Diabetes mellitus (DM) and its associated disease outcomes are a growing concern worldwide. The current global prevalence of DM for all ages has been estimated at 2.8 percent and is predicted to reach 4.4 percent by 2030.1 There is intense interest in identifying and treating risk factors that may prevent the onset of this disease and minimize morbidity.

Impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) are the intermediate metabolic states between normal and diabetic glucose homeostasis. These conditions are thought to be the precursors of DM, but the progression to overt disease is not straightforward. The risk for both macrovascular and microvascular complications increases across the distribution of blood glucose concentrations well below the overt DM, and the risk is more strongly associated with post-challenge hyperglycemia than fasting glucose levels. However, it is unclear whether this “glucose effect” is independent of classical risk factors, such as blood pressure and lipids, or occurs due to abnormalities of other metabolites, such as free fatty acids.

Objective of This Systematic Review

The goal of this systematic review is to evaluate the state of the evidence in the areas of the diagnosis, prognosis, and treatment of IFG or IGT. This evidence report was requested by the American College of Physicians-American Society of Internal Medicine; other partners were the American Academy of Pediatrics and the American Academy of Family Physicians.

Key Questions

Preliminary questions were subsequently modified and refined in consultation with the partner medical agencies, the Agency for Healthcare Research and Quality, and McMaster University Evidence-based Practice Center. The revised key questions are as follows:

1. **Diagnosis**—What is the reliability of the diagnosis of IFG or IGT (e.g., does individual variability or measurement error require multiple measurements to ensure reliability of diagnosis)? What is the relationship between IFG and IGT?

2. **Prognosis**—For those identified with IFG or IGT, what are the short- and long-term risks for developing the following outcomes:
   a) Progression to DM or reversion towards normal glucose tolerance or fasting glucose level.
   b) Cardiovascular events and stroke (fatal and nonfatal).
   c) Microvascular disease, specifically retinopathy and nephropathy as measured by proteinuria, microalbuminuria, elevated creatinine, albumin-to-creatinine ratio in the urine, dialysis, or renal transplant. Does this risk vary by subpopulation, such as sex, race, obesity, age or other risk factors (e.g., blood pressure, elevated lipid levels)?

3. **Treatment**—What is the effectiveness of pharmaceutical and behavioral interventions for reducing the risks associated with IFG or IGT on the following outcomes:
a) Delay in onset of DM or reversion towards normal glucose tolerance or fasting glucose level.

b) Reducing risk for cardiovascular events and stroke (fatal and nonfatal).

c) Reducing risk for microvascular disease, including early markers such as retinopathy/proteinuria.

d) Improving other metabolic parameters, independently associated with increased risk, such as blood pressure and lipid levels.

Are some treatments more effective than others for any of the above outcomes, and does the effectiveness of interventions vary by subpopulation (e.g., age, sex, and obesity)?

4. Pediatric population—What is known of the development of IFG or IGT in the pediatric population?

**Methods**

**Eligibility Criteria**

Primary studies were eligible if they evaluated subjects with IGT or IFG, were published after 1978, and were written in the English language. Excluded publications included systematic reviews, narrative reviews, editorials, letters to the editor, unpublished position papers, consensus conference reports, and practice guidelines.

Study design eligibility varied with the research question:

- **Diagnosis**—All study designs with a maximum of 8-week retest for reproducibility were eligible.

- **Prognosis**—Any prospective cohorts, or randomized or controlled clinical trials (RCTs) were eligible for evaluation (with a minimum followup of 1 year).

- **Treatment**—Only RCTs that analyzed the effects of lifestyle, behavioral, or pharmaceutical treatment (with a minimum followup of 6 months) were eligible.

- **Pediatric population**—All study designs for children age 0 to 18 years were eligible.

The study had to include an IFG or IGT group as the study population or analyzed as a subgroup. The specific criteria reference (for example, WHO-85) used within a study was checked relative to the procedures described in the methods and results sections of each study. The following inclusion/exclusion criteria were used for the testing procedure for dysglycemia:

- All testing must have been done on venous blood plasma or venous blood serum, not on whole blood or on capillary samples.

- For oral glucose tolerance testing (OGTT), the subject must have been given 75 g of oral glucose (1.75 g per kg to maximum of 75 g for children) and measurement taken at 2 hours post-glucose ingestion (2-hr PG).

- All measurements must have been done in a laboratory and not with a point-of-care device or not undertaken in an acute care setting, such as an emergency ward following a myocardial infarction (MI) or pneumonia.

Study outcomes included glycemic disturbances, nonfatal cardiac outcomes, fatal cardiac outcomes, mortality, lipid and blood pressure disorders, amputation, nephropathy, and ocular problems.

**Literature Search Strategy**

A comprehensive search was undertaken to capture all relevant studies. In addition to MEDLINE®, HealthSTAR, CINAHL®, AMED (alternative medicines), PsycINFO®, and EMBASE®, the personal files of the local research team and the reference lists of included articles were searched from 1979 onward.

**Study Selection and Extraction**

The title and abstract lists and the full-text papers were screened using the eligibility criteria, standardized forms, and a guide manual. Data from the Access database were summarized into summary tables, which included data about the general study characteristics (study design, location, source of funding, population, mean age, and diagnosis criteria), interventions, and outcomes assessed.

Studies were grouped according to classification of the IFG and IGT status. Five categories were considered, including: 1) isolated IGT (I-IGT), 2) isolated IFG (I-IFG), 3) non-isolated IGT, 4) non-isolated IFG, and 5) combined IGT/IFG.

A classification of I-IGT indicates that 2-h OGTT level was between 7.8 and 11.0 mmol/L and the fasting plasma glucose (FPG) level was less than 6.1 mmol/L. Similarly, the I-IFG classification indicates that the 2-h OGTT level was less than 7.8 mmol/L and the FPG level was between 6.1 and 7.0 mmol/L.

The isolated classifications indicate that both forms of glucose testing were undertaken and only one of the two tests was abnormal. Each eligible study was rated for quality using standardized instruments.

**Results**

The original search yielded 25,521 citations for all four questions combined. From these, 1,243 proceeded to full-text screening. After the final eligibility screening, data were extracted from a total of 156 studies.

**Key Question 1: Diagnosis**

Fifty-three studies provided data on the reproducibility of repeat testing of fasting glucose or OGTTs, comparison of IGT diagnosis by different criteria, and the relationship between IGT and IFG diagnosis in the same population.
Reproducibility of IGT and IFG Tests. Five reports of four studies\textsuperscript{8-9} assessed the reproducibility of the OGTT for diagnosis of IGT and three reports of two studies\textsuperscript{5-7} assessed the reproducibility of FPG for the diagnosis of IFG in publications after 1978. All repeat tests were done within 6 weeks of the first test. The populations studied were mostly Caucasians,\textsuperscript{5-7} except for two reports of one study on Hong Kong Chinese.\textsuperscript{8,9}

The study populations were subgroups of larger studies and did not provide detailed characterization for the subgroup. All studies used the same classification criteria. IGT was FPG < 7.8 mmol/L and 2-hr PG 7.8 to 11.0 mmol/L and IFG was FPG 6.1 to 6.9 mmol/L.

The kappa coefficients for IGT ranged from 0.04 to 0.56, indicating poor to moderate agreement. The proportion of participants classified as IGT by the first OGTT and upon repeat testing ranged from 33 percent to 48 percent. A similar proportion (range 39.3 percent to 46.2 percent) of participants was recategorized as normal glucose tolerance, with the remainder reclassified as DM (range 6 percent to 12.6 percent).

Two studies retested participants based on FPG for IFG.\textsuperscript{5,9} The kappa coefficients for these studies were 0.22 and 0.44, indicating fair to moderate reproducibility. The proportions of participants classified as IFG by the first FPG and upon repeat testing were 63.7 percent and 51.4 percent, respectively. The reclassified subjects had mostly normal fasting glucose with some newly diagnosed DM. Two studies that evaluated coefficient of variation for biological variation (CV) for repeat testing gave similar CVs for FPG (6 percent and 6.3 percent) and 2-hr PG (18 percent and 16.6 percent) concentrations, indicating consistency in variation between the different populations studied.\textsuperscript{5-7}

Comparison of IGT diagnosis using different criteria. Only four studies\textsuperscript{10-13} provided data for a comparison between diagnosis using different IGT criteria (i.e., using both IFG and 2-hr PG concentrations for classification). Studies that assessed IGT based on the 2-hr PG concentration only (WHO epidemiological criteria) were excluded.\textsuperscript{14}

The characteristics of the study populations represent a broad spectrum of populations (Asian, Dutch, Pima Indians, and women with previous gestational DM). The IGT criteria included were WHO-85, WHO-98, and WHO-99. All of these criteria use a 2-hr PG range of 7.8 to 11.0 mmol/L, but the WHO-85 criteria use an FPG cutpoint of < 7.8 mmol/L whereas both the WHO-98 and WHO-99 criteria use a cutpoint of < 7.0 mmol/L. More IGT diagnoses were made using a FPG cutpoint of < 7.8 mmol/L (13.6 percent to 31.5 percent) than 7.0 mmol/L (8.3 percent to 29.7 percent). There were fewer cases of I-IGT (6.0 percent to 11.9 percent) compared to IGT regardless of the FPG cutpoint.

Relationship between IGT and IFG. Forty-nine studies provided data on the relationship between diagnostic criteria for IGT and IFG. Most studies were prospective cohort studies (n = 14) and cross-sectional studies (n = 31). Data were extracted to give seven classifications:

1) IGT—2-hr PG 7.8 to 11.0 mmol/L.
2) IGT—FPG < 7.8 mmol/L and 2-hr PG 7.8 to 11.0 mmol/L.
3) IGT—FPG < 7.0 mmol/L and 2-hr PG 7.8 to 11.0 mmol/L.
4) IFG—FPG 6.1 to 6.9 mmol/L.
5) I-IGT—FPG < 6.1 mmol/L and 2-hr PG 7.8 to 11.0 mmol/L.
6) I-IFG—FPG 6.1 to 6.9 mmol/L and 2-hr PG < 7.8 mmol/L.
7) Combined IFG/IGT—FPG 6.1 to 6.9 mmol/L and 2-hr PG 7.8 to 11.0 mmol/L.

Comparison of studies that present both IGT and I-IGT data show that the number of participants in the IGT classification is approximately 40 percent greater than in the I-IGT group (p < 0.0001). Also, IGT classification using the limited criteria, which omits the fasting plasma glucose value, classified 10 percent more participants as IGT (p = 0.0033). Evaluation of studies containing data for all classification categories (n = 16) show a change in proportion between each classification group and between studies. In general, the proportion of participants decreased with increased stringency of the diagnostic criteria—that is, IGT as 2-hr PG > IGT as FPG and 2-hr PG > I-IGT > IFG > I-IFG > IFG/IGT.

The prevalence of IGT and IFG varied greatly among studies ranging from a few percent to over 30 percent. Comparisons between categories of IGT and IFG were significant (p < 0.01) for all combinations except for I-IGT versus IFG and I-IFG versus IGT/IFG. Correlations were much higher for IGT and I-IGT than for IFG and I-IFG.

Key Question 2: Prognosis

A total of 104 studies met the initial eligibility criteria. From these, only some provided sufficient data (frequency counts) versus a reference group of subjects with normal glucose to estimate the following:

- Annualized risk per 100 persons in the exposed group.
- Unadjusted annualized relative risk (RR), with the confidence interval (CI).
- Risk difference\textsuperscript{1}
- Attributable risk (AR), expressed as a percentage for the observed study duration.

All included studies prospectively followed cohorts; 90 were observational studies and 14 were RCTs (placebo arm only). The duration of followup varied from 1 year to 18 years. Five

\textsuperscript{1} Risk differences are discussed in the full evidence report.
The number of studies that evaluated women only, and nine studies evaluated men only. The mean age and the ranges varied significantly among studies, but most included middle-aged and older subjects. There was a broad representation of populations.

The measures of risk were calculated from data provided in prospective studies that included both normal and dysglycemic people in either observational studies or the placebo arm of RCTs. The risk estimates for all outcomes were classified into five diagnostic groups: 1) IGT, 2) I-IGT, 3) IFG, 4) I-IFG, and 5) combined IFG/IGT. Findings are summarized for three main outcomes: progression to DM, cardiovascular disease (CVD) outcomes (fatal and nonfatal), and mortality.

**Risk for progression to DM.** The number of studies that provided data for the five classification groups varied. Studies with IGT subjects (n = 36) were the most numerous, whereas five studies included people with IFG and three studies included people with I-IGT, I-IFG, and both IGT/IFG.

*Annualized risk per 100 persons in the exposed groups.* The minimum and maximum annualized risk estimates for each of the five dysglycemic classification groups are as follows:

- **IGT group**—1.83 (minimum) to 34.12 (maximum)
- **I-IGT group**—4.35 to 6.35
- **IFG group**—1.60 to 23.44
- **I-IFG group**—6.07 to 9.15
- **IGT/IFG group**—9.96 to 14.95.

Two studies and four RCTs had high annualized risk estimates, and these included populations with many risk factors for DM. The variation in the annualized risk per 100 persons observed are likely related to the different populations, mean age, and the sample sizes evaluated within these studies.

**Unadjusted annualized relative risk.** Three of the 28 studies within the IGT classification group were nonsignificant, indicating no association with IGT and progression to DM. Most of these studies had small sample sizes. In the remaining studies, the unadjusted annualized RR with 95 percent CI varied as a function of the diagnostic groups in the following manner:

- **IGT group**—range 3.58 (95 percent CI 2.12 to 6.06) to 10.60 (6.38 to 17.60)
- **I-IGT group**—3.51 (2.22 to 5.54) to 8.63 (5.46 to 13.64)
- **IFG group**—2.40 (1.71 to 3.37) to 9.04 (6.28 to 13.03)
- **I-IFG group**—5.05 (2.86 to 8.90) to 9.85 (6.65 to 14.60)
- **IGT/IFG group**—5.50 (2.86 to 8.90) to 20.69 (12.51 to 34.22).

There were fewer studies in the IFG and I-IFG diagnostic categories than for IGT; and, as such, interpretation across classification groups may be limited.

Meta-analysis was undertaken with unadjusted annualized RR for DM where sufficient numbers of studies were available for combining. The pooled estimates with the 95 percent CI are as follows:

- **IGT group**—6.02 (95 percent CI 4.66 to 7.38)
- **I-IGT group**—5.55 (3.15 to 7.95)
- **IFG group**—4.70 (2.71 to 6.70)
- **I-IFG group**—7.24 (5.30 to 9.17)
- **IGT/IFG group**—12.21 (4.32 to 20.10).

All pooled estimates were significant. Heterogeneity tests were significant for all of the dysglycemic groups except for the I-IGF group. Sensitivity analyses did not affect the significance of the Q test for heterogeneity.

**Attributable risk in the exposed group.** High estimates of AR were calculated for the outcome of DM in dysglycemic individuals. Estimates for each dysglycemic group are as follows:

- **IGT group**—range 52.8 percent to 97.0 percent
- **I-IGT group**—68.8 percent to 86.6 percent
- **IFG group**—57.3 percent to 86.9 percent
- **I-IFG group**—77.1 percent to 88.5 percent
- **IGT/IFG group**—78.6 percent to 93.3 percent.

**Risk for nonfatal CVD outcomes.** Estimates of risk for any nonfatal CVD outcomes were based on six studies. The outcomes characterizing CVD included atherothrombosis, nonstenotic atherosclerosis, clinical MI, percutaneous transluminal coronary angioplasty (PTCA), stroke, unstable angina, heart failure, and combinations of these (major event or any event). Study durations varied from 5 to 9 years and studies were published from 1998 forward. Three of the five studies evaluating IFG as the risk factor are RCTs.

*Annualized risk per 100 persons in the exposed groups.* Estimates of annualized risk per 100 persons varied between the types of CVD events. The highest observed annualized risk was within the only IGT study for the outcome of nonstenotic atherothrombosis. The lowest observed annualized risk was for stroke in people with IFG. The annualized risk estimates for any nonfatal CVD event are as follows: IGT group—11.58 to 12.39; IFG group—0.63 to 9.68.

**Unadjusted annualized relative risk.** Only two studies had significant unadjusted annualized RRs. The single study within the IGT group had similar RR and CI estimates: 2.43 (95 percent CI 1.44 to 4.10) and 2.46 (1.46 to 4.12) for both atherothrombosis groups. Five studies evaluated subjects in the IFG group and RR estimates varied from 1.24 (1.08 to 1.43) to 1.41 (1.17 to 1.69).

In a meta-analysis, nonfatal CVD outcomes were combined according to these subgroups: 1) PTCA and coronary artery bypass graft; 2) stroke, and 3) any other major cardiovascular event. Tests for heterogeneity were not significant. Only one combination for the IFG of any major cardiovascular event was significant with an overall estimate of 1.28 (CI 1.15 to 1.41, p = 0.0001).
Eight studies reported fatal CVD outcomes. Some studies subdivided the outcomes into ischemic heart disease, cardiocerebrovascular disease, and coronary heart disease (CHD). There were no eligible studies to evaluate the I-IGT and IFG/IGT combined classifications. The duration of the studies varied from 7 to 18 years. Three of the studies21,25,27 were based on a male-only cohort (Paris Police study) for the IGT, I-IGT, and IFG groups. Similarly, one study within the IFG group included only postmenopausal women with a history of MI.18 Two other studies in the IFG group recruited subjects with a history of either MI or CHD.35,36

**Unadjusted annualized relative risk.** Only four studies25,35,37,38 had unadjusted annualized RRs that were significant. The calculated estimates are as follows:

- IGT group—range 1.67 (95 percent CI 1.23 to 2.26) to 3.08 (1.47 to 6.47)
- I-IGT group—1.59 (1.07 to 2.28) to 1.72 (1.23 to 2.41)
- IFG group—1.32 (1.04 to 1.67)

In a meta-analysis, within the IGT group, CVD and ischemic heart disease were grouped and the pooled overall estimate of relative risk was 1.66 (95 percent CI 1.21 to 2.11). Within the IFG group, estimates for the CHD/CVD subgroup (1.25 [0.99 to 1.51] and ischemic-related disease subgroup (1.27 [1.06 to 1.54]) were pooled; these estimates did not differ substantively. Overall, the pooled estimates do not provide evidence of a significant association with IFG or IGT and fatal CVD outcomes.

**Attributable risk in the exposed group.** The AR for fatal CVD outcomes was higher in the IGT group (range 52.8 percent to 52.9 percent) than in the IFG group (0 percent to 32.9 percent).

**Risk for fatal CVD outcomes.** Eight studies reported fatal CVD outcomes. Some studies subdivided the outcomes into ischemic heart disease, cardiocerebrovascular disease, and coronary heart disease (CHD). There were no eligible studies to evaluate the I-IGT and IFG/IGT combined classifications. The duration of the studies varied from 7 to 18 years. Three of the studies21,25,27 were based on a male-only cohort (Paris Police study) for the IGT, I-IGT, and IFG groups. Similarly, one study within the IFG group included only postmenopausal women with a history of MI.18 Two other studies in the IFG group recruited subjects with a history of either MI or CHD.35,36

**Annualized risk per 100 persons in the exposed group.** The annualized risks in the exposed group per 100 persons are as follows: IGT group—0.06 to 0.76; I-IGT group—0.23 to 0.34; IFG group—0.10 to 1.54. The differences in annualized risk are likely a function of the different study populations and categorizations of the CVD mortality subgroup classification.

**Key Question 3: Treatment**

Twenty-three reports of 14 RCTs published between 1992 and 2003 evaluated lifestyle or pharmacotherapeutic interventions in adults with IFG or IGT. Duration of followup ranged from 6 months to 6 years. Studies involved 14 to 3,234 participants from Europe, North America, Australia, and Asia with their mean ages ranging from 37.5 to 70 years. Interventions included diet and exercise, oral hypoglycemic agents (metformin, acarbose, and chromium), a statin (pravastatin), and an ACE inhibitor (enalapril). Outcomes included progression to DM or reversion to normal glucose tolerance, cardiovascular events, mortality, and effects on blood pressure and lipid levels.
Progression to DM or reversion to normal. Most studies of the effects of lifestyle or pharmacotherapeutic interventions involved people with IGT.

Lifestyle interventions. Six RCTs evaluated the effect of lifestyle interventions on the risk for developing DM or reverting to normal glucose tolerance in adults with IGT. Intensive combined diet and exercise programs that involved frequent study visits were compared with lifestyle advice alone in five studies.40-44 One study41 compared an exercise program with advice alone, and two studies45,46 evaluated the effect of dietary intervention alone. One trial, the Diabetes Prevention Program, also included a metformin arm.40

All but one of the trials that evaluated a combined diet and exercise program found a significant reduction in the risk for developing DM, or a higher rate of reversion to normal glucose tolerance, with aggressive lifestyle modification. The absolute risk reduction of progressing to DM per year in the studies was between 1.6 percent and 7.1 percent, corresponding to a number needed to treat for 1 year to prevent a case of DM between 14 and 62. Dietary intervention alone significantly reduced the risk for progressing to DM in one trial45 but had no effect in a second study.46 The trial45 that evaluated an exercise intervention alone showed a significantly reduced rate of progression to DM (absolute risk reduction 3.9 percent, number needed to treat 25.5, relative risk reduction 37 percent).

Pharmacotherapeutic interventions. Four RCTs evaluated the effects of pharmacotherapeutic interventions on the risk for developing DM in people with IGT.40,46-48 These studies assessed the effect of acarbose and metformin.

The study46 with acarbose demonstrated a reduced risk of progressing to DM (32 percent versus 42 percent; relative risk reduction 0.25, 95 percent CI 0.10 to 0.37). This effect did not vary by age, sex, or body mass index (BMI). The study also demonstrated an increased rate of reversion to normal glucose tolerance with acarbose relative to placebo (35 percent versus 31 percent, p < 0.0001).

A large study40 found a significantly reduced risk for progressing to DM when taking metformin relative to placebo (7.8 percent versus 11.0 percent per year; relative risk reduction 0.31, 95 percent CI 0.17 to 0.43). Two smaller studies47,48 in people with IGT found no difference in those treated with metformin.

The effect of enalapril in people with IFG and left ventricular dysfunction was assessed in a retrospective post-hoc subgroup analysis. This study45 found a decreased risk for progression to DM in the enalapril arm relative to the placebo arm (3.3 percent versus 48 percent, p = 0.0001). The effect of pravastatin on the development of DM in people with IFG and a previous MI was assessed in a retrospective post-hoc subgroup analysis. This study found no effect on the rate of development of DM, based on a fasting blood glucose level of ≥ 7 mmol/L, or reported use of oral hypoglycemic medication or insulin.

Lifestyle versus pharmacotherapeutic interventions in people with IGT. Only one trial to date, the Diabetes Prevention Program,40 has directly compared lifestyle intervention with pharmacotherapeutic intervention for the prevention of diabetes in people with IGT. It found a significantly lower risk for progressing to DM with aggressive lifestyle intervention compared with taking metformin (4.8 percent versus 7.8 percent per year; relative risk reduction 0.39, 95 percent CI 0.24 to 0.51), especially in individuals 60 years of age or older.

Cardiovascular event outcomes. No RCTs of lifestyle interventions evaluated cardiovascular outcomes.

Pharmacotherapeutic interventions in people with IGT. A single trial49 evaluated the effect of acarbose on cardiovascular event rates in people with IGT.

The primary outcome found a significant reduction in the risk for developing a major cardiovascular event in the acarbose arm compared with the placebo arm of the study (relative risk reduction 0.49, 95 percent CI 0.05 to 0.72, absolute risk reduction 2.5 percent).

Pharmacotherapeutic interventions in people with a previous MI and IFG. Two post-hoc retrospective subgroup analyses evaluated the effect of pravastatin therapy on cardiovascular event rates in people with a previous MI and IFG. In one trial,32 the rate of cardiovascular death or nonfatal MI was significantly lower in the pravastatin group; the relative risk was not significantly different from the values for the post MI patients. In a second trial48 the relative risk for the outcome of cardiovascular death or a nonfatal MI in individuals with IFG was also not significantly different from those within individuals with normal fasting glucose levels at baseline.

Mortality outcomes. One trial46 reported the effect of lifestyle intervention on total mortality rates in individuals with IGT. One trial45 reported the effect of statin therapy on mortality rates in individuals with a previous MI and IFG. In both trials, mortality rates did not differ significantly between groups.

Effects on blood pressure and lipid levels. All studies involved people with IGT.

Lifestyle interventions. Three RCTs45,46,51 evaluated the effect of lifestyle interventions on blood pressure and lipid levels. Significant differences (decline) in blood pressure (systolic and diastolic) were found in two studies and in lipid levels (ratio of total to HDL cholesterol and serum triglycerides only) in one study.

Pharmacotherapeutic interventions. Four RCTs reported the effects of oral hypoglycemic agents on blood pressure and lipid levels. Two trials47,48 reported the effects of metformin on blood pressure levels in people with IGT and demonstrated no significant effect of metformin on blood pressure or lipid levels.
One study reported the effects of acarbose therapy on blood pressure and lipid levels in people with IGT and found significant differences in blood pressure (systolic and diastolic) and hypertension (defined as a blood pressure of at least 140/90 on two consecutive visits or the addition of antihypertensive medications between visits). The trial noted a significant reduction in triglyceride levels. A trial of chromium found no significant effects on lipid levels.

**Key Question 4: Pediatric Population**

All articles that met the general criteria (English language, full-text publication, published since 1979, and results for IFG or IGT analyzed separately from other study populations) and included children with IFG or IGT were collected (36 articles). Of these, a subset of five articles met the criteria for diagnosis, prognosis, or treatment according to the criteria outlined in the methodology. These articles are included in the analysis of their respective sections above.

Four articles included within the analysis (one diagnosis, three prognosis) included participants 15 to 18 years of age, but the pediatric data were not presented separately. These studies were therefore excluded from the pediatric analysis. Nineteen studies were excluded for the following reasons: nine discussed cystic fibrosis, one discussed endemic fluorosis, one dealt with Turner’s syndrome, six related to type 1 DM risks, and no specific pediatric data could be extracted in two articles.

Thus, 13 of 36 articles had extractable pediatric data in articles relevant to either the prevalence, diagnosis, prognosis, or treatment of IFG and/or IGT. The information from these articles forms the basis of the analysis that follows.

Most studies (12 out of 13) addressed the prevalence of IFG or IGT in various at-risk populations and in the population at large. Two studies compared IFG and IGT diagnosis in children. Four studies examined longitudinal followup of a cohort of children and addressed the prognosis of IFG or IGT. One study examined treatment in an open-label trial with metformin.

**Prevalence.** As DM in childhood was initially recognized in Aboriginal populations, most prevalence studies examine these groups. Population-based prevalence of IGT in childhood Aboriginal populations varies from 3.5 percent in Tuvalu to 6.25 percent of Australian Aboriginals aged 7 to 18 years. The prevalence of IGT has been studied in one population-based study. The Third National Health and Nutrition Examination Survey (NHANES III), conducted from 1988 to 1994, measured fasting glucose in 1,083 adolescents age 12 to 19. IFG (glucose 6.1 – 6.9 mmol/L) was present in 1.8 percent (n = 20/1,083). Of these 20 children, 4 were non-Hispanic white, 9 were non-Hispanic black, and 7 were Mexican American. The majority of the children were overweight (mean BMI at 86th percentile), but the range extended from the 10th to 99th percentile. Prevalence of IGT in children not “at-risk” is available from the control group of a single study in which 2.5 percent of 80 children age 10 to 16 had IGT.

The prevalence of IGT in obese children has been examined in two studies of children referred to a tertiary care center for obesity management; IGT was found in 25 percent of children (age 4 to 10 years) and 21 percent of adolescents (age 11 to 18 years) in a U.S. study and in 4.2 percent of 6- to 18-year-olds using the same diagnostic criteria in an Italian population. In the U.S. study, 51 percent of those with IGT were non-Hispanic white, 30 percent were non-Hispanic black, and 19 percent were Hispanic (compared to 58 percent, 23 percent, and 19 percent, respectively, in the population studied). “Silent” DM was diagnosed in four participants (two non-Hispanic black and two Hispanic).

Other “at-risk” populations have been identified. These include children with a history of DM in first degree relatives. In a study of 150 Latino children with a family history of DM, 28 percent were noted to have IGT. Furthermore, 25 percent of Hispanic children whose sibling had type 2 DM had IGT.

Offspring of mothers with pregestational or gestational DM (ODM) also have a higher prevalence of IGT. In a longitudinal study, the prevalence of IGT in ODM was 1.2 percent in children < 5 years (n = 168), 5.4 percent in 5- to 9-year-olds (n = 111), and 19.3 percent (95 percent CI 12.1 to 28.6) in 10- to 16-year-olds (compared to 2.5 percent [95 percent CI 0.4 to 8.1] in controls). Although the control group was somewhat lighter (BMI 20.3 ± 4.0 versus 22.8 ± 5.4 kg/m²) and had 37 percent of participants other than Caucasian compared to 51 percent in the ODM group, it is unlikely that these differences would account for the difference in IGT prevalence. Within this same cohort, 36 percent of those in the ODM group had at least one abnormal OGTT result by 14 to 17 years of age.

Finally, 11 of 21 adolescents with polycystic ovary syndrome had abnormal OGTT results (9 IGT, 2 DM).

The prevalence of IGT is related to increasing age in several studies, but few studies have examined children less than 10 years of age. Children under 10 with obesity have IGT rates comparable to adolescents, although type 2 DM is reported with much less frequency in this young group. Two longitudinal studies with repeated OGTT in Aboriginal and ODM children suggest that rates of IGT increase with increasing age, particularly during the peripubertal period.

**Diagnosis.** A comparison of IGT with IFG is presented in two articles and IFG and hemoglobin A1c are compared in the NHANES III study. In obese children, 6.6 percent of children and adolescents with IGT had IFG, indicating that this method of screening for IGT is very insensitive.
Similarly, hemoglobin A1c is a poor screen for IFG in children. The reproducibility of OGTT testing has not been well studied. Sinha et al. showed that, upon retesting, 10 of 10 children (4 with normal glucose tolerance and 6 with IGT) had the same categorization 3 months later. One article included in the full review for reproducibility of diagnosis that included adolescents concluded that the reliability of test results was likely lower in younger populations.

**Prognosis.** The prognosis of IGT in childhood and adolescence has not been well studied. Three studies had longitudinal data in IGT, but the numbers were very small and did not allow a prediction or rate of conversion from IGT to DM. All of these longitudinal studies were in high-risk populations (two in Aboriginal populations in the United States and the South Pacific) and one in ODM.

**Treatment.** Treatment of IGT in childhood has been examined in a single small open-label trial of metformin for 3 months in 15 adolescents with polycystic ovary syndrome and IGT. Eight of 15 children had normal glucose tolerance when re-evaluated after 3 months of metformin therapy. This was associated with a significant decline in BMI, although there was no significant change in fat mass.

**Discussion**

**Diagnosis**

An accurate diagnosis of DM is required because the consequences for the individual are considerable and lifelong. The diagnosis of IFG or IGT is used as a risk indicator for future DM and/or CVD. The problem with these arbitrary classifications is that test reproducibility is poor, and this encourages repeat testing that adds to the uncertainty and confusion of the diagnosis when results are different.

**Reproducibility of IGT and IFG.** The observed reproducibility for both IGT and IFG classification in these studies was roughly 50 percent. The kappa coefficients for the IGT category were quite low and indicate overall fair agreement. The potential factors contributing to the variation and poor reproducibility were not assessed for this review.

The probability that a significant change has occurred in serial measurements can be estimated by calculating the reference change value (RCV). For FPG, the RCV = \(2^{1/2} \times 1.96 \times (1.42 + 6.32)^{1/2}\) or 17.9 percent. For 2-hr PG, the RCV = \(2^{1/2} \times 1.96 \times (1.42^2 + 16.62)^{1/2}\) or 46.4 percent. The difference between two fasting glucose values would therefore need to be greater than 17.9 percent to be significantly different. A lower RCV would increase the sensitivity to change, or reduce the variation noise, and could be achieved if the analytical and/or the biological variation are lowered. In the best case scenario, the lowest biological variability reported for fasting glucose was an FPG CVI of 4.8 percent. If this value is used along with an intra-laboratory imprecision of 1 percent and no bias, the RCV can be reduced to 13.6 percent. This is the very best or lowest amount of variation possible for a fasting plasma glucose measurement.

**Comparison of IFG and IGT diagnosis.** This review also compared among studies the proportion of participants classified as IGT (2-hr PG), IGT (FPG and 2-hr PG), I-IGT, IFG, I-IFG, and IGT/IFG. Comparisons among these categories were statistically significant except for I-IGT versus IFG and I-IFG versus IGT/IFG. This exemplifies the importance of clearly distinguishing categories as this can affect the proportion of study subjects and the conclusions from prognosis and treatment data.

The reproducibility for both IGT and IFG categorization is poor by both observed and kappa analysis. Because of the large variability in glucose measurement, the absolute FPG and 2-hr PG measurements may be more informative than categorization into IFG and IGT, respectively. Comparison of IGT and IFG categories shows a wide degree of variation among populations. The prevalence of IGT is greater than for IFG in almost all studies. High-risk populations have an equal or greater proportion of IFG compared to IGT diagnoses. Statistically, the proportion of study participants classified as IGT by 2-hr PG alone is greater than if the diagnostic criteria of both 2-hr PG and FPG are used. This will affect the conclusions of prognosis and possibly treatment data in population studies using only the 2-hr PG concentration (WHO epidemiological criteria).

**Prognosis**

This review provides further evidence of the relevance of the OGTT as a diagnostic test. Despite the many shortcomings of the OGTT reviewed here, it detects a very high-risk group for future DM and may either need to be more accessible to clinicians or replaced by a simpler test that provides comparable predictive information. The OGTT also detects a group at risk for CVD; and if IGT is causally related to CVD, the AR estimates suggest that its treatment may reduce CVD risk by as much as 20 percent to 40 percent.

These studies highlight the relevance of fasting and post-challenge glucometabolic abnormalities to clinically relevant outcomes. Intervention studies have already shown that DM can be prevented in these individuals with some interventions.

**Risk for progression to DM.** The results of this systematic review clearly show that IGT, IFG, I-IGT, I-IFG, and combined IGT/IFG are strong risk factors for future DM. The combined group has the strongest risk factor, and this observation is not surprising given the fact that the diagnostic threshold for DM is just a farther point along the dysglycemic spectrum than the threshold for either IFG or IGT.

Nevertheless, these large risk estimates clearly do suggest that any clinical approach directed at preventing DM should include a policy of detecting IFG or IGT. They do not support
suggestions that measures of glucose are not necessary to detect individuals at risk for future DM. However, such a policy may be useful to reduce the number of individuals who require a glucose test.

**Risk for CVD outcomes.** The reviewed studies provide confirmation that IFG or IGT are risk factors for fatal and nonfatal CVD and are consistent with other studies that were excluded because whole blood or capillary samples were used to assay glucose levels. Moreover, the suggestion that IGT is a greater risk factor for CVD than IFG is supported by this systematic review but is based on the findings of a single study.\(^7\) This is not surprising given the fact that IGT is detected in response to stressing the physiology with a nonphysiological glucose load, thus exposing a degree of metabolic dysregulation that would not be apparent on the basis of fasting glucose levels alone.

**Treatment**

**Prevention of DM: lifestyle interventions.** This systematic review clearly demonstrates that DM can be prevented or delayed with lifestyle modification. All but one of the five studies that evaluated a combined diet and exercise program found significant benefits, with a pooled relative risk of 54 percent for progression to diabetes. The only trial to show no effect of a combined diet and exercise intervention was of short duration (6-month followup). Interventions with diet or exercise alone showed mixed results between studies. Efforts to modify dietary intake and activity levels in individuals at increased risk for developing DM are clearly warranted.

**Prevention of DM: pharmacotherapeutic interventions.** Only four trials to date have evaluated the effect of pharmacotherapeutic interventions on the risk for developing DM in individuals with IGT. Two of these studies, one involving acarbose and one involving metformin, demonstrated reduced rates of progression to DM with a relative risk reduction of about 25 percent. Given this relative paucity of information, recommendation of pharmacological intervention for the prevention of DM would seem premature at this time.

**Pediatric Population**

Despite the paucity of population-based studies, several cohort studies in high-risk groups suggest that IGT is a significant and potentially growing problem in the pediatric population. Indeed, larger proportions of children may have IGT than is currently recognized. It is critical to acquire an understanding of the precursors of type 2 DM development in children and youth. However, few conclusions can be made based on the current pediatric literature. Further investigation of prevalence in children and adolescents is necessary to clarify the magnitude of the problem.

**Diagnosis.** The reproducibility of the diagnosis of IGT with OGTT testing and the clinical significance of IFG versus IGT have not been widely examined in the pediatric literature. Although young age has been implicated as a predictor of poor reproducibility of OGTT results in adults, suggesting that reproducibility may be worse in adolescents and children, this was not the experience in one small pediatric study (n = 10).\(^7\)

Clearly, further investigation of the reliability of diagnostic criteria for IFG and IGT is warranted. Furthermore, given the importance of the prevention of type 2 DM, it may be advantageous to identify children who have disturbed glucose metabolism (insulin resistance and/or beta cell dysfunction) before they develop IFG or IGT.

**Prognosis.** An understanding of how disturbed glucose metabolism progresses to IGT and to type 2 DM is key to the primary prevention of DM. Currently, details of this progression are completely lacking in the pediatric population. Prevalence data for type 2 DM suggest prognosis may vary with age, pubertal status, and ethnicity. Family history of DM, exposure to a diabetic environment in utero, fitness and physical activity, fat distribution, and characteristics of nutritional intake may also influence the prognosis of IFG and IGT. Longitudinal studies are required to examine mid- and long-term outcomes of IGT and the determinants of outcome in multiple ethnic groups and across a broad age range. Investigation of other metabolic outcomes in children and adolescents with IFG and IGT would further improve our understanding of disturbance in health in this population. Better understanding of the prognosis of IGT in children and adolescents will clarify the need for intervention and contribute to optimal intervention study design.

**Treatment.** A single study has described the pharmacological treatment of IGT, and no randomly controlled lifestyle intervention has been reported in the pediatric age group. Given the increasing rates of IFG/IGT, research on the optimal approach to the management of these children should be a research priority. This research should compare lifestyle intervention and pharmacotherapy and identify optimal methodologies for young populations and their families. Although glycemic status is a key outcome variable, other metabolic and psychosocial outcomes should also be examined.

**Conclusions**

Analysis from this systematic evidence review suggests the following:

- **Diagnosis**—The reproducibility for both IGT and IFG categorization is poor. Therefore the absolute FPG and 2-hr PG measurement may be more informative than categorization into IFG and IGT respectively. The distribution of study participants in the IGT category varies significantly with the diagnostic criteria used. This will affect findings in epidemiological studies evaluating prognosis and treatment.

- **Prognosis**—Many studies consistently show that both IFG and IGT are strong risk factors for the development
of DM. Fewer studies also show that they are risk factors for future CVD and all-cause mortality.

• **Treatment**—There is evidence that combined diet and exercise, as well as drug therapy (metformin, acarbose), may be effective at preventing progression to DM in IGT subjects.

• **Pediatric population**—IGT is relatively common in childhood, particularly in children who are overweight. Further clarification of population-based prevalence and investigation to improve understanding of the diagnosis, clinical significance, and optimal management of IFG and IGT in childhood is required.

### Availability of the Full Report

The full evidence report from which this summary was taken was prepared for the Agency for Healthcare Research and Quality (AHRQ) by the McMaster Evidence-based Practice Center under Contract No. 290-02-0020. It is expected to be available in September 2005. At that time, printed copies may be obtained free of charge from the AHRQ Publications Clearinghouse by calling 800-358-9295. Requesters should ask for Evidence Report/Technology Assessment No. 128, *Diagnosis, Prognosis, and Treatment of Impaired Glucose Tolerance and Impaired Fasting Glucose*. In addition, Internet users will be able to access the report and this summary online through AHRQ’s Web site at www.ahrq.gov.

### Suggested Citation


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