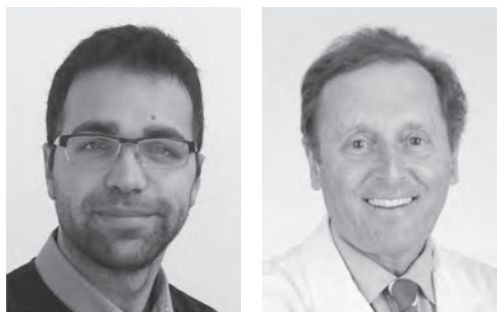


Will we ever cure diabetes?



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“Type 2 diabetes mellitus is one of the most prevalent noncommunicable diseases claiming millions of victims around the world.”

Type 2 diabetes (T2DM) is a chronic metabolic disorder characterized by hyperglycemia due to an imbalance between insulin requirement and insulin production. T2DM is one of the most prevalent noncommunicable diseases claiming millions of victims around the world. The International Diabetes Federation defines diabetes as a “huge and growing problem”: the total number of people with diabetes in 2013 worldwide is approximately 382 million, more than 5 million people die for diabetes and many more suffer from diabetes related complications [1]. It is therefore worrisome that the pandemic of T2DM is so far from stopping: the global prevalence of T2DM is expected to rise from 8.3% to 10.1% by 2035 with approximately three new cases every 10 seconds, or almost 10 million per year. Even if with some differences, this trend is almost the same independently from regions, with no country showing a reversal trend.

Luckily there is a large-scale effort to face the global burden of diabetes and its

complications. Billions of Euros are spent to cure diabetes and even more to support diabetes research. When searching for ‘diabetes mellitus’ on ClinicalTrials.gov, the largest clinical trials database in the world, run by the US National Library of Medicine at the National Institutes of Health, 10,527 studies are found, mostly conducted in the USA, Europe and China [2]. Moreover, thousands of basic research studies are daily carried out and millions of scientists, biomedical engineers, biologists and medical doctors work to fight T2DM and to improve the quality of life and the prognosis of people with T2DM. Altogether these efforts made available a broad spectrum of therapies to doctors involved in the cure of T2DM with ten pharmacological classes of oral and injectable drugs/hormones and more than 25 molecules associable with each other in several combinations are to date at the fingertips of diabetologists. While this is, of course, richness for clinicians, on the

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other hand the so widely available therapeutic options can comprehensively cause difficulties in the choice and in the management of the appropriate therapy, but a smart approach can turn this therapeutic complexity from a problem into an opportunity [3]. Sadly, despite the large number of available treatment strategies, the overall results of therapies for diabetes are not really satisfactory. T2DM is still the second cause of disability-adjusted life years lost [4] and in most countries it is the leading cause of deaths. In particular, subjects with T2DM continue to have excess cardiovascular morbidity and mortality compared with the general population. The risk for T2DM individuals to develop cardiovascular diseases is at least two fold than those without T2DM [5]. Even multifactorial approaches including lowering of blood pressure, levels of cholesterol and blood glucose, and smoking cessation do not completely eliminate the increased cardiovascular risk associated with T2DM. In this view, new approaches to halt cardiovascular events in subjects with T2DM are needed.

“...type 2 diabetes mellitus can be defeated by targeting several weak points.”

Since diabetes is a multifaceted disease, personalized medicine has been proposed as the answer to the failure of standardized treatments [6], but some unmet medical needs still prevent the achievement of a satisfactory cure for T2DM. In particular, new drugs for T2DM should be simple to administer without onerous glucose monitoring requirements, not to impact the quality of life of patients and thus increasing their compliance. Crucially, new therapies should have no long-term adverse effects such as further increasing patients' cardiovascular risk or promoting weight gain or hypoglycaemia [7].

To overcome current limitations in the cure of overt T2DM and since the etiology of T2DM is multifactorial and involves a complex interaction between genetic, epigenetic and environmental factors, T2DM can be defeated by targeting several weak points. Physical inactivity, weight gain and a large intake of unhealthy food have been demonstrated to be independent risk factors for the development of insulin resistance, metabolic syndrome and T2DM. More importantly, all these are modifiable risk factors and thus appealing targets for preventive strategies. Large-scale randomized controlled trials have been conducted to evaluate the

feasibility and effectiveness of lifestyle interventions in preventing T2DM in individuals at high risk of developing T2DM. Behavioral strategies for the reinforcement of prescribed changes in nutritional intake, physical activity or both, with and without pharmacological treatments, are the main preventive strategies studied to reduce the incidence rate and to ameliorate risk factor profiles associated with both T2DM and cardiovascular morbidity and mortality [8]. The Da Quing IGT and Diabetes Trial and the Study on Lifestyle Intervention and IGT Maastricht showed that the combination of diet and physical exercise prevents the onset of T2DM in subjects with impaired glucose tolerance, even after quite long follow-up [9,10]. On the contrary, trials evaluating the effectiveness of pharmacological interventions versus physical activity showed that drugs, with the exception of thiazolidinediones, lose their beneficial effect after discontinuation, indicating that they do not change the natural history of the disease [11,12].

Thus, overall results of the major trials indicate that the best strategy that stands out as effective in the sustained prevention of T2DM is the implementation of a healthy lifestyle through the promotion of regular physical activity and consumption of a healthy diet. In this view, to decrease the risk of T2DM on national scales, governments can either encourage healthy lifestyles by making more information and services available, or they can attempt to legislate, for example, against unhealthy foods. This can be of particular interest for developing countries, where there is the most alarming increase of diabetes prevalence. Obesity thrives in low-income communities due to the invasion of junk food and sedentary lifestyle in people possibly with thrifty genotype [13]. Interventions that have been shown to improve those environments include subsidies to farmers' markets and more healthful school lunches, as well as investments in the creation of bicycling and walking trails [14]. An open issue is to recognize who can really take advantage from large-scale prevention programs: for sure, people affected by impaired glucose tolerance or impaired fasting glucose and obese people can benefit from preventive strategies but perhaps we can act earlier. We know now that atherosclerosis begins in childhood. Hence, starting treatment of risk factors early in life is essential to prevent cardiometabolic diseases later: a guiding maxim is that pre-adult health has direct consequences

during adulthood. In this view, the best prevention starts in childhood. Estimates of the number of overweight infants and children in the WHO European Region rose steadily from 1990: data from the Health Behaviour in School-Aged Children study show a prevalence of overweight and obesity of 5–25% in 36 countries in the WHO European Region [15]. A similar prevalence was registered in the USA by the Centers for Disease Control and Prevention (17%) [16]. Worryingly, children are now more frequently subject to many obesity-related health conditions once confined to adults [17,] and over 60% of children who are overweight before puberty will be overweight in early adulthood [18]. This is of particular concern as this means that they are at much higher risk for Type 2 diabetes, heart disease and stroke, thus greatly increasing the burden on health services [19]. Currently there is a universal agreement that toddlers and preschoolers should have television exposure limited to less than 2 h a day, and infants should have no television exposure at all. Moreover, young

people should participate in physical activity for at least 1 h every day. From a metabolic point of view, the future of the world depends on our children's future.

In conclusion, while a definitive cure for T2DM still remains elusive and far to be achieved, we definitely have weapons to prevent it. Nowadays the best approach to defeat diabetes is to prevent it and not to cure it. In this view, there is an urgent need to address the socio-economic, behavioral and public health issues responsible for the T2DM epidemic.

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