Type 2 diabetes: Primary health care approach for prevention, screening and diagnosis in South Africa

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Abstract

We have reviewed large studies that demonstrate different methods that have been adopted to prevent or delay the progression to Type 2 diabetes in high-risk individuals. The principal interventions include behavioural modifications in diet and physical activity, use of insulin sensitisers such as metformin and glitazones, and alpha-glucosidase inhibitors.

Although there is no evidence of benefit in health outcomes from large-scale population screening for impaired glucose tolerance (IGT) or impaired fasting glucose (IFG), screening of high-risk individuals has merit. During prolonged periods of dysglycaemia that precede diabetes, individuals remain largely asymptomatic. These periods can be from 8-10 years as extrapolated from the United Kingdom Prospective Diabetes Study data. This phase of pre-diabetes is not innocuous, and is often associated with the concurrent development of complications, which highlights the importance of early detection and treatment of this 'silent killer'. Although different methods for screening of diabetes are available, preferred techniques include measurement of fasting plasma glucose and 2 hr post-load plasma glucose. People should be encouraged to eat correct diets, be active, and maintain a healthy weight - these behaviours have other benefits in addition to preventing or delaying the onset of Type 2 diabetes. There are various diagnostic criteria used for the diagnosis of diabetes. In this article we have presented two sets of criteria, one from the World Health Organization (WHO) and the other from the American Diabetes Association (ADA).

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Prevention

Diabetes is a worldwide pandemic associated with significant morbidity and mortality. The worldwide incidence of diabetes is projected to increase to 220 million by 2010 and 300 million by 2025.[1] Early detection of those at risk for the development of diabetes and early intervention strategies can prevent the progression of diabetes and its associated complications. We need to develop materials that will help people understand their risks for pre-diabetes and what they can do to halt the progression to diabetes and even to "turn back the clock" if possible.

Patients with high risk pre-diabetic conditions like IGT and IFG have about a 25%–50% lifetime risk of developing Type 2 diabetes and should be targeted for primary prevention.[2] A number of well-designed intervention studies using lifestyle (diet and exercise) or drug therapy have been performed to this end.

The Finnish Diabetes Prevention Study (FDPS)[3] and the Chinese Da Qing Study[5] have both conclusively shown that the development of Type 2 diabetes in people with pre-diabetes can be prevented by making changes in the diet to promote moderate weight loss, and by increasing their level of physical activity. The FDPS established a precedent for effectively altering lifestyle in patients with a high risk for diabetes. It studied 522 subjects with IGT using 1999 WHO criteria (FPG < 7.8 mmol/l; 2 hrs post glucose load 7.8-11.1 mmol/l). The intensive lifestyle modification group showed a 58% relative risk reduction as compared to controls, and continued effects were seen as a result of lifestyle change.[3]

The Da Qing study was undertaken in some 33 community clinics in Da Qing, China. A total of 577 subjects with IGT were randomised to a control group, diet control, exercise, or a combination of diet and exercise, and followed over 6 years. All the intervention groups showed a reduction in development of diabetes by 31% to 46% as compared with the control group.[5] Guangwei Li, from the China-Japan Friendship Hospital in Beijing, presented follow-up data in San Francisco at the 2008 ADA Conference, and concluded: *"Group-based lifestyle interventions provided over 6 years can prevent or delay Type 2 diabetes for up to 14 years after the active intervention. Whether lifestyle intervention also leads to a reduction in CVD events and mortality remains unclear."*

A few other trials have been done using, in addition to behavioural modifications, pharmacological interventions, to delay the onset of diabetes, notably, the U.S based Diabetes Prevention Program (DPP),[4] the Troglitazone in Prevention of Diabetes Trial (TRIPOD),[6] Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication (DREAM) trial,[7] the STOP-NIDDM Trial[8] and the Indian Diabetes

Prevention Programme (Indian DPP).[20] More recently, results from the Actos Now for Prevention of Diabetes (ACT Now) trial were released at the ADA Congress (June 2008).[9]

The US-based DPP trial, with 3,234 subjects, focused on prevention of Type 2 diabetes in patients with IGT (2-hour post-glucose load of 7.8–11.1 mmol/l) and/or IFG (FPG of 5.3–6.9 mmol/l). The patients were divided into 3 groups:

- Intensive lifestyle intervention group
- Standard lifestyle recommendations with metformin 850mg bd, and
- Placebo group

The study showed that 30-min/day of moderate physical activity (150-min per week), coupled with a 5–10% reduction in body weight, produced a 58% reduction in diabetes, whilst pharmacological intervention using metformin produced a 31% reduction in these high-risk patients. The secondary objectives of the study assessed differences between the three groups in the development of cardiovascular disease and its risk factors. Intensive lifestyle modification resulted in a decrease in cardiovascular risk factors.[4]

The TRIPOD study was done to assess if chronic treatment of insulin resistance can preserve beta-cell function and prevent or delay the onset of Type 2 diabetes in high-risk patients. The efficacy of thiazolidinediones (TZD) in the treatment of diabetes was shown. This was due to the positive effect of TZDs on insulin sensitivity with reduction in hepatic glucose production, and increased peripheral utilisation of glucose, and preservation of pancreatic beta-cell function, The incidence of diabetes was 12,1% in the placebo group compared to 5,4% in the troglitazone group over 8 months. Troglitazone was removed from the market due to liver safety concerns in 2000.[6]

The DREAM study conducted using another thiazolidinedione, rosiglitazone, showed that in combination with lifestyle changes, it decreased progression from IGT to Type 2 diabetes by 60%. There were 14 cases of non-fatal heart failure in the rosiglitazone group and 2 in the placebo group. However, there were no differences in mortality between the two groups. Treatment with ramipril did not lower the risk of diabetes but improved post-meal glucose profiles.[7]

In a study that randomised 1,429 subjects with IGT, the use of the alpha-glucosidase inhibitor acarbose in the STOP-NIDDM trial lowered post-prandial plasma glucose levels, reducing thereby the insulin demand and preserving beta-cell function. The primary endpoint of the study was the development of diabetes determined by an annual oral glucose tolerance test (OGTT).In this study the risk of patients with IGT developing diabetes was reduced by 25%, and the relative risk of cardiovascular events was reduced by 34%.[8]

In the Indian DPP, 531 subjects with IGT (WHO criteria) were randomised to four groups and followed for three years:

- Control
- Lifestyle intervention
- Metformin (250 mg bd)
- Lifestyle and metformin (250 mg bd)

The relative risk reductions in the three intervention groups ranged from 26.4% to 28.5%. There were no significant differences between the three intervention groups.[20]

In the latest trial, using the thiazolidinedione pioglitazone, called the Actos Now for Prevention of Diabetes (ACT NOW) study, a combination of impaired glucose tolerance and impaired fasting glucose was present in 68% of patients, and the rest had isolated impaired glucose tolerance. Patients also had one or more other high-risk characteristics – at least one component of the metabolic syndrome, a family history of Type 2 diabetes, a history of gestational diabetes, the presence of polycystic ovary syndrome, or minority ethnic background. Patients were randomised to treatment with placebo or 30 mg/day pioglitazone. If the drug was tolerated after one month, the dose was increased to 45 mg/day. Compared with 102 healthy matched controls, patients in the study showed a 48% reduction in insulin sensitivity and a 78% decrease in the insulin secretion/insulin resistance index. People with impaired glucose tolerance were 81% less likely to develop Type 2 diabetes over a 3-year period if treated with pioglitazone.[9]

Table I: Summary of clinical trials for the prevention of Type 2 diabetes

Study	Therapy	Relative Risk Reduction
Finnish Diabetes Prevention Study (FDPS)	Diet + Exercise	58%
Da Qing Study	Diet Exercise Diet + Exercise	31% 46% 42%
Diabetes Prevention Program (DPP)	Diet + Exercise Metformin 850 mg bd	58% 31%
Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication (DREAM)	Rosiglitazone + Diet + Exercise + Ramipril	60%
Study to Prevent Non-Insulin-Dependent Diabetes Mellitus (STOP-NIDDM) trial	Acarbose	25%
Actos now (ACT NOW) for prevention of Diabetes Study	Pioglitazone	81%
Indian DPP	Diet + Exercise Metformin 250 mg bd Diet, Exercise + Metformin 250 mg bd	28.5% 26.4% 28.2%

There is much merit in identifying prediabetes and preventing its progression. The studies summarised in Table I establish the positive impact of lifestyle modifications on limiting progression. Currently, pharmacological intervention for IGT is not funded. Ideally, exceptions should be made for high-risk patients.

Screening

Three tests have been used to screen for diabetes:

- Fasting plasma glucose (FPG)
- 2-hour post load plasma glucose and
- Haemoglobin A_{1c}

However, the ADA has recommended the FPG test for screening because it is easier and faster to perform, more convenient and acceptable to patients, and relatively inexpensive compared to other screening tests. The FPG test has more reproducible results than does the 2-hour post load plasma glucose test, has less intra-individual variation, and has similar predictive value for development of microvascular complications of diabetes.

The ADA defines diabetes as a FPG level of $\leq$7 mmol/L and recommends confirmation with a repeated screening test on a separate

day, especially for people with borderline results. The optimal screening interval is not known, but the ADA recommends a three year interval.

Nearly 21% of people above the age of 60 years have diabetes. People with diabetes present with symptoms, but unfortunately most people with Type 2 diabetes live for years without realising that they have the disease. For some the disease becomes evident only after developing complications, such as cardiovascular disease, retinopathy, neuropathy that can lead to amputations, and nephropathy. Adults with diabetes have heart disease death rates about two to four times higher than adults without diabetes. Diabetes is the leading cause of new cases of blindness in adults 20-74 years of age, and is the leading cause of kidney failure. The rate of amputation for people with diabetes is 10 times higher than for people without diabetes. It therefore becomes important to detect the disease early.[10]

Screening recommendations

There is no evidence of benefit in health outcomes from whole population screening for IGT, IFG or diabetes.[21] However, screening of high-risk groups within a population has merit as potential diabetics may be discovered, and, with early treatment, complications may be prevented or reduced.

The National Institutes of Health (NIH) recommends that people of age ≥ 45 years consider getting tested for diabetes,[11] and the ADA suggests a routine test every three years for those over 45 years, *particularly* if they are overweight, or for those under 45 years if they are overweight and have other diabetes risk factors.[12] Those with additional diabetes risk factors may require more frequent testing.

Screening for gestational diabetes mellitus should be reserved for use in women who meet one or more of the following criteria:

- 25 years of age or older, obese (defined as more than 120% above their desirable body weight)
- A family history of a first-degree relative with diabetes mellitus and
- Belonging to a high-risk ethnic population.[12]

The recommendations for screening for diabetes in asymptomatic individuals are provided in Table II.

Table II: Recommendations for diabetes screening of asymptomatic persons[13]

Test at age 45 years; repeat every three years if the patient is 45 years or older
Test before age 45 years; repeat more frequently than every three years if patient has one or more of the following risk factors:
• Obesity: ≥ 120% of desirable body weight or BMI ≥ 27 kg per m^2 • First-degree relative with diabetes mellitus • Member of high risk-ethnic group (black, Hispanic, Native American, Asian) • History of gestational diabetes mellitus or delivering a baby weighing more than 4,032 g • Hypertensive (≥ 140/90 mmHg) • HDL cholesterol level < 0.90 mmol/L and/or triglyceride level ≥ 2.83 mmol/L • History of IGT or IFG on prior testing
BMI = body mass index HDL = high-density lipoprotein IGT = impaired glucose tolerance IFG = impaired fasting glucose

To date a few studies have been done in isolated populations to determine the prevalence of diabetes mellitus, impaired glucose tolerance (IGT) and impaired fasting glycaemia (IFG) in South Africa.[15,16] Overall, these studies reveal a moderate prevalence of diabetes and high prevalence of total disorders of glycaemia suggesting that this community is well into the epidemic of glucose intolerance. The prevalence rate of diabetes in South African Indians is higher than in other population groups (See Table III).[22]

Table III[22]: Prevalence rate of diabetes per population group and gender

Populations group	Males %	Females %	Total %
Urban black African	5.4	7.3	6.4
Non-urban black African	5.4	8.4	7.4
Coloured	5.1	7.3	6.2
White	5.1	7.3	6.2
Asian/Indian	18.0	16.4	17.1
South Africa	4.7	6.2	5.5

Haemoglobin A_{1c} is currently not recommended for the diagnosis of diabetes, based upon expert consensus.[25] This is because HbA_{1C} is difficult to standardise between laboratories and lacks the sensitivity to distinguish IGT from diabetes.[23] It is, however, the most widely accepted laboratory test for the measurement of glycaemic control, and is recommended for routine use in the management of patients with diabetes.

Diagnosis

Diagnosis of diabetes defines a group of patients at a high risk for developing micro- and macrovascular disease. For individuals with symptoms of diabetes, such as polyuria, polydipsia or unexplained weight loss only elevated FPG ≥ 7.0 mmol/l or elevated random plasma glucose ≥ 11 mmol/l is required to confirm the diagnosis. The diagnostic criteria and classification recommendations have been established by the WHO (1980), and so too by the ADA (1997) and (2003), who use more stringent criteria.

In order to make a diagnosis of diabetes it becomes necessary to establish hyperglycaemia. The plasma glucose must be measured by a laboratory method. The presence of diabetes symptoms with a single random venous plasma glucose value ≥ 11.1 mmol/L, or elevated fasting venous plasma glucose of ≥ 7.0 mmol/l are diagnostic of diabetes.[23] In the absence of unequivocal hyperglycaemia with acute metabolic decompensation, these criteria should be confirmed by repeat testing on a different day.

An oral glucose tolerance test (OGTT) is not normally needed in routine clinical practice, but as many as 30% of people with diabetes will not be diagnosed if only fasting measurements are done. An OGTT to establish diagnostic status need only be considered if blood glucose values lie in the uncertain range (i.e. between the levels that establish or exclude diabetes) and fasting blood glucose levels are below those, which establish the diagnosis of diabetes. If an OGTT is performed, it is sufficient to measure the blood glucose values while fasting and at 2-hours after a 75 gm oral glucose load. For children the oral glucose load is related to body weight: 1.75 g glucose per kg. The diagnostic criteria in children are the same as for adults.[18,19]

Diagnostic interpretations of the fasting and 2 hr post-load concentrations in non-pregnant subjects are shown in Table IV and V

below. It must be pointed out that there are different criteria adopted by different national and international groups for the diagnosis of diabetes. We present here diagnostic criteria used by the two large international groups – the ADA and the WHO.[23] Local South African guidelines use the same values as the ADA.[24]

Table IV: WHO criteria for diabetes and impaired glucose tolerance[23]

	Glucose concentration in mmol/l			
	Plasma		Whole blood	
	Venous	Capillary	Venous	Capillary
Diabetes Mellitus				
Fasting value	≥ 7.8	≥ 7.8	≥ 6.7	≥ 6.7
Or				
2 hr after 75 gm glucose load	≥ 11.1	≥ 12.2	≥ 10.0	≥ 11.1
Impaired Glucose Tolerance				
Fasting value	< 7.8	< 7.8	< 6.7	< 6.7
2 hr after 75 gm glucose load	7.8 – 11.0	8.9 – 12.1	6.7 – 9.9	7.8 – 11.0

In June 1997, the ADA announced new recommendations for the diagnosis of diabetes,[23] and in 2003 these guidelines were updated with modifications regarding the diagnosis of IFG. The new guidelines also lowered the cut-off values for fasting glucose concentrations used to diagnose diabetes.[25]

Table V: ADA diagnostic criteria, 1997[23]

1	Symptoms + random plasma glucose ≥ 11.1 mmol/l
2	Fasting plasma glucose ≥ 7.0 mmol/l
3	75 gm OGTT 2 hr plasma glucose ≥ 11.1 mmol/l
	• Each method confirmed on a subsequent day by any method
	• Impaired fasting glucose (IFG) ≥ 6.1 and < 7.0 mmol/l

Glucose tolerance is classified into three categories based on the FPG:

- Normal: FPG < 5.6 mmol/l
- IFG: FPG ≥ 5.6 mmol/l but <7.0 mmol/l
- Diabetes: FPG ≥ 7.0 mmol/l

IFG is comparable to IGT, which is defined as plasma glucose levels between 7.8 and 11.1 mmol/l 2-hr after a 75 g OGTT. Individuals with IFG or IGT are at substantial risk for developing Type 2 diabetes (a 40% risk over the next five years) and cardiovascular disease.

FPG is the preferred screening test for children and non-pregnant adults, whereas OGTT is the recommended test for Gestational Diabetes Mellitus (GDM), although the diagnostic levels for GDM are different than for others (See Table VI).[27,28]

Table VI: Diagnosis of GDM with a 100 g or 75 g glucose load[27,28]

	mmol/l
100 g glucose load	
Fasting	5.3
1-hr	10.0
2-hr	8.6
3-hr	7.8
75 g glucose load	
Fasting	5.3
1-hr	10.0
2-hr	8.6

Two or more of the venous plasma concentrations must be met or exceeded for a positive diagnosis of GDM. The test should be done in the morning after an overnight fast of between 8 and 14 hr and after at least 3 days of unrestricted diet (≥ 150 g carbohydrate/day) and unlimited physical activity. The subject should remain seated and should not smoke throughout the test.

Diabetes mellitus is clinically and genetically a heterogeneous disorder due either to insulin deficiency or to resistance to the action of insulin. Research has led to the recognition that the different types of diabetes have different causes although their pathology after onset of diabetes may be similar. The classification of this heterogeneous group of disorders is summarised in Table VII below. The WHO Expert Committee on Diabetes recommends this classification.[18,19]

Table VII highlights the different clinical presentations and genetic and environmental aetiologic factors that distinguish the types of diabetes.

Table VII: Classification of the types of diabetes class name characteristics[17,18,19]

Type 1	• Low or absent levels of circulating endogenous insulin • Onset predominantly in youth but can occur at any age • Associated with certain HLA and GAD antigens • Abnormal immune response and islet cell antibodies are frequently present at diagnosis • Aetiology probably only partially genetic, as only ~35% of monozygotic twins are concordant for insulin dependent diabetes
Type 2	• Insulin levels may be normal, elevated, or depressed • Hyperinsulinaemia and insulin resistance in most patients • Insulinopaenia develops as beta-cell function declines • Not insulin-dependent or ketosis-prone under normal circumstances, but may use insulin as disease progresses • Onset predominantly after age 40 years but can occur at any age • Approximately 50% of men and 70% of women are obese • Aetiology probably strongly genetic as 60%-90% of monozygotic twins are concordant for non-insulin dependent diabetes
Gestational diabetes (GDM)	• Glucose intolerance that has its onset or recognition during pregnancy • Associated with older age, obesity, family history of diabetes • Conveys increased risk for the woman for subsequent progression to non-insulin dependent diabetes mellitus (NIDDM) • Associated with increased risk of macrosomia
Other types of diabetes	• Pancreatic disease • Hormonal disease • Causes of hyperglycaemia are known for some conditions e.g. pancreatic disease • Drug or chemical exposure • Insulin receptor abnormalities • Certain genetic syndromes

Conclusion

Although typically Type 2 diabetes presents at about the age of 40 years, there are recent trends for the disease to present at earlier

ages, in particular related to increasing obesity and lack of regular exercises or physical activity. It has become imperative to implement lifestyle modifications most aggressively if we are to stem the increasing incidence of Type 2 diabetes. It requires an ownership of the responsibility to achieve this. Not only is it an initiative in which individual patients and their care providers have to be involved, but also parents, schools, medical aid funders, Departments of Health and Government. Regular physical training must be reintroduced at all grades in the school. Perhaps then our fight against diabetes will begin.

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