

# Natural History of Type 2 Diabetes in Chinese

## Lessons from the islands of Taiwan

The understanding of the natural history of type 2 diabetes has been fostered by studies of island populations. Zimmet (1) and colleagues have identified groups at extremely high risk for diabetes in the islands of the South Pacific (Nauru, Papua New Guinea, and others). By analogy, the "island" that is the relatively isolated Pima Indian population in the U.S. Southwest has led to crucial insights into the natural history of type 2 diabetes (2,3). The article by Chou et al. (4) in this volume adds interesting natural history results from the islands of Kinmen, Taiwan, Republic of China. It also raises important questions for further work.

Chou and coworkers screened >4,500 island inhabitants at baseline in 1992 and 1994 using a two-step screening approach. First, they measured fasting plasma glucose, and if the values were 5.6–7.8 mmol/l (100–139 mg/dl), participants were asked to return for an oral glucose tolerance test (OGTT). The investigators were able to complete the OGTT for 725 of 940 eligible fasting individuals (77%). At baseline, there were 654 people without diabetes who were eligible for retesting 2 years later. Testing was completed for 481 of the original 654 subjects (74%), and the incidence and risk factors for progression to type 2 diabetes were explored.

Overall, 4.1% of subjects progressed to type 2 diabetes per year. Among subjects with impaired glucose tolerance (IGT) by World Health Organization (WHO) criteria (and with the additional requirement that the screening fasting glucose level was also elevated), the rate was 8.8% per year. The authors also defined a subgroup of subjects with persistent fasting hyperglycemia (PFH). These subjects had fasting glucose levels on the two tests between 101 and 139 mg/dl (5.6 to <7.8 mmol/l) and a 2-h glucose level <140 mg/dl (<7.8 mmol/l). Thus, they did not meet WHO criteria for IGT (5), nor were they normal. In this group, the average annual incidence of type 2 diabetes was only 3.7% per year. Among subjects classified as normal (fasting glucose

level <100 mg/dl and 2-h level <140 mg/dl, but with a screening fasting glucose level  $\geq 100$  mg/dl), the annual incidence was 1.8%. In logistic regression analyses predicting development of type 2 diabetes, the commonly found factors of higher BMI, higher baseline fasting and 2-h glucose levels, and elevated uric acid were replicated.

How do these rates compare with other populations, and what do they suggest about the risk of type 2 diabetes for people of Chinese origin? Additionally, what does the two-step screening strategy teach us about ways to identify individuals with type 2 diabetes and those who are at risk for it? Lastly, do these results tell us that fasting glucose elevation precedes postchallenge hyperglycemia in the natural history of type 2 diabetes?

Chou et al. suggest that the risk in Chinese with IGT is especially high. While their conclusion that Chinese are at high risk if they have IGT is likely correct (6), their use of different criteria than the other studies makes the actual risk to subjects uncertain, since direct comparisons are difficult. The primary difference between the data from Chou et al. and those from other epidemiologic studies is their requirement for an elevated fasting glucose before the OGTT, an approach that is not widely used. To my knowledge, the impact of serial testing on subsequent incidence rates has not been published. However, following the analysis of several studies used in the planning phase of the Diabetes Prevention Program (DPP) (7), study planners estimated that the average annual incidence of type 2 diabetes would be increased by ~30% by the restriction of the fasting level on a single OGTT to 100–139 mg/dl, compared with the WHO criterion of any fasting level <140 mg/dl. This increase in the progression rates is substantial and may be an estimate of the increased incidence induced by serial tests. It is not possible to determine what proportion of the incidence reported by Chou et al. is due to the serial testing and what proportion is due to the actual risk in these islanders. This highlights the

importance of using strictly standardized criteria in any comparison across population groups, since the resulting prevalence and incidence results will depend strongly on the criteria used.

The two-step screening used by Chou et al. has both advantages and disadvantages. Such a two-step screening strategy was proposed by Narayan et al. (8) as an efficient way to identify high-risk subjects for prevention of type 2 diabetes, and this strategy has been incorporated into the DPP. In addition, the use of fasting glucose levels helps reduce the intraindividual variability inherent in the OGTT. This was one of several reasons that the use of the fasting glucose level was recently recommended by the American Diabetes Association (ADA) Task Force on Diagnostic Criteria (9). However, any two-stage screening approach to identify people with diabetes or those who are at risk for it inevitably has losses between the screening steps. In Kinmen, only three-quarters of the individuals who had elevated levels returned for a classifying OGTT. Such loss will result clinically in missed cases of diabetes, and it introduces possible selection bias in the follow-up phase, since it is not known how the individuals who did not return differed from those who did. In addition, no information is available on the levels of glucose intolerance among people who were not asked to return (false-negative test results). Such a two-step approach may be most useful for identifying subjects in intervention studies, but it severely limits comparability in observational studies. With the advent of the new ADA criteria that recommend the use of fasting glucose alone (with confirmation) as the diagnostic criteria for type 2 diabetes (9), such a two-step approach becomes unnecessary.

Chou et al. use a diagnostic category that they label "persistent fasting hyperglycemia," which is said to be "a relatively new definition." It differs from the new ADA category "impaired fasting glucose" (IFG) (9) both in diagnostic levels (those in Chou et al. are higher) and in the use of two fast-

ing glucose levels over a short (and undefined) time period. I suspect they have developed this term de novo, since no reference to its origin is given. Therefore, it will not help much in understanding what the risk of type 2 diabetes will be from IFG, something that must be defined for the new ADA criteria to have clinical predictive value. Their results do show that patients with PFH had twice the incidence of people who had normal glucose tolerance, but only 50% of the incidence of people with IGT. Thus, elevated fasting glucose levels alone definitely increase risk of type 2 diabetes.

What are we to make of the conclusion by Chou et al. that elevations in fasting glucose level may precede those of the postchallenge levels? This may be largely speculation. The answer requires extension of the design reported here with larger numbers of sequential tests over longer time periods. A single follow-up OGTT cannot determine the temporal sequence of fasting versus postchallenge glucose elevations. It is an important question to answer, since it may help us clarify the pathophysiology of glucose intolerance. As O'Rahilly et al. (10) have noted, our understanding of the relative roles of insulin resistance and islet decompensation as contributing factors may be partly determined by which classification criteria are used. Grouping subjects by arbitrary levels of either fasting or postchallenge glucose levels will result in different incidence rates. Such different rates do not by themselves imply a temporal sequence, as Chou et al. have suggested. Instead of the single etiologic pathway implied by the authors, there is likely to be important heterogeneity with respect to etiology and natural history. This has recently been shown for patients presenting clinically with maturity-onset diabetes of the young (11). Such heterogeneity could result in some subjects having elevations in fasting glucose levels as the first sign of decompensation, whereas others may have elevations of postprandial and postchallenge levels because of different etiologic pathways. Additional prospective

studies of the natural history of glucose intolerance leading to type 2 diabetes, with careful characterization of genetic heterogeneity and environmental interaction, are clearly needed.

Chou and colleagues have highlighted the relatively high incidence of type 2 diabetes in people of Chinese ancestry and have provided useful data on the excess risk from moderate hyperglycemia and other risk factors. Their article focuses attention on the fact that individuals of Chinese (and all Asian) origin (6), especially those who have migrated to (12) or adopted (13) a Westernized environment, are now at high risk to develop type 2 diabetes. The diabetes community must continue to highlight the epidemic of type 2 diabetes sweeping the world (14) and seek effective and efficient ways to prevent further increases (15).

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