

# Preventing Type 2 Diabetes Mellitus: A Call for Personalized Intervention

Harry Glauber, MD; Eddy Karnieli, MD

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## Abstract

In parallel with the rising prevalence of obesity worldwide, especially in younger people, there has been a dramatic increase in recent decades in the incidence and prevalence of metabolic consequences of obesity, in particular prediabetes and type 2 diabetes mellitus (DM2). Although approximately one-third of US adults now meet one or more diagnostic criteria for prediabetes, only a minority of those so identified as being at risk for DM2 actually progress to diabetes, and some may regress to normal status. Given the uncertain prognosis of prediabetes, it is not clear who is most likely to benefit from lifestyle change or medication interventions that are known to reduce DM2 risk. We review the many factors known to influence risk of developing DM2 and summarize treatment trials demonstrating the possibility of preventing DM2. Applying the concepts of personalized medicine and the potential of “big data” approaches to analysis of massive amounts of routinely gathered clinical and laboratory data from large populations, we call for the development of tools to more precisely estimate individual risk of DM2.

## Introduction

Recent decades have seen a dramatic rise in the incidence and prevalence of childhood and adult obesity, physical inactivity, glucose intolerance, metabolic syndrome, and type 2 diabetes mellitus (DM2) throughout the world. It is predicted that by 2030 almost 10% of the world's population will have diabetes mellitus (DM) (overwhelmingly type 2).<sup>1</sup> Because obesity and DM2 are associated with a wide range of serious chronic health complications affecting renal, neurologic, retinal, cardiac, and vascular systems with consequent decreased life span, the anticipated impact on global health and health care costs is enormous. The International Diabetes Federation estimated that in 2012, more than 371 million people worldwide had DM and that treating DM accounted for at least \$471 billion (11% of total health care expenditures in adults).<sup>2</sup> Although numerous medical treatments and advances in recent years have somewhat reduced the impact of DM2 and its complications, in practice less attention is given to primary prevention of DM2.<sup>3</sup> Although a large body of literature<sup>4-7</sup> provides a basis for recognizing increased risk

for DM2 and high-quality clinical studies provide evidence for effective interventions to reduce or delay DM2 onset, less research has been carried out to provide individuals with useful estimates of their personal probability of developing DM2 (absolute risk) and of the potential impact of preventive interventions. We will use the lens of personalized medicine and evidence-based medicine to review the concept of prediabetes and the evidence supporting the possibility of preventing DM2 onset.

As scientific and clinical knowledge advances, it becomes increasingly difficult for practitioners to stay current with basic scientific and clinical research, including newly recognized molecular mechanisms, and recent medical and therapeutic guidelines and their use in the clinic or at the bedside. Development of strategies and tools to bridge this knowledge-implementation gap is increasingly urgent. Medically relevant and novel scientific discoveries can already be applied to assess risk factors at the genomic level for chronic diseases like cancer and DM as well as the sensitivity to and efficacy of drug therapy using tools like bioinformatics and

pharmacogenomics. These fields together with the evolving fields of proteomics and metabolomics constitute the premise and promise of personalized medicine.<sup>8,9</sup>

Evidence-based medicine seeks to narrow the gap between research and practice by explicitly and conscientiously focusing the attention of clinicians on the current best evidence, as determined by epidemiologic and clinical trial methodologies. Specifically, evidence-based medicine promotes the judicious use of meta-analyses of randomized controlled trials and other sources of knowledge for clinical decision making. However, an inherent weakness of a meta-analytic focus is that individual patients present with a large degree of variability regarding the manifestation of disease states, symptoms, comorbidities, genetic predisposition, and variance in molecular sensitivity to drugs. Guidelines derived from meta-analyses of large studies of selected populations cannot reflect this variation. Furthermore, lack of knowledge about evolving discoveries results in slow translation to new diagnostic and treatment modalities and slow implementation of these modalities in routine clinical practice. Given the considerable health and economic impact of DM2, there is an understandable interest in identifying those individuals who are at greatest risk of developing DM2, in order to apply measures that are proven to delay or prevent progression to DM2 and its subsequent complications.

## Defining Increased Risk

The disordered metabolic state of DM2 is characterized by elevated levels of glucose resulting from reduced effectiveness of insulin on its target tissues and a relative reduction in secretion of insulin. The precise glucose levels at which DM2 is diagnosed are necessarily arbitrary (based

**Harry Glauber, MD**, is an Endocrinologist at the Sunnyside Medical Center in Clackamas, OR, and former Visiting Scientist at the Galil Center for Telemedicine, Medical Informatics and Personalized Medicine at RB Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel. E-mail: [harry.glauber@kp.org](mailto:harry.glauber@kp.org). **Eddy Karnieli, MD**, is the Chief of the Institute of Endocrinology, Diabetes and Metabolism at Rambam Medical Center; Director of the Galil Center for Telemedicine, Medical Informatics and Personalized Medicine and Professor of Medicine at RB Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel. E-mail: [eddy@rambam.health.gov.il](mailto:eddy@rambam.health.gov.il).

mainly on the threshold for presence of background retinopathy in epidemiologic studies),<sup>10</sup> such that many people without the formal diagnosis of DM2 nevertheless have abnormally elevated levels of glucose, along with a degree of insulin resistance and inadequate insulin secretion. Their risk for microvascular and macrovascular complications increases continuously with worsening glucose tolerance, from normal to overt DM2.<sup>11</sup>

Criteria for determining increased risk for DM2 have changed with time and have been based on fasting or postchallenge glucose or, most recently, hemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>) testing.<sup>12</sup> On the basis of current American Diabetes Association recommendations, increased risk for DM2 (often termed *prediabetes*) may be identified in 1 of 3 ways: a) fasting plasma glucose of 100-125 mg/dL (characterized as impaired fasting glucose), b) glucose 2 hours after a 75-g oral glucose challenge of 140-199 mg/dL (impaired glucose tolerance), or c) HbA<sub>1c</sub> test result of 5.7%-6.4%.<sup>10</sup> It should be recognized that these criteria (fasting glucose, postchallenge glucose, and HbA<sub>1c</sub>) do not identify identical groups of people and that pathophysiology and susceptibility to complications may differ. For example, the risk for macrovascular complications may be greater in those with impaired glucose tolerance than in those with impaired fasting glucose.<sup>13</sup> Furthermore, laboratory results can vary from one test to the next because of analytic and biologic variability; and even within the "normal" range of glucose there is a continuum of increasing risk for development of DM2.<sup>14,15</sup>

Although the prevalence of prediabetes is now as high as 35% of US adults (50% of those age 65 years and older), as few as 3% of these may develop DM2 each year.<sup>16</sup> Even with the categorical diagnosis of prediabetes, an individual's risk for progression to DM2 over 5 years can vary from 100% (for those with HbA<sub>1c</sub> = 6.0%-6.4% and fasting plasma glucose = 116-125 mg/dL) to close to 0% (for those with HbA<sub>1c</sub> < 6% and fasting plasma glucose < 110 mg/dL), on the basis of prospective studies in a Japanese population.<sup>17</sup> Thus, a more precise individual estimate of absolute risk for developing DM2 is highly desirable. Although most research studies report relative risks or odds ratios

for a disease or other outcome, what is most important for each patient is their individual absolute risk.

Intervention studies employing dietary change, exercise, weight loss, and a range of medications have shown that these meaningfully delay or reduce risk for progression to DM2, making it a priority to identify those individuals with the highest risk for progressing to DM2 and the greatest likelihood of benefiting from these interventions. As the diagnostic threshold for prediabetes is lowered, preventive interventions become increasingly less cost-effective.<sup>18</sup> Available preventive measures differ in their effectiveness, tolerance, cost and availability, persistence of effect, and acceptability to patients. Thus, there are implications for public health and resource utilization, as well as clinical implications in the precise estimation of individual risk for developing DM2 and prediction of individual response to preventive interventions.<sup>19</sup> There is also value in providing reassurance to those individuals who acquire the diagnostic label of prediabetes, who nevertheless do not have a greatly increased absolute risk for progression to DM2.

### An Overview of Diabetes Prevention Interventions

**Lifestyle:** Observational studies associate a healthy lifestyle (for example, regular physical activity, moderate alcohol consumption, abstinence from smoking, healthy diet, and avoidance of overweight) with a greatly reduced risk for developing DM2.<sup>20</sup> A number of dietary and lifestyle intervention studies have demonstrated ability to favorably affect DM2 incidence in those at increased risk.<sup>21</sup> These include the Finnish Diabetes Prevention Study,<sup>19</sup> the US Diabetes Prevention Program (DPP),<sup>22</sup> the China Da Qing Diabetes Prevention Study,<sup>23</sup> and the Japanese Zensharen Study for Prevention of Lifestyle Diseases.<sup>24</sup> A meta-analysis found that lifestyle interventions can reduce DM2 incidence by 50%.<sup>25</sup> In the DPP, which recruited 3234 subjects with impaired glucose tolerance, an intensive lifestyle intervention with the goal of losing 7% of body weight and increasing physical activity to 150 minutes per week reduced DM2 incidence over 3 years from 29% in the control group to 14% in

the intervention group. Follow-up studies showed persistence of protection for up to 10 years.<sup>26</sup> The strongest predictor of DM2 prevention was weight loss, yet only about half the subjects achieved the weight loss goal, and fewer maintained this goal for the duration of the study. Risk of DM2 was 16% lower for every kilogram of weight lost.<sup>27</sup> Those who attained normal results at least once on annual glucose tolerance testing during either treatment arm of the DPP were about half as likely to develop DM2 during long-term follow-up.<sup>28</sup> Subgroups more likely to respond to the lifestyle intervention were older subjects, and those who more frequently monitored caloric and fat intake, and those who were more physically active.<sup>29</sup> The lifestyle intervention component of the DPP was resource intensive, and not necessarily easy to replicate for the entire population. Nevertheless, a range of potentially less costly interventions led by professionals or nonprofessionals provides opportunities to effectively implement lifestyle change for DM2 prevention.<sup>30</sup> Technology (eg, smart phone-based and DVD-based coaching programs) has potential to greatly expand access to effective interventions for large numbers of individuals at high risk.<sup>31,32</sup> Simulation modeling suggests that a national screening and intervention program to prevent DM2 onset would provide long-term cost savings.<sup>33</sup> Cost-effectiveness decreases with decreasing risk for DM2, making it a priority to improve stratification of individual risk for progression to DM2. Primary prevention of DM2 is now a national priority in the US, spearheaded by the Centers for Disease Control and Prevention's National Diabetes Prevention Program.<sup>34</sup> This program is working to bring evidence-based lifestyle change interventions to communities across the nation. It will also be critical to focus on social and environmental determinants of unhealthy lifestyles,<sup>35</sup> especially opportunities to acquire healthy dietary and physical exercise habits in schools.

**Pharmacotherapy:** One of the 3 treatment arms of the DPP study used metformin 850 mg twice daily, which resulted in a 31% reduction in DM2 incidence relative to the placebo arm (a smaller effect than the 58% reduction seen with the lifestyle intervention).<sup>22</sup> Cost-effectiveness analysis of DPP interventions suggests that metformin,

although not as effective as lifestyle change, is less costly and has a more sustained effect to prevent DM2 and may therefore actually offer cost savings during a 10-year period.<sup>36</sup> Subgroups more likely to respond to metformin include younger patients, obese patients, and women with a history of gestational DM. Conversely, the lifestyle intervention was particularly effective in preventing DM2 in the older subgroup of DPP participants.<sup>37</sup> Other drugs investigated for prevention of DM2 onset include insulin,<sup>38</sup> thiazolidinediones,<sup>39</sup> intestinal lipase inhibitor,<sup>40</sup> and  $\alpha$ -glucosidase inhibitors.<sup>41</sup> However, there are concerns about either the limited efficacy, safety, or tolerability of these drugs, so they are unlikely to be used widely for prevention.

**Bariatric surgery:** In contrast to robust data demonstrating efficacy of bariatric surgery in treating or “curing” DM2, there are no adequately powered, prospective randomized studies of its impact on prevention of DM2 in obese subjects without DM2. A recent report from the nonrandomized Swedish Obese Subjects trial suggested that surgically treated patients have a substantially reduced risk of progression to DM2 (hazards ratio = 0.17) for up to 15 years.<sup>42</sup>

**Predicting Diabetes Risk**

Numerous patient-level historic, clinical, biochemical, and genetic risk factors for development of DM2 have been identified (Table 1), and a range of pre-

dictive models have been proposed to more precisely estimate risk.<sup>47</sup> A variety of models have been developed by incorporating simple clinical parameters (eg, age, weight or body mass index, family history of DM2, and blood pressure); basic laboratory measures (eg, glucose and lipid levels)<sup>43</sup>; or more complex inflammatory, biochemical, and genetic markers. Such models typically use relative rather than absolute risk and explain more than 80% of the variance in DM occurrence in the population studied (area under the curve  $\geq 0.8$ ).<sup>44</sup> Existing tools that do provide an estimate of absolute risk for DM2 use categorical rather than continuous variables and do not incorporate HbA<sub>1c</sub>, which is superseding glucose testing. To date at least

<b>Table 1. Variables of potential value in models predicting individual risk for type 2 diabetes mellitus<sup>a</sup></b>	
Simple clinical variables	<b>Age, sex, weight/BMI, waist-to-hip ratio or waist circumference, percentage body fat, BP</b>
	<b>Ethnicity, family history of DM2</b>
	Habitual physical activity (exercise as vital sign)
	Sleep duration <sup>1</sup>
	Use of tobacco, alcohol, caffeine
Comorbid medical conditions	Hypertension/use of BP-lowering medications, dyslipidemia, ASCVD
	Depression, PCOS, sleep apnea, nonalcoholic fatty liver disease <sup>2</sup>
	Use of potentially diabetogenic medications <sup>b</sup>
Medical history	Gestational DM, birth weight, SGA status, maternal history of gestational DM, adolescent weight and weight trend, adolescent glucose and glucose trends, history of glucose normalization with prior lifestyle intervention
Simple laboratory variables	<b>Fasting blood glucose, nonfasting blood glucose, HbA<sub>1c</sub></b>
	<b>Cholesterol, HDL/LDL, triglyceride</b>
	Uric acid, ferritin, iron/transferrin saturation, WBC, ALT, AST, GGT, alkaline phosphatase
Specialized laboratory information unlikely to be available in large clinical data sets	Markers of beta-cell function <sup>c</sup>
	Systemic inflammatory markers and additional novel biomarkers, <sup>3</sup> including markers of endothelial cell dysfunction and adipocytokines, especially adiponectin <sup>4</sup>
	Metabolic and proteomic information <sup>d</sup>
	Genomic information
	Oxidative stress and energy expenditure biomarkers

<sup>a</sup> Items in boldface appear most commonly in existing DM2 prediction models.  
<sup>b</sup> Glucocorticoids, atypical antipsychotics, antiretrovirals.  
<sup>c</sup> Basal hyperinsulinemia is a strong predictor of risk of metabolic deterioration.<sup>5</sup>  
<sup>d</sup> Circulating levels of aromatic and branched-chain amino acids are independent predictors of insulin resistance.<sup>6</sup>

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ALT = alanine aminotransferase; ASCVD = atherosclerotic cardiovascular disease; AST = aspartate aminotransferase; BMI = body mass index; BP = blood pressure; DM = diabetes mellitus; DM2 = type 2 diabetes mellitus; GGT = gamma glutamyl transferase; HbA<sub>1c</sub> = hemoglobin A<sub>1c</sub>; HDL = high-density lipoprotein; LDL = low-density lipoprotein; PCOS = polycystic ovary syndrome; SGA = small for gestational age; WBC = white blood cells.

**Table 2. Type 2 diabetes mellitus preventive measures preferred for different types of patients**

Patients	Preferred preventive measure
Older age	Lifestyle changes
History of gestational diabetes mellitus	Metformin
Failure to normalize glucose tolerance with lifestyle	Metformin
Long history of obesity and/or many prior attempts at weight loss	Metformin
Low levels of physical activity	Lifestyle changes

100 genetic variants contributing to DM2 have been identified,<sup>45</sup> but these account for less than 5% of cases. Earlier studies of a limited number of DNA markers showed only modest additional value of adding genetic data to clinical information in predicting risk for DM2.<sup>46-48</sup> Nevertheless, none of these predictive models have been adopted for everyday clinical use at the bedside and point of care.<sup>4,6,7</sup>

#### “Big Data” and Diabetes Prediction

None of the published DM2 risk prediction models have seen widespread adoption in clinical practice, and many lack adequate external validation in different settings and ethnic groups.<sup>44</sup> Thus, estimation of an individual's absolute risk for developing DM2 remains a challenge. One potential approach only recently becoming available is the use of very large clinical databases from diverse settings to develop, refine, and validate practical tools to predict individual absolute risk for developing DM2. The rapid increase in computer storage and database analysis capacity, along with the advent of comprehensive electronic medical record systems in recent years, has facilitated the aggregation of a vast amount of patient-level clinical data. An excellent example is the Surveillance, Prevention, and Management of Diabetes Mellitus (SUPREME-DM) project,<sup>49</sup> which has accrued clinical, laboratory, and pharmacy information for more than 15,000,000 individuals followed for 5 years, of whom about 1,000,000 are already known to have DM. The Northwest, Hawaii, Southern and Northern California, Colorado, and Georgia Regions of Kaiser Permanente are contributing to this data set. Tools to predict absolute DM2 risk will clearly need to take into account “missing data,” as clinically derived, real-world data sets will never contain all of the systematically gathered elements typical of a prospective

cohort study. Where possible, clinical and laboratory parameters (eg, weight, age, and glucose level) should be treated as continuous rather than categorical variables. The many factors and parameters known or suspected to be related to DM2 risk and that could be used in a “big-data” approach to DM2 risk predictions are summarized in Table 1. Collins et al provide an excellent overview of the issues affecting development of DM2 risk prediction models.<sup>6</sup> A recent overview of big data in health care highlights the wide variety of work in the business, information technology, and academic sectors that are only slowly making their way into the medical literature.<sup>50</sup>

With advances in affordability, quality, and quantity of genomic, metabolomic, and proteomic technology and knowledge, in combination with the ability to analyze and model vast amounts of real-world, patient-level clinical data, we expect a narrowing of the gap between knowledge and clinical practice and anticipate the development of user-friendly prediction tools that will provide: 1) individuals with the most accurate prediction of their shorter-term (1 to 2 years) and longer-term (3 to 5 years) absolute risks for developing DM2, and an estimate of the impact of available prevention measures on this risk; 2) clinicians with real-time decision-support tools in the electronic medical record at the point of care, allowing them to counsel each patient about their personal risk for developing DM2 and to implement the preferred preventive measures; and 3) provide health care systems and government/public health agencies with tools to refine population-level outreach to better recognize and manage risk for DM2 and to improve quality of care while reducing cost.

In the field of endocrinology and metabolism, a number of individual-level tools to predict absolute risk of a disease

or event are already in daily use and have proven helpful in assessing disease risk, determining treatment indications, and helping patients understand their anticipated benefit and risk from treatment. Examples include the Framingham Coronary Disease Risk Score<sup>51</sup> and the FRAX tool<sup>52</sup> for estimating osteoporotic fracture risk. Systematic study of the impact of such risk estimators on clinical outcomes is limited. However, there is evidence that they improve patient satisfaction with shared decision making<sup>53</sup> and improve the recommended clinical care.<sup>54</sup>

#### Conclusion

A large and growing number of people worldwide already have DM2 or are likely to develop DM2. Nevertheless, available evidence shows very low rates of identification and management of diabetes risk.<sup>3</sup> In the US Diabetes Prevention Program and similar studies, structured lifestyle change programs aiming to increase physical activity to 150 minutes per week and to achieve a 7% weight loss cut DM2 risk by more than half. Such interventions are especially effective in older people. On the basis of the drug treatment arm of the DPP, twice-daily metformin may be a cost-effective alternative for younger, obese people; women with a history of gestational DM; and those unsuccessful with lifestyle change (Table 2). It is possible to identify DM2 risk years or decades in advance on the basis of numerous personal, historic, and laboratory measures, although there is not yet a robust, user-friendly clinical decision-support tool to estimate absolute risk for individuals. Given the large population at risk for DM2 and given the cost and limitations of preventive interventions, there is increasing recognition that identification of those at greatest risk for progression to DM2 will maximize the cost-effectiveness of an intervention program.<sup>55</sup> It is likely that a big-data approach to personalized medicine will be such a tool, allowing personalized application of proven lifestyle and other primary prevention measures in the most

... clinical, laboratory, and pharmacy information has been accrued for more than 15,000,000 individuals followed for 5 years, of whom about 1,000,000 are already known to have DM.

efficient and cost-effective manner.<sup>56</sup> Until then, families, communities, and health organizations should encourage healthy eating and physical activity and should focus the most intensive DM2 prevention efforts on those at highest risk for progression to DM2. ❖

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### Begin To Dig The Well First

Hence the sages did not treat those who were already ill; they instructed those who were not yet ill ... . To administer medicines to diseases which have already developed and to suppress revolts which have already developed is comparable to the behavior of those persons who begin to dig a well after they have become thirsty, and of those who begin to cast weapons after they have already engaged in battle.

— Huang Ti (The Yellow Emperor), 2697-2597 BC, legendary Chinese sovereign and cultural hero, considered the initiator of Chinese civilization