Progression to Impaired Glucose Regulation and Diabetes in the Population-Based Inter99 Study

Susanne Engberg, MD¹
Dorte Vistisen, PhD¹
Cathrine Lau, MSC¹
Charlotte Glümer, MD, PhD²
Torben Jørgensen, MD, DMSC²,³
Oluf Pedersen, MD, DMSC¹,³,⁴
Knut Borch-Johnsen, MD, DMSC¹,⁴

OBJECTIVE — The purpose of this study was to estimate the progression rates to impaired glucose regulation (impaired fasting glucose or impaired glucose tolerance) and diabetes in the Danish population–based Inter99 study and in a high-risk subpopulation, separately.

RESEARCH DESIGN AND METHODS — From a population-based primary prevention study, the Inter99 study, 4,615 individuals without diabetes at baseline and with relevant follow-up data were divided into a low- and a high-risk group based on a risk estimate of ischemic heart disease or the presence of risk factors (smoking, hypertension, hypercholesterolemia, obesity, or impaired glucose tolerance). High-risk individuals (57.1%) were examined with an oral glucose tolerance test at 1 and 3 years, and all of the participants were reexaminated at the 5-year follow-up. Person-years at risk were calculated. Progression rates to impaired glucose regulation and diabetes were estimated directly from baseline to the 5-year follow-up for all the participants and from baseline through the 1- and 3- to 5-year follow-up examinations for the high-risk individuals, separately.

RESULTS — In the combined low- and high-risk group, 2.1 individuals per 100 person-years progressed from normal glucose tolerance (NGT) to impaired glucose regulation or diabetes. Among high-risk individuals, 5.8 per 100 person-years with NGT progressed to impaired glucose regulation or diabetes, and 4.9 per 100 person-years progressed from impaired glucose regulation to diabetes.

CONCLUSIONS — Progression rates to impaired glucose regulation using the current World Health Organization classification criteria were calculated for the first time in a large European population–based study. The progression rates to diabetes show the same pattern as seen in the few similar European studies.

Epidemiology/Health Services Research
ORIGINAL ARTICLE

From the ¹Steno Diabetes Center, Gentofte, Denmark; the ²Research Centre for Prevention and Health, Glostrup, Denmark; the ³Faculty of Health Sciences, University of Copenhagen, Copenhagen, Denmark; and the ⁴Faculty of Health Sciences, University of Aarhus, Aarhus, Denmark. Corresponding author: Susanne Engberg, segb@steno.dk. Received 15 October 2008 and accepted 17 December 2008. Published ahead of print at http://care.diabetesjournals.org on 29 December 2008. DOI: 10.2337/dc08-1869. Clinical trial reg. no. NCT00289237, clinicaltrials.gov.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked “advertisement” in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Diabetes Care 32:606–611, 2009
The sample was a priori randomized into two groups comprising 90% (group A: high-intensity intervention) and 10% (group B: low-intensity intervention) (17).

All 13,016 individuals in groups A and B were invited to a health screening program and a personal risk assessment of their absolute 10-year risk of developing ischemic heart disease (IHD) by the Copenhagen Risk Score (17). High-risk individuals were defined as individuals with an absolute risk of IHD in the upper quintile of their age and sex strata or with one or more of the following risk factors: daily smoker, systolic blood pressure ≥160 mmHg/antihypertensive therapy, total cholesterol ≥7.5 mmol/l, BMI ≥30 kg/m², history of diabetes, or diabetes or IGT diagnosed at baseline. Based on the personal risk estimate, each individual was offered lifestyle counseling dealing with smoking, physical activity, diet, and alcohol. High-risk individuals in group A were further offered lifestyle counseling in groups on smoking cessation or physical activity/diet with six meetings during a 4- to 6-month period, whereas high-risk individuals in group B were referred to their family physician. Baseline data were collected from March 1999 until January 2001. The Inter99 study and baseline results are described in detail elsewhere (17,18).

All high-risk individuals were reinvited at 1 and 3 years for a health examination including a new risk assessment and lifestyle counseling. If still at high risk at the reexamination, individuals in group A were again offered lifestyle counseling in groups, and individuals in group B were again referred to their family physician. All participants at baseline were reinvited at 5 years for a final health examination.

Methods and definitions

Of the 13,016 individuals invited at baseline, 82 were noneligible because they had died or could not be traced. Of the remaining 12,934 individuals, 6,906 participated in the investigation. Of these, 122 individuals were excluded because of alcoholism, drug abuse, or linguistic barriers, leaving 6,784 (52.5%) for analysis at baseline (17,18). In general, the participation rate was higher in younger women than in younger men, and it increased with increasing age until 55 years of age, after which it declined. The participation rate was identical in group A (high-intensity intervention) and group B (low-intensity intervention) (17).

Glucose tolerance status was classified according to the 1999 WHO criteria by a single OGTT (9), and IGT was divided into i-IGT and IFG-IGT. At baseline, 374 (5.5%) were nonclassifiable because of lack of either FPG or 2-h plasma glucose measurements, and 404 (6.0%) had either self-reported diabetes or diabetes diagnosed by the OGTT (18), leaving 6,006 individuals without diabetes. The high-risk group comprised 57.1% (3,429 of 6,006) at baseline.

At the 5-year follow-up, 1,975 individuals were lost to follow-up or were nonclassifiable, leaving 4,031 individuals with relevant data for the calculation of the progression rates in the high-risk group, separately. These analyses include all individuals with relevant follow-up data for the direct progression rates from baseline to 5 years and high-risk individuals with relevant follow-up data from 1, 3, or 5 years (n = 4,615).

To calculate the crude progression rates in this study, the Inter99 study was analyzed as if it were a cohort study. Participants in the low-risk group were only examined at baseline and at the 5-year follow-up. Hence, when we calculated the overall progression rates in the Inter99 study for both the high-risk and the low-risk groups combined, only information from baseline and the 5-year follow-up was used. Incident cases were defined as individuals with newly detected i-IFG, i-IGT, IFG-IGT, or diabetes/self-reported diabetes at the 5-year examination.

Progression rates for the high-risk group were calculated separately, and all information on glucose tolerance status from the 1-, 3-, and 5-year follow-up examinations was used. Incident cases were defined as individuals with newly detected i-IFG, i-IGT, IFG-IGT, or diabetes/self-reported diabetes at the 1-, 3-, or 5-year examinations. Diabetes is considered an absorbing state. Thus, individuals with known diabetes were not offered an OGTT at subsequent examinations. Individuals without diabetes may change glucose tolerance status between the examinations. Hence, an individual may progress to different states of glucose intolerance at different time points and thereby be included in more than one of the subanalyses. In this study we did not look at regression in glucose tolerance status during follow-up.

Statistical analysis

Statistical analyses were performed using SAS (version 9.1; SAS Institute, Cary, NC). Exact 95% CIs were calculated for proportions. Proportions were compared between groups using χ² tests. The Wilcoxon signed-rank test was used to compare means of continuous variables.

Progression rates were estimated by dividing the number of outcomes by person-years at risk using interval-censoring (19). Years at risk were calculated as the time difference between date of entry and date of exit. Date of entry was the date of the baseline examination. For individuals progressing to a relevant outcome, the date of exit was set at the midpoint be-
Progression rates in the Inter99 study

Table 1—Clinical characteristics of the participants with relevant follow-up data according to glucose tolerance status at baseline

| Glucose tolerance status at baseline | n (%) of total | Men (%) | Age (years) | BMI (kg/m²) | Waist circumference (cm) | Diabetes | IFG-IGT | Total |
|------------------------------------|----------------|---------|-------------|-------------|--------------------------|----------|---------|-------|
| NGT                                | 3,590 ± 78.0   | 48.0    | 45.7 ± 7.7  | 25.5 ± 4.0  | 84.3 ± 12.1              | 414 ± 9.0| 433 ± 9.4| 169 ± 3.7|
| i-IFG                              | 414 ± 9.0      | 74.4    | 49.3 ± 6.9* | 27.7 ± 4.5* | 93.6 ± 11.7*             | 433 ± 9.4| 433 ± 9.4| 169 ± 3.7|
| i-IGT                              | 433 ± 9.4      | 42.7    | 48.1 ± 7.8* | 27.7 ± 5.2* | 89.4 ± 14.2*             | 433 ± 9.4| 433 ± 9.4| 169 ± 3.7|
| IFG-IGT                            | 169 ± 3.7      | 69.8    | 50.0 ± 6.8* | 29.2 ± 4.9* | 96.2 ± 11.9*             | 169 ± 3.7| 169 ± 3.7| 169 ± 3.7|
| Total                              | 4,615          | 56.2    | 46.4 ± 7.7  | 26.0 ± 4.3  | 86.1 ± 12.7              | 4,615    | 4,615   | 4,615 |

Data are proportions (95% CI) or means ± SD, unless otherwise indicated. *P < 0.0001 compared with NGT. †P < 0.05 compared with NGT. ‡P = 0.0001 compared with NGT.

Table 2—Progression rates to impaired glucose regulation and diabetes directly from baseline to 5-year follow-up in the combined low- and high-risk group

| Glucose tolerance status at baseline | Outcomes (n) | Person-years | Rate per 100 person-years (95% CI) |
|------------------------------------|--------------|--------------|-----------------------------------|
| NGT                                | 3,187        | 16,918       | 0.5 (0.4–0.6)                     |
| i-IFG                              | 83           | 16,918       | 1.2 (1.0–1.3)                     |
| i-IGT                              | 192          | 16,918       | 0.2 (0.1–0.2)                     |
| IFG-IGT                            | 28           | 17,063       | 1.9 (1.7–2.1)                     |
| i-IFG, i-IGT, or IFG-IGT           | 303          | 16,328       | 0.3 (0.2–0.3)                     |
| Diabetes                           | 44           | 17,019       | 2.1 (1.9–2.4)                     |
| i-IFG, i-IGT, IFG-IGT, or diabetes | 347          | 16,210       | 0.5 (0.4–0.6)                     |
| IFG-IGT                            | 23           | 1,864        | 1.2 (0.8–1.9)                     |
| Diabetes                           | 45           | 1,804        | 2.5 (1.9–3.3)                     |
| IFG-IGT                            | 68           | 1,743        | 3.9 (3.1–4.9)                     |
| Diabetes                           | 66           | 1,722        | 3.8 (3.0–4.9)                     |
| IFG-IGT                            | 79           | 1,688        | 4.7 (3.8–5.8)                     |
| Diabetes                           | 52           | 560          | 9.3 (7.1–12.2)                    |
| i-IFG, i-IGT, or IFG-IGT           | 163          | 4,087        | 4.0 (3.4–4.7)                     |
| Diabetes                           | 207          | 21,106       | 1.0 (0.9–1.1)                     |

*Number of individuals at baseline.
CONCLUSIONS — In this large population-based study with a 5-year follow-up, we found that 2% per year of all individuals with NGT at baseline progressed to impaired glucose regulation or diabetes. Among individuals at high risk with NGT at baseline, almost 6% per year progressed to impaired glucose regulation or diabetes. This relatively higher rate of progression in the high-risk group compared with the combined group was expected, because at least one criterion for being in the high-risk group was obesity, which is a well-known risk factor for diabetes (1,7). Furthermore, the high-risk individuals were additionally reexamined at 1 and 3 years, which makes any progression in glucose tolerance status more likely to be detected and at an earlier time, thus decreasing their risk time and increasing the progression rate. On the other hand, the high-risk group was offered a relatively more intensive intervention that could underestimate the spontaneous progression rates in this group.

Among individuals with impaired glucose regulation, 4% per year in the combined low- and high-risk group and almost 5% per year in the high-risk group progressed to diabetes. All individuals with i-IGT or IFG-IGT were in the high-risk group in this study because IGT was one of the criteria for being considered at high risk. Therefore, the progression rates from i-IGT to IFG-IGT and/or diabetes and from IFG-IGT to diabetes are almost the same among all of the study participants (Table 2) and in the high-risk group (Table 3). However, the use of up to four OGTG examinations in calculating the progression rates in Table 3 makes these rates more accurate than the rates in Table 2, which only use baseline and 5-year measurements.

In the high-risk group, the progression rate from IFG-IGT to diabetes was 2.8 times higher than the progression rates from the isolated states of impaired glucose regulation, i-IGT and i-IGT, to diabetes. This was expected because the IFG-IGT group has more severe metabolic abnormalities than the isolated states (15) and therefore has an increased risk of progression to diabetes. In addition, the risk of misclassification is lower. Both FPG and 2-h plasma glucose can be randomly high, but because the classification of IFG-IGT requires both an abnormal FPG and an abnormal 2-h plasma glucose, there is a low risk of a simultaneously random high FPG and 2-h plasma glucose.

In the present follow-up study, we analyzed the Inter99 study as if it was a cohort study, but because the Inter99 study was designed as an intervention study, the rates of progression might have been higher without the intervention. However, for the high-risk group, the group-based intervention (high-intensity group A) had no additional effect beyond the individualized intervention (low-intensity group B) with respect to plasma glucose levels (C.L., D.V., Ulla Toft, Inge Tetens, O.P., T.J., K.B.-J., unpublished observations). A recent study from the Danish National Diabetes Register has shown age- and sex-specific incidence rates in the Danish population (20) that are approximately one-third of the rate of progression to diabetes in our study (1.0% per year, Table 2). This reflects an underdiagnosing of diabetes in the background population, and, therefore, we cannot estimate the total effect of the lifestyle intervention in the Inter99 population by comparing our findings with those for the background population via central registries in Denmark.

Although the Inter99 study is potentially underestimating the spontaneous progression rates because of the lifestyle intervention, we compared the rate ratios with those from the few European population-based studies that have calculated progression rates from NGT or impaired glucose regulation to diabetes in Caucasians using the current WHO classification criteria (10,11,13). These studies have not calculated progression to impaired glucose regulation. None of the studies have performed interval-censoring in the calculation of progression rates, and, thus, they have potentially underestimated their crude rates. We have chosen not to compare the high-risk group with highly selected European populations (21,22) because of different criteria for being at high risk.

In the Dutch Hoorn study, 1,342 white Caucasians aged 50–75 years with-
out diabetes at baseline in 1989–1992 were followed for 6.4 years. The progression rates from i-IFG, i-IGT, and IFG-IGT to diabetes were 7.3, 8.3, and 16.0 times higher, respectively, than the progression rate from NGT to diabetes (0.7 per 100 person-years) (10). These rate ratios are all lower than the similar rate ratios in our study.

In the Asturias study from Northern Spain, 630 mostly Caucasians aged 30–75 years without diabetes at baseline in 1998–1999 were followed for 6.3 years. The progression rates from i-IFG, i-IGT, and IFG-IGT to diabetes were 6.9, 4.2, and 19.0 times higher, respectively, than the progression rate from NGT to diabetes (0.5 per 100 person-years) (11). The rate ratios are all lower than the rate ratios in our study.

The British Ely study included 1,040 nondiabetic individuals aged 40–69 years of predominantly white-European origin. An OGTT was performed at baseline in 1990–1992 and at the 4.5- and 10-year follow-up examinations (13). The Ely study used a lower threshold (<5.6 mmol/l) for defining NGT than that recommended by the WHO in 1999 (<6.1 mmol/l) (9), and, therefore, the rates would have been higher if the WHO definition of NGT had been used. The ratio between the rate of progression from IFG to diabetes and the rate of progression from NGT to diabetes (0.2 per 100 person-years) was 7.3, which is lower than the rate ratios comparing progression to diabetes from i-IFG or IFG-IGT and NGT in our study.

Strengths of the present population-based study include its large size with 4,615 participants at baseline with follow-up data. Furthermore, the study was initiated <10 years ago, which is important because the rates of progression in a given population change over time (23,24) because of changes in modifiable risk factors (e.g., BMI and level of physical activity) and in the demography of the population. Further strengths are the separation of impaired glucose regulation into i-IFG, i-IGT, and IFG-IGT and thereby the presentation of progression rates to and from the isolated states as well as the combined state. The multiple examinations with OGTTs in the high-risk group make the progression rates among high-risk individuals very accurate. Other strengths are the calculation of person-years at risk and the use of interval-censoring, which takes into account the fact that conversion to a more severe glucose tolerance state occurs before the time of the examination.

As mentioned above, the spontaneous progression rates may be underestimated because the Inter99 study is an intervention study. A further limitation of this study is the loss to follow-up. However, a follow-up rate of 76.8% is comparable to that for the Hoorn study (73.5%) (10), the Asturias study (75.3%) (11), and the Ely study (72%) (13). In accordance with the WHO 1999 criteria, the classification of glucose tolerance status in this epidemiological study was based on a single OGTT examination (9). Nevertheless, because of the known high intrapersonal variation in plasma glucose levels, especially for postload glucose, some misclassification might have occurred when participants were categorized into glucose tolerance categories (10). Furthermore, there is an additional risk of misclassification because we did not look at regression in glucose tolerance status during follow-up. However, because there was no difference in plasma glucose between the intervention groups, we consider the risk of misclassification to be random.

The relatively low participation rate at baseline (52.5%) introduces a selection bias and weakens the possibility of generalizing the results. Nevertheless, it does not affect the validity of the progression rates in this study.

The rate ratios in our study are higher than similar rate ratios in the few other European studies, which also used the current WHO classification. This may be due to a relatively low progression rate from NGT to diabetes in the Inter99 study compared with that in the Hoorn and the Asturias study. The NGT group has a lower proportion of high-risk individuals than the other glucose tolerance groups (Table 1). Therefore, the relatively low progression rate from NGT to diabetes compared with the rates from impaired glucose regulation to diabetes cannot be attributed to an intervention effect. Although the rate ratios in our study are higher than those in the other European studies, the pattern is the same with relatively low rates of progression from NGT to diabetes, intermediate rates from i-IFG and i-IGT to diabetes, and high rates from IFG-IGT to diabetes.

In summary, we have presented for the first time progression rates to i-IFG, i-IGT, and IFG-IGT in a large European population-based study, which uses the current WHO classification criteria. Progression rates to diabetes show the same pattern as that seen in the few similar European studies.

Acknowledgments—This study was supported by the Danish Medical Research Council, the Danish Center for Evaluation and Health Technology Assessment, Novo Nordisk, Copenhagen County, the Danish Heart Foundation, the Danish Diabetes Association, the Danish Pharmaceutical Association, the Augustinus Foundation, the Ib Henriksen Foundation, and the Becket Foundation.

O.P. is an employed professor of the Steno Diabetes Center, a hospital integrated in the Danish National Health Care Service, but owned by Novo Nordisk, and holds stock shares in Novo Nordisk. K.B.-J. is head of the Steno Diabetes Center and holds shares in Novo Nordisk. No other potential conflicts of interest relevant to this article were reported.

We thank all of the participants who took part in the survey. The staff from the Research Centre for Prevention and Health and the laboratory at Steno Diabetes Center are thanked for their serious efforts that made this study possible.

References

1. Edelstein SL, Knowler WC, Bain RP, Andres R, Barrett-Connor EL, Dowse GK, Haffner SM, Pettitt DJ, Sorkin JD, Muller DC, Collins VR, Hamman RF: Predictors of progression from impaired glucose tolerance to NIDDM: an analysis of six prospective studies. Diabetes 46:701–710, 1997

2. Schranz AG: Abnormal glucose tolerance in the Maltese: a population-based longitudinal study of the natural history of NIDDM and IGT in Malta. Diabetes Res Clin Pract 7:7–16, 1989

3. Skarforos ET, Selinus KI, Lithell HO: Risk factors for developing non-insulin dependent diabetes: a 10 year follow up of men in Uppsala. BMJ 303:755–760, 1991

4. Njølstad I, Arnesen E, Lund-Larsen PG: Sex differences in risk factors for clinical diabetes mellitus in a general population: a 12-year follow-up of the Finnmark study. Am J Epidemiol 147:49–58, 1998

5. Qiao Q, Lindstrøm J, Valle TT, Tuomilehto J: Progression to clinically diagnosed and treated diabetes from impaired glucose tolerance and impaired fasting glycaemia. Diabet Med 20:1027–1033, 2003

6. Perry IJ, Wannamethee SG, Walker MK, Thomson AG, Whincup PH, Shaper AG: Prospective study of risk factors for development of non-insulin dependent diabetes in middle aged British men. BMJ 310: 560–564, 1995

7. Bonora E, Kiechl S, Willeit J, Oberhollenzer F, Egger G, Meigs JB, Bonadonna RC, Muggeo M: Population-based incidence
rates and risk factors for type 2 diabetes in white individuals: the Bruneck study. *Diabetes* 53:1782–1789, 2004
8. Nichols GA, Hillier TA, Brown JB: Progression from newly acquired impaired fasting glucose to type 2 diabetes. *Diabetes Care* 30:228–233, 2007
9. World Health Organization: *Definition, Diagnosis and Classification of Diabetes Mellitus and Its Complications. Report of a WHO Consultation, Part 1: Diagnosis and Classification of Diabetes Mellitus.* Geneva, World Health Org., 1999
10. de Vegt F, Dekker JM, Jager A, Hienkens E, Kostense PJ, Stehouwer CD, Nijpels G, Bouter LM, Heine RJ: Relation of impaired fasting and postload glucose with incident type 2 diabetes in a Dutch population: the Hoorn Study. *JAMA* 285:2109–2113, 2001
11. Valdés S, Botas P, Delgado E, Alvarez F, Cadorniga FD: Population-based incidence of type 2 diabetes in northern Spain: the Asturias Study. *Diabetes Care* 30:2258–2263, 2007
12. Hanley AJ, Williams K, Gonzalez C, D’Agostino RB, Wagenknecht LE, Stern MP, Wagenknecht LE, Stern MP, Haffner SM, San Antonio Heart Study, Mexico City Diabetes Study, Insulin Resistance Atherosclerosis Study: Prediction of type 2 diabetes using simple measures of insulin resistance: combined results from the San Antonio Heart Study, the Mexico City Diabetes Study, and the Insulin Resistance Atherosclerosis Study. *Diabetes* 52:463–469, 2003
13. Forouhi NG, Luan J, Hennings S, Wareham NJ: Incidence of type 2 diabetes in England and its association with baseline impaired fasting glucose: the Ely study 1990–2000. *Diabet Med* 24:200–207, 2007
14. Magliano DJ, Barr ELM, Zimmet PZ, Cameron AJ, Dunstan DW, Colagiuri S, Jolley D, Owen N, Phillips P, Tapp RJ, Welborn TA, Shaw JE: Glucose indices, health behaviors, and incidence of diabetes in Australia: the Australian Diabetes, Obesity and Lifestyle Study. *Diabetes Care* 31:267–272, 2008
15. Abdul-Ghani MA, Tripathy D, DeFronzo RA: Contributions of \( \beta \)-cell dysfunction and insulin resistance to the pathogenesis of impaired glucose tolerance and impaired fasting glucose. *Diabetes Care* 29:1130–1139, 2006
16. Gabir MM, Hanson RL, Dabelea D, Imperatore G, Roumain J, Bennett PH, Knowler WC: The 1997 American Diabetes Association and 1999 World Health Organization criteria for hyperglycemia in the diagnosis and prediction of diabetes. *Diabetes Care* 23:1108–1112, 2000
17. Jørgensen T, Borch-Johnsen K, Thomsen TF, Ibisen H, Glümer C, Pisinger C: A randomized non-pharmacological intervention study for prevention of ischaemic heart disease: baseline results Inter99. *Eur J Cardiovase Prev Rehabil* 10:377–386, 2003
18. Glümer C, Jørgensen T, Borch-Johnsen K: Prevalences of diabetes and impaired glucose regulation in a Danish population: the Inter99 study. *Diabetes Care* 26:2335–2340, 2003
19. Armitage P, Berry G, Matthews J: *Statistical Methods in Medical Research.* Blackwell Publishing, London, 2002
20. Carstensen B, Kristensen J, Ottosen P, Borch-Johnsen K, National Diabetes Register: The Danish National Diabetes Register: trends in incidence, prevalence and mortality. *Diabetologia* 51:2187–2196, 2008
21. Rasmussen SS, Glümer C, Sandbaek A, Lauritzen T, Borch-Johnsen K: Progression from impaired fasting glucose and impaired glucose tolerance to diabetes in a high-risk screening programme in general practice: the ADDITION Study, Denmark. *Diabetologia* 50:293–297, 2007
22. Tuomilehto J, Lindstrom J, Eriksson JG, Valle TT, Hamalainen H, Ilanne-Parikka P, Keinanen-Kiukaanniemi S, Laakso M, Louheranta A, Rastas M, Salminen V, Aunola S, Cepaitis Z, Moltchanov V, Hakumaki M, Mannelin M, Martikka V, Sundvall J, Uusitupa M, Finnish Diabetes Prevention Study Group: Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N Engl J Med* 344:1343–1350, 2001
23. Burke JP, Williams K, Gaskill SP, Hazuda HP, Haffner SM, Stern MP: Rapid rise in the incidence of type 2 diabetes from 1987 to 1996: results from the San Antonio Heart Study. *Arch Intern Med* 159:1450–1456, 1999
24. Söderberg S, Zimmet P, Tuomilehto J, deCourten M, Dowse GK, Chitson P, Stenlund H, Gareeboo H, Alberti KG, Shaw J: High incidence of type 2 diabetes and increasing conversion rates from impaired fasting glucose and impaired glucose tolerance to diabetes in Mauritius. *J Intern Med* 256:37–47, 2004