Is Prediabetes Overdiagnosed? Yes: A Patient-Epidemiologist's Experience

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I was recently diagnosed with prediabetes, based on slightly elevated glycemia and no other risk factors. To allay my confusion and anxiety, I applied my epidemiology and health services research training to the scientific literature. My conclusion: I and many others are over diagnosed.

Type 2 diabetes is an internationally mushrooming public health problem with high morbidity and mortality.[1] It is the costliest chronic condition in the United States,[2] afflicting approximately 37 million people (11% of the population), 23% of whom are undiagnosed.[3] Diabetes is linked to our obesity epidemic, and disproportionately affects those with low incomes and people of color.

But prediabetes, intended to identify high-risk persons and prevent progression to diabetes, is a relatively new idea. And experts disagree vigorously regarding terminology, screening criteria, interpretation, and implications.

MY PREDIABETES JOURNEY

I am a healthy White female aged 62 years: normal weight, rigorous daily exercise, excellent diet, minimal family diabetes history (only my maternal grandfather). My new primary care physician (PCP) suggested rescreening after marginally elevated HbA_{1c} 6 months prior (6.1%; current normal US standard: 4.8% to 5.6%). She conveyed alarm. I asked worriedly if I could have diabetes despite marginal test results and lack of risk factors. "Oh yes!" she replied, I might have full-blown diabetes. My electronic health record (EHR) further fueled my concern: recent test results were flagged with red exclamation points, "H" for high, and standard, prediabetes, and glucose control ranges. Yet, patient education materials from my PCP and online didn't slot me into a risky category.

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VISUAL ABSTRACT

Meanwhile, I repeatedly encountered prediabetes messaging. A billboard depicted a bikini-clad woman on an inflatable ring, a shark below: "Risk of Shark Attack: 1 in 11.5 Million. Risk of Prediabetes: 1 in 3 Adults." My dentist told me so many patients were announcing they had prediabetes she had begun ignoring this "news."

The messaging distracted me by day and woke me at night. Was I on a runaway diabetes train? Would I beg, as my diabetic grandfather implored my grandmother, for morsels of prohibited food? When would my vision fail, a limb require amputation, or other terrible consequences occur?

On repeat testing, my HbA_{1c} was 5.9%; my PCP commented favorably, and we dropped the issue. But I remained anxious. Then I scrutinized my EHR and the literature. My HbA_{1c} was marginally elevated in 2007 (6.0%) and 2008 (5.9%). The standard range then was 4.5% to 6.1%, so my PCP was unconcerned. What changed?

PREDIABETES SCREENING & LABELING

Between 1979 and 1999, doctors commonly used 2 glucose tests (OGTT [oral glucose tolerance test], and FPG [fasting plasma glucose]) to capture an at-risk intermediate group.[4-6] A third test, HbA_{1c}, available in 1978 and originally for monitoring diabetes glucose control, subsequently became popular. HbA_{1c} is appealing because it is stable, doesn't require fasting, and reflects average blood glucose for 3-4 months prior. In 2001 the American Diabetes Association (ADA) lowered the impaired fasting glucose threshold and coined the term prediabetes; the World Health Organization (WHO) disagreed. In 2009 the International Expert Committee (IEC) (appointed by the ADA, the European Association for the Study of Diabetes, and the International Diabetes Foundation [IDF]) achieved consensus on HbA_{1c}-defined diabetes (>6.5%) and recommended eliminating the prediabetes risk group because of the risk continuum and inadequate progression data.[4-6] WHO agreed with prediabetes' problematic classification; other international organizations retained the category, but with stricter criteria (6.0% to 6.4%) than the ADA (5.7% to 6.4%). The IEC's caution is well-founded and relevant to my experience.

Concordance between the 3 prediabetes screening tests used in the United States (HbA_{1c}, FPG, and OGTT) is poor,[7] identifying different people and metabolic processes.[6] Prediabetes prevalence varies widely by test: from 4.3% to 43.5% using just 1 test; 2.5% using all 3; and 51.3% using any.[6]

United States' organizations disagree on prediabetes definitions and screening criteria. Over one-third of US adults

have prediabetes according to ADA guidelines (endorsed by the Centers for Disease Control and Prevention [CDC]).[8] They recommend universal screening using 1 of the 3 tests for adults aged 35 years and older (aged 45 years and older in 2022), informal or validated risk factor assessment (as of 2022), and screening all overweight or obese adults with 1 or more risk factors.[9] United States Preventive Services Task Force (USPSTF) guidelines recommend screening only overweight or obese persons aged 35-70 years.[10] Current ADA guidelines identify more persons with prediabetes or diabetes than USPSTF guidelines but necessitate screening twice as many (>80% of asymptomatic adults), a potentially "cost prohibitive" approach.[11]

Why am I so concerned about prediabetes screening? Why not cast the net widely to avoid missing anyone, especially if intervening with false positives may decrease other chronic diseases or do little harm? There are good reasons to focus screening more narrowly and interpret laboratory findings cautiously.

Strict interpretation of marginal test results can result in overdiagnosis and overtreatment. Lowered thresholds (eg, current ADA and CDC prediabetes standards) are not well supported by the evidence.[12] Glycemia values are imprecise, and cutoffs can be misleading: analytical and biologic variation can classify someone with HbA_{1c} midway in the prediabetes range (eg, 6.2%) as normal or diabetes, and a different repeat test result may not reflect meaningful change.[13] Further, HbA_{1c} can overestimate or underestimate glycemia depending on patient conditions.[14]

PROGRESSION TO DIABETES

Prediabetes is stigmatizing and deceptively implies progression to diabetes,[4] identifying many who will develop disease, but countless lower-risk individuals not requiring intervention, while missing scores who will develop disease.[4,7] In cohort studies, 17% to 59% revert to normal glycemia.[15]

Intermediate HbA_{1c} is a poor diabetes predictor. Five-year conversion from prediabetes to diabetes (11.1 years mean follow-up) comparing 5 international prediabetes definitions found similar accuracy identifying persons at risk for subsequent diagnosis.[16] The HbA_{1c} and incident diabetes relationship was nonlinear, however, and lower cut points (eg, HbA_{1c} 5.0%) identified many more at-risk individuals but also many who were less likely to progress (incurring psychological or economic harms). Importantly, the gain in identifying at-risk persons was nonsignificant. Analysts couldn't compare the 3 glycemia tests used in the United States since only 1 study assessed the same individuals. Findings support WHO and IDF recommendations[6] that glycemia evaluation include known risk factors and not rely on a single test.

Prediabetes (IFG and/or IGT) was associated with 39% higher mortality and specific diseases (moderate certainty, not reported by risk factor), but HbA_{1c}-defined diabetes results were equivocal.[17]

PATIENT HARMS

My PCP followed ADA/CDC—not more-targeted USPSTF guidelines—and didn't assess my risk factors (per 2022 ADA guidelines). We didn't review my historic HbA_{1c} values nor discuss test uncertainty. According to the ADA's online assessment tool, I was not at risk.

Perhaps my PCP was being cautious, but this is potentially harmful. I experienced distress and had numerous consultations, tests, and co-pays.

To be fair, discussing risk and engaging in shared decision making is challenging.[18] Practical prediabetes guidance and language for physicians is available.[4] Primary care clinicians require authoritative evidence, however; sufficient time for contemplation and interaction with patients,[18,19] and openness to uncertainty.[12,18,19] Guidelines address population-level health but inadequately account for individual patient differences and preferences.[19]

Prediabetes is turning legions of healthy people like me into patients by conflating risk with disease, lowering thresholds, and developing new "borderline" or "pre-disease" categories that target an unaffected population.[20] An ethnographic study found that most physicians regarded marginally elevated test results as requiring immediate action; patients with "pre-disease" (eg, prediabetes and hypertension) perceived themselves as ill, equating risk with disease; and physicians and patients viewed intervention as treatment, not prevention.[20] Aggressive treatment of at-risk conditions fulfills "the illusion that healthy people are sick."[20] Prediabetes has been called "a risk factor for developing a risk factor."[4] ADA's 2021 guidelines state prediabetes is not a clinical entity but an increased risk for diabetes and cardiovascular disease,[21] but CDC publicity indicates otherwise.[8]

PREDIABETES INTERVENTION EFFICACY

Individual and population-level prediabetes intervention assessments tell a mixed and uncertain story. Outcome data are frequently inadequate to reach confident conclusions, results are inconsistent and time-limited, impact on diabetes incidence when detected is low, and widespread implementation is challenging.

For example, medications for prediabetes appear to provide some benefit for specific populations, albeit with uncertainties and risks. Metformin apparently decreases diabetes incidence in persons with prediabetes or no diabetes, but data are mostly low or very low quality.[22] Experts advise caution before prescribing due to drug efficacy only in those at the very highest risk,[7] the need to remain on such drugs in perpetuity, common reversion to normal glycemia, and absence of cardiovascular complications addressed by the drugs.[23] These diabetes experts,[7,23] among others, favor aggressive treatment of diabetes when it develops. Long-term benefits of pharmacologic intervention with prediabetes are questionable[24] and quantification of harms is scant.[22,24] In those who will develop diabetes, postponing onset for 2 years comes at the expense

of longer overall treatment duration, while many who will never develop disease are placed on long-term drug regimens.[24] Pharmacologic treatment for marginally elevated glucose targets those who benefit least from treatment and are more likely to experience harm since medications frequently decrease glucose to dangerously low levels.[25]

Individual lifestyle interventions appear insufficiently effective and too costly to implement widely. Diet and exercise interventions prevent or delay diabetes progression with only moderate certainty,[10] and intervention trials are of inadequate duration and fail to assess long-term health outcomes.[26] Some advocate supplementing lifestyle interventions in high-risk individuals with broader population level efforts,[27] others suggest population approaches if resources are limited.[28] Certain population-based interventions, such as taxing sweetened drinks, are cost-saving, with mixed results for other population interventions.[29] Population-wide interventions demonstrate an effect on body mass index (BMI) but not on prevalence of overweight, obesity, and diabetes.[30] Successful population-level efforts require substantial funding, complex collaboration, and evaluation.[31]

Clinical trial successes, with highly selected risk groups and intensive interventions, have not been replicated in the general population. It is nearly impossible to achieve and maintain the required weight loss and lifestyle modification.[7,23,26] Such strategies are high contact and high cost, suggesting that intervening with all persons with prediabetes is infeasible[4,23,32] and distracts from and usurps resources for those at truly high risk.[5]

The cost effectiveness of screening widely is uncertain. Targeted screening for type 2 diabetes in hypertensive US adults was cost effective, screening African Americans aged 45 to 54 years was very cost effective, but universal opportunistic screening for all adults aged 45 years and older was not cost effective.[33] Furthermore, USPSTF's review of diabetes and prediabetes screening trials found no mortality benefit at 10 years and insufficient data on other health outcomes.[26] One review found some evidence of cost effectiveness of lifestyle and pharmacologic diabetes prevention programs in high-risk individuals, despite low reduction in incident diabetes (0.1% to 1.6%).[34] The evidence on lifestyle intervention efficacy was inadequate, due to heterogeneity of prediabetes definitions, populations, intervention intensity and duration, and modeling methods; including screening costs worsens cost effectiveness.[34] A subsequent study of diabetes prevention, based on limited clinical data, examined 3 "at-risk" populations defined by elevated glycemia (IFG, IGT, and/or HbA_{1c} 6.0% to 6.4%).[35] It found low-intensity lifestyle intervention (per UK guidelines) very cost-effective vs no intervention, high-intensity lifestyle intervention (per US Diabetes Prevention Program) probably cost effective, and metformin cost effective for individuals identified by elevated HbA_{1c} (not other tests).

Lowering diagnostic thresholds, as with prediabetes, has physician workload consequences.[12] Limited physician time is deflected to prediabetes rather than to caring for patients with diabetes.[24] Further, reimbursement can deter physicians from addressing behavior change since fee-for-service prediabetes management compensation is low compared with diabetes management.[36]

WHITHER PREDIABETES?

My experience and review of the evidence suggests that low-risk healthy persons are receiving unduly worrisome prognoses and overly aggressive intervention recommendations. I wish my PCP had explained important caveats: prediabetes does not inevitably lead to diabetes, individual tests and readings vary and can revert over time, and US prediabetes thresholds have lowered and exceed other countries. Indeed, my results have been consistent for many years, and I am healthy and at very low risk. In my view, screening should be targeted to high-risk populations, the US prediabetes threshold should align with international organizations, and prediabetes should be replaced with more appropriate, less alarming terms (eg, elevated or intermediate glycemia). Clinicians require time and resources to better communicate with patients but should focus their efforts on persons at high risk or with diabetes. Let's put out fires, not fan flames.

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Key words: evidence based medicine; health promotion/disease prevention: screening; patient experience; patient physician communication; prediabetes; primary care; standards of care

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