ≥ 155 mg/dL were shown to present a decreased β-cell function [19, 22, 23], a recognized pathophysiological defect of overt T2D. Jagannathan et al. demonstrated that the 1-h PG ≥155 mg/dL was a more precise correlate of insulin sensitivity and β-cell function than HbA1c [24]. The 1-h PG was also found to correlate more strongly with the acute insulin response compared with 2-h post-load plasma glucose [25]. Moreover, the 1-h PG was proven to increase the risk for microvascular disease, myocardial infarction, fatal ischemic heart disease, and mortality when the 2-h glucose was < 140 mg/dl [26]. Indeed, in a real-world clinical practice setting, the 1-h PG ≥155 mg/dL was found to be superior for detecting high-risk individuals compared to HbA1c [24]. By the way, Fiorentino et al. investigated these aspects, showing that the 1-h PG together with HbA1c can help identifying subjects with prediabetes with a higher cardiovascular burden (evaluated by intima-media thickness and pulse pressure as surrogate markers of early atherosclerosis and cardiovascular disease) [27]. Similarly, in individuals without diabetes, the combination of the 1-h PG ≥155 mg/dL and HbA1c has been found to identify those subjects at risk for developing a composite of cardiovascular disease (coronary artery and cerebrovascular disease) and individual coronary artery disease [28]. In light of the increasing importance of the 1-h PG documented by a wealth of studies, a group of experts in diabetes claimed a petition to propose that the 1-h PG, during the 75-g OGTT, should be used to detect prediabetes earlier than the current screening criteria [26].

The early identification of individuals with prediabetes at high risk to develop T2D is of utmost importance to limit the progressive development of classical pathophysiological mechanisms of T2D, especially the deterioration of β-cell function, finally increasing the incidence of microvascular complications and mortality [29]. This would also mean to simplify the management of these patients by addressing them first to lifestyle modifications explaining their importance, so that only later pharmacological treatment will be taken into account based on defects highlighted during the 75-g OGTT. Last but not least, when the diagnosis of prediabetes and T2D is anticipated, a greater reduction of healthcare costs is likely to be provided due to the poor need of an expensive pharmacological treatment and the potential slowing or blocking of diabetic complications and their consequences in terms of outpatient visits and hospitalizations [30].

In conclusion, we believe that a wider group of individuals at risk for developing T2D should be screened to find as soon as possible those subjects with prediabetes at high risk for T2D or those with T2D at the very beginning of the disease. Indeed, the decline of the β-cell function is known to start several years before T2D diagnosis with the progressive increase in fasting glycemia peaking 2 years before diagnosis as a result of an acute β-cell decompensation [31], as confirmed by the 50% reduction of β-cell mass at the time of T2D diagnosis [32]. Actually, the most likely scenario may include a variable combination of loss of mass and function of pancreatic β-cells in T2D considering the close relationship between mass of pancreatic β-cells and insulin secretion [33]. The easiest tool to assess these aspects remains the 75-g OGTT, with a particular attention to the 1-h PG. In this view, an update of criteria for T2D diagnosis and prediabetes screening based on the OGTT is mandatory to not exclude from diagnosis a group of subjects with normal glucose tolerance, but with an elevated risk for developing T2D [34].

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

Ethical approval This article does not contain any studies with human participants performed by any of the authors.

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