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An overview of Diabetes Mellitus: Past, Present and Future development

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Abstract

Diabetes of all types can lead to complications in many parts of the body and can increase the overall risk of dying prematurely. Globally, an estimated 422 million adults were living with diabetes in 2014, compared to 108 million in 1980.This reflects an increase in associated risk factors such as being overweight or obese. Diabetes caused 1.5 million deaths in 2012. 43% of these 3.7 million deaths occur before the age of 70 years. The most common is type 2 diabetes, usually in adults, which occurs when the body becomes resistant to insulin or doesn't make enough insulin. Healthy diet, regular physical activity, maintaining a normal body weight and avoiding tobacco use are ways to prevent or delay the onset of type-2 diabetes. For the past several decades, diagnosis and treatment of diabetes has been based on blood glucose criteria. There are a number of different classes of anti-diabetic medications. Some are available by mouth, such as metformin (decreasing the liver's production of glucose) and thiazolidinediones (TZD), while others are only available by injection such as GLP-1 agonists. Type-1 diabetes can only be treated with insulin, typically with a combination of regular and NPH insulin, or synthetic insulin analogs. New technologies, and therapies those are now available, such as rapid glucose estimation from a drop of blood, insulin pumps (artificial pancreas), stem cell therapy, islet cell transplants (through genetic engineering, xenotransplantation) and point of care HbA1c to diagnose the diabetes.

Keywords: Diabetes mellitus, Type 2 Diabetes, HbA1c, Metformin, Thiazolidinediones (TZD), artificial pancreas

Introduction

Around 600 B.C., a Hindu physician described the sweet taste of urine in people with extreme thirst. Innovations testing of DM are being developed day to day. In 2000, India (31.7 million) topped the world than China (20.8 million) and United States (17.7 million) diabetes is predicted to double globally 366 million in 2030 with a maximum increase in India (1). Diabetes mellitus (DM) is most devastating, chronic, common non-communicable disease and has become a serious problem globally. In this review, we summarize the available evidence regarding classical treatments for diabetic mellitus under basic and clinical investigation.

Risk factors

Ethnic origin, family history, and specific gene mutations are risk factors beyond our control. However, many lifestyle choices have great influence over the risk of developing type-2 diabetes. The most prominent are obesity and physical inactivity. Additional risk factors for type 2 diabetes include low HDL (<35mg/dL) and high triglycerides (>250 mg/dL) as well as elevated blood pressure or having given birth to a child over 9 lb (2).

These risk factors may be present in a person presenting with prediabetes, in which the blood glucose level is higher than normal but not yetdiagnostic of type 2 diabetes (3).The good news for people with pre-diabetes is that a weight loss of only 5% of body weight can prevent or delay the onset of disease. The impact of obesity on developing diabetes has been demonstrated in data taken from the National Health and Nutrition Examination Survey of 2006. In Figure 1, these data show the lifetime risk of developing diabetes based on weight categories at 18 years of age. It is striking to note that a female who is classified as obese at 18 years of age has more than a 50% risk of developing diabetes over her lifetime. This risk jumps to more than 75% in a female classified as very obese (3).

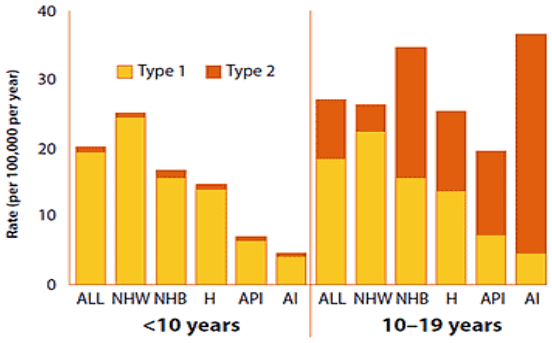

Figure 1: Lifetime risk based on 18 years of age at baseline.

Signs and symptoms

The classic symptoms of untreated diabetes are weight loss, polyuria (increased urination), polydipsia (increased thirst), and polyphagia (increased hunger) (4). Symptoms may develop rapidly (weeks or months) in type 1 DM, while they usually develop much more slowly and may be subtle or absent in type 2 DM. In addition to the known ones above, they include blurry vision, headache, fatigue, slow healing of cuts, and itchy skin. Prolonged high blood glucose can cause glucose absorption in the lens of the eye, which leads to changes in its shape, resulting in vision changes. A number of skin rashes that can occur in diabetes are collectively known as diabetic dermadromes. Effects can range from feelings of unease, sweating, trembling, and increased appetite in mild cases to more serious issues such as confusion, changes in behavior such as aggressiveness, seizures, unconsciousness, and (rarely) permanent brain damage or death in severe cases (5), hypoglycemia may easily be mistaken for drunkenness (6); rapid breathing and sweating, cold, pale skin are characteristic of hypoglycemia but not definitive(7). People (usually with type 1 DM) may also experience episodes of diabetic ketoacidosis, a metabolic disturbance characterized by nausea, vomiting and abdominal pain, the smell of acetone on the breath, deep breathing known as Kussmaul breathing, and in severe cases a decreased level of consciousness. A rare but equally severe possibility is hype-rosmolar non-ketoticstate which is more common in type 2 DM and is mainly the result of dehydration (8). Impaired glucose tolerance (IGT) and impaired fasting glycaemia (IFG) are intermediate conditions in the transition between normal blood glucose levels and diabetes (especially type 2), though the m transition is not inevitable. People with IGT or IFG are at increased risk of heart attacks and strokes.

Complications of diabetes

Diabetes doubles increased the risk of cardiovascular disease(9), long-term complications relate to damage to blood vessels and 75% of deaths in diabetics are due to coronary artery disease (10). Other "macrovascular" diseases are stroke, and peripheral vascular disease.

The primary complications of diabetes due to damage in small blood vessels include damage to the eyes, kidneys, and nerves. Damage to the eyes (diabetic retinopathy, is caused by damage to the blood vessels in the retina of the eye, and can result in gradual vision loss and blindness(11).Damage to the kidneys, known as diabetic nephropathy, can lead to tissue scarring, urine protein loss, and eventually chronic kidney disease, sometimes requiring dialysis or kidney transplant(12). Damage to the nerves of the body, known as diabetic neuropathy, is the most common complication of diabetes (11) result numbness, tingling, pain, and altered pain sensation, foot problems (such as diabetic foot ulcers) may occur, and can be difficult to treat, occasionally requiring amputation. Additionally, proximal diabetic neuropathy causes painful muscle wasting and weakness. There is a link between cognitive deficit and diabetes. Compared to those without diabetes, those with the disease have a 1.2 to 1.5-fold greater rate of decline in cognitive function (13).

Diagnosing and Prevention of diabetes

Rudimentary forms of diagnostics for diabetes have existed for millennia. Around 600 B.C., a Hindu physician described the sweet taste of urine in people with extreme thirst. Diagnosis as we know it dates to medieval times, when urine was routinely collected in a flask and examined for sediment related to disease said to be in different parts of the body.

Just over 100 years ago, Benedict developed a standardized method to measure glucose in urine (14). In 1921, at the Annual Meeting of the Association of Life Insurance Medical Directors, Dr. Elliott Joslin extended the use of Benedict's method in the "glucose diet test." This version of the glucose tolerance test required the patient to eat two meals, each containing 125 grams of carbohydrate, including apple pie and ice cream, followed by collection of urine for the following two hours. He stated that this was the most reliable method for diagnosis of diabetes (15). He also noted that blood tests for glucose were not satisfactory due to complicated methods that resulted in high error rates. Today, this would be known as unacceptable coefficients of variation.

Diabetes mellitus is characterized by recurrent or persistent high blood sugar, and is diagnosed by demonstrating any one of the following (18):

- Fasting plasma glucose level $\geq$ 7.0 mmol/l (126 mg/dl)
- Plasma glucose $\geq$ 11.1 mmol/l (200 mg/dl) two hours after a 75 g oral glucose load as in a glucose tolerance test
- Symptoms of high blood sugar and casual plasma glucose $\geq$ 11.1 mmol/l (200 mg/dl)
- Glycated hemoglobin (HbA1C) $\geq$ 48 mmol/mol ($\geq$ 6.5 DCCT %) (2).

There is no known preventive measure for type1 diabetes (19). Type 2 diabetes can often be prevented by maintaining a normal body weight, engaging in physical exercise, and consuming a healthful diet (19). Dietary changes known to be effective in helping to prevent diabetes include maintaining a diet rich in whole grains and fiber, and choosing good fats, such as the polyunsaturated fats found in nuts, vegetable oils, and fish. Limiting sugary beverages and eating less red meat and other sources of saturated fat can also help prevent diabetes (20). Active smoking is also associated with an increased risk of diabetes, so smoking cessation can be an important preventive measure as well (21).

a. Criteria for diabetes diagnosis

For the past several decades, diagnosis of diabetes has been based on blood glucose criteria, either a fasting sample or the two-hour value in the 75-g oral glucose challenge test. Several recent studies have shown the limited usefulness of glucose testing in the diagnosis of adolescents (22).

In this population, the glucose tolerance test can give misleading results due to the effects of puberty and hormones, according to a recent presentation at the Excellence in Diabetes Conference, February 28 through March 2, 2014, in Doha, Qatar. The upper limit of normal used to diagnose diabetes has been reduced, and an intermediate category of impaired glucose has been added to the diagnostic algorithm(23).

Numerous research studies have confirmed that lowering the acceptable levels of blood glucose assists with earlier diagnosis and reduces the morbidity associated with this disease (24).However, another impact of the lower limits is the diagnosis of diabetes in people who would have been excluded earlier (2).Therefore, the large rise in cases in recent years results from this reclassification as well as actual numbers of people presenting with diabetes. In 2009, an International Expert Committee recommended the use of hemoglobin A1c (HbA1c) to diagnose diabetes. The American Diabetes Association adopted this criterion in 2010(2)(Figure2).

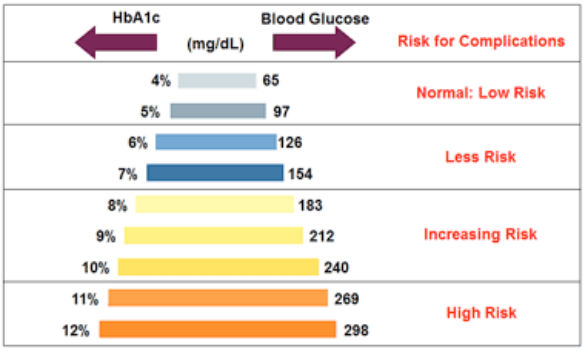

Figure 2: Relationship between HbA1c, blood glucose, and complications.

HbA1c had been recognized for its clinical utility in diabetes management as early as the 1980s, but it had not been recommended for diagnosis. This marker is a stable adduct where glucose binds to the N-terminal valine of the hemoglobin B chain. The tight binding gives it a lifespan coincident with that of the erythrocyte, about 120 days. When the recommendation was made for the use of HbA1c in diagnosis, it was with the understanding that the test be performed by a method that is certified by the National Glycohemoglobin Standardization Program (NGSP) or traceable to the Diabetes Control and Complications Trial reference assay. Earlier methods to measure HbA1c showed wide variability, but with the NGSP and proficiency testing, standard deviations have been reduced considerably (23).

However, HbA1c levels (Figure 3) may vary with patients' race or ethnicity. Glycation rates may be higher in some racial groups, but this is controversial.18 Also, whether the cut point for diagnosis should be the same for children and adolescents as it is for an adult is unclear (25). For conditions with abnormal red cell turnover, such as pregnancy, recent blood loss or transfusion, and some anemia's, the diagnosis of diabetes must rely on blood glucose and not HbA1c (23).In addition to HbA1c, two other long-term indices of glycemia-fructosamine and 1, 5 anhydroglucitol (1, 5-AG)-are available but less widely used. Fructosamine, the product of post-translational glycation of serum proteins, predominantly albumin, provides a reflection of glycemia over a shorter time frame than does HbA1c. The reliability of the fructosamine assay is variable, bringing into question its clinical utility. One study found the mean glycemia over a prior two-week period was better predicted by HbA1c than fructosamine(26).Even as an adjunct to home blood glucose monitoring, weekly fructosamine testing did not improve HbA1c levels.

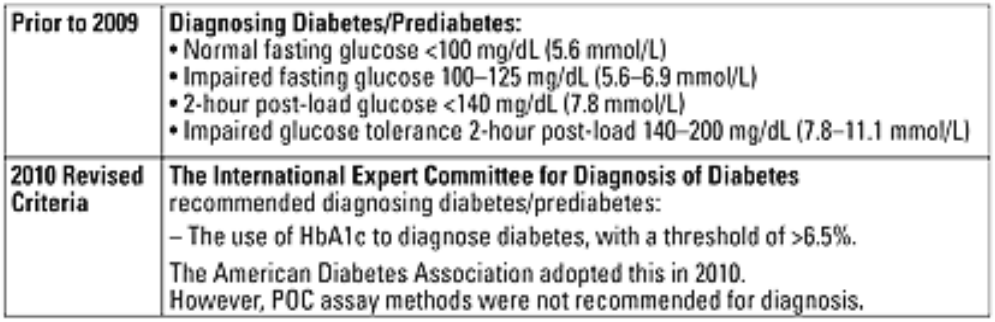

Figure 3: It shows the changing criteria regarding blood glucose level and HbA1c.

Table 1: WHO diabetes diagnostic criteria (16, 17).

Condition	2hr glucose	Fasting glucose	HbA_{1c}	
Unit	mmol/l(mg/dl)	mmol/l(mg/dl)	mmol/mol	DCCT %
Normal	<7.8 (<140)	<6.1 (<110)	<42	<6.0
Impaired fasting glycaemia	<7.8 (<140)	≥6.1(≥110) & <7.0(<126)	42-46	6.0–6.4
Impaired glucose tolerance	≥7.8 (≥140)	<7.0 (<126)	42-46	6.0–6.4
Diabetes mellitus	≥11.1 (≥200)	≥7.0 (≥126)	≥48	≥6.5

b. Populations based measured

At the current time, type 1 diabetes is predictable with the measurement of antibodies directed against insulin and proteins in beta cells but not yet preventable. It naturally follows that diabetes should be a preventable disease and ultimately cured and this aspect is highlighted in the section on population-based measures. Notwithstanding, some 85–90% of new cases develop within the general population (those not having such a history), and effective screening and prevention measures must target this group. Childhood type1 diabetes cannot be explained solely on genetic grounds, some form of environmental explanation seems likely, and the environment can be manipulated. The challenges, ranging from the practical to the financial, are considerable (27).

c. New Therapy

Steady improvements of existing therapies have driven many of the advances leading up to our current therapy for diabetes, and this pattern is likely to hold true for the future. These ranges are from tweaking standard therapies, such as insulin, to more radical concepts, including the therapeutic manipulation of other hormones in the attempt to imitate normal physiology more closely in type 1 diabetes patients.

d. New technology

New technologies for type 1 diabetes have been introduced at an accelerating rate over recent years. From the patient's perspective, this is not only exciting, but has also led to growing optimism amongst healthcare providers. Technologies that are now commonplace, such as rapid glucose estimation from a drop of blood, insulin pumps and point of care HbA1c results were 'new technologies' not that long ago. Indeed, it could be argued that the major advances in type 1 diabetes care made within the last quarter of a century have come from technology rather than biology. The optimal solution would be a closed-loop system or 'artificial pancreas' capable of continuous glucose monitoring linked to an implanted or external insulin delivery device and controlled by a simple computer algorithm (28). Mathematicians, engineers, physicians, computer scientists, patients and clinicians have combined their efforts to develop an

'artificial pancreas', and the section on new technologies describes the progress that has been made.

e. Stem cell therapy

Over the last decade, few topics in type 1 diabetes research have attracted more attention, conveyed a larger sense of promise, or – as some might argue – provided more 'hype' than the notion of stem cell therapies (29). Indeed, stem cell therapies have not only stimulated major scientific effort, but also political debate, extensive financial investment, controversy over intellectual property rights, battles over ethics, morality and religion, and more. Although the road that has brought us to the present state of affairs has been long and hard, type 1 diabetes we may soon see a variety of stem cell therapies entering clinical trials. These might finally resolve the debate over 'embryonic versus adult' stem cells, at least in terms of which has the most therapeutic potential. A series of major hurdles still remain before the promise of stem cell therapies becomes reality. The section on stem cell therapies discusses the promise, the hype, the remaining hurdles, and the hope that this form of therapy offers for those with the disease.

f. Genetic engineering

Genetic engineering is the process by which a functional gene is introduced into a new tissue or organ in order for it to express a new characteristic or feature. Genetic engineering, in the form of 'gene therapy', reached the public media through attempts in the early 1990s to cure severe combined immunodeficiency disorder (SCID; aka, 'bubble boy disease'). Investigators in type 1 diabetes, as in many other fields of medicine, rushed into this promising area; leading objectives were modification of islet cells to render them resistant to immune destruction prior to transplantation, altering various cell types to convert them into insulin-producing cells for later transplantation into the same individual, or altering bone marrow cells in such a way that they would improve therapeutic outcomes (such as prevention of late complications) following transplantation (30).

g. Xenotransplantation

One word with many letters, 'xenotransplantation', is a process whereby an individual receives a transplant of tissues or cells obtained from another species. Indeed the word 'xeno' derives from the Greek word meaning *stranger*. The notion is not new (ancient civilizations attempted it) nor is it without modern success stories (e.g. pig heart values rendered non-living by chemicals are commonly used). While the organ transplantation field would, in theory, see a revolution were all forms of cell and tissues subject to such a method, significant hurdles – from those real in nature (xenorejection) to those more theoretical (genetic transfer of harmful viruses from the donor animal species to the recipient human) – have thus far severely limited this procedure. However, the promise for this approach is so great and recent advances so transforming, that much hope resides for the future of this field (31) including what it would bring to those with type 1 diabetes.

Management

Diabetes mellitus is a chronic disease, for which there is no known cure except in very specific situations (32). Management concentrates on keeping blood sugar levels as close to normal, without causing low blood sugar. This can usually be accomplished with a healthy diet, exercise, weight loss, and use of appropriate medications (insulin in the case of type 1 diabetes; oral medications, as well as possibly insulin, in type 2 diabetes).

Learning about the disease and actively participating in the treatment is important,

since complications are far less common and less severe in people who have well-managed blood sugar levels (33). The goal of treatment is an HbA1C level of 6.5%, but should not be lower than that, and may be set higher. Attention is also paid to other health problems that may accelerate the negative effects of diabetes. These include smoking, elevated cholesterol levels, obesity, high blood pressure, and lack of regular exercise(34). Specialized footwear is widely used to reduce the risk of ulceration, or re-ulceration, in at-risk diabetic feet.

a. Lifestyle

People with diabetes can benefit from education about the disease and treatment, good nutrition to achieve a normal body weight, and exercise, with the goal of keeping both short-term and long-term blood glucose levels within acceptable bounds. In addition, given the associated higher risks of cardiovascular disease, lifestyle modifications are recommended to control blood pressure (35).

b. Curb your blood sugar

You can also improve blood sugar levels after meals without using drugs. There are two important approaches. Firstly, if a small, protein rich snack is taken first thing in the morning, and breakfast is delayed for two hours, the rise in blood glucose after breakfast is reduced by about one half. This is called the second meal effect and although it has been recognized in non-diabetic individuals for almost a century, it has only recently been shown to work in people with type 2 diabetes. Secondly, if you go out for a half hour walk after a meal (or do any physical activity) then the rise in blood glucose will be very much less compared to just sitting in a chair. This is because muscle tissue takes up glucose more rapidly during exercise, and the meal time rise in glucose is blunted.

c. Medications

Medications used to treat diabetes do so by lowering blood sugar levels. There are a number of different classes of anti-diabetic medications. Some are available by mouth, such as metformin, while others are only available by injection such as GLP-1 agonists. Type-1 diabetes can only be treated with insulin, typically with a combination of regular and NPH insulin, or synthetic insulin analogs.

Thiazolidinediones (TZD) were also introduced in the 1990s. Known as TZDs, these oral medications address the body's inability to use insulin effectively to control blood sugar. Marketed under the brand names Actos and Avandia, TZDs temporarily increase the body's sensitivity to insulin, enabling it to process insulin more effectively.

In 2006, the FDA approved the first DPP-IV inhibitor, an oral medication that increases the body's ability to produce insulin when needed by blocking the actions of an enzyme. Glucagon-like peptide-1 (GLP-1) agonists, taken by injection, also increase insulin levels when needed, reduce the amount of glucose produced by the liver and reduce the rate of digestion. As a result, patients may have less appetite and lose weight. Both DPP-IV inhibitors and GLP-1 agonists help glucose remain stable for longer periods of time and have few side effects. Unlike the sulfonylureas used decades earlier, these medications do not increase the risk of hypoglycemia. Non-incretin beta cell stimulants still in development include glucokinase activators, G-protein-coupled receptors, and anti-inflammatory and anti-oxidant therapies. Additional agents that target glucose synthesis include glucose-6-phosphatase and glycogen phosphorylase.

Metformin is generally recommended as a first line treatment for type2 diabetes, as there is good evidence that it decreases mortality (36). It works by decreasing the

liver's production of glucose. Several other groups of drugs, mostly given by mouth, may also decrease blood sugar in type II DM. When insulin is used in type 2 diabetes, a long-acting formulation is usually added initially, while continuing oral medications. Doses of insulin are then increased to effect (36).Other recent medications include starch blockers such as Acarbose, which slows the digestion of food to prevent blood sugar from increasing significantly after meals. Symlin, an injectable medicine used with insulin, also helps to control blood sugar after meals.Among medications that lower blood pressure, angiotensin converting enzyme inhibitors (ACEIs) improve outcomes in those with DM while the similar medications angiotensin receptor blockers (ARBs) do not(37).Aspirin is also recommended for people with cardiovascular problems, however routine use of aspirin has not been found to improve outcomes in uncomplicated diabetes (38).

d. Surgery

One of the most exciting areas of research is islet cell transplants. These involves taking the islet cells - the cells in the pancreas that produce insulin - from dead donors and putting them into people with Type 1 diabetes, whose own islet cells have stopped working. Diabetes UK funded the UK's first 15 islet cell transplants. It is now available on the NHS and 34 people have benefited since 2005. The treatment is very effective. However, there are still issues to solve. The transplanted cells only last for a few years; there is a very limited supply of cells; and it is difficult to stop the body rejecting them. A pancreas transplant is occasionally considered for people with type 1 diabetes who have severe complications of their disease, including end stage kidney disease requiring kidney transplantation(39).

Weight loss surgery in those with obesity and type-2 diabetes is often an effective measure many are able to maintain normal blood sugar levels with little or no medications following surgery and long-term mortality is decreased. There however is some short-term mortality risk of less than 1% from the surgery (40).

e. Artificial Pancreas

A California-based medical device company, Medtronic, has combined a glucose monitoring system with an insulin delivery pump to create an automatic insulin delivery system for diabetes treatment, one that works like your natural pancreas. The device, which would be worn externally, monitors your blood glucose leveland stops insulin delivery if your blood glucose level becomes too low. One of the most important features is that it protects you from developing type 1 diabetes when they used a gene that prompted liver cells to produce insulin as part of a gene therapy diabetes treatment. The mice responded to the treatment within one week, with blood glucose levels dropping to normal and staying that way for the rest of their lives.

Future challenging for prevention of diabetes

The level of morbidity and mortality due to diabetes and its potential complications are enormous, and pose significant healthcare burdens on both families and society. In India, the steady migration of people from rural to urban areas, the economic boom, and corresponding change in life-style are all affecting the level of diabetes. To reduce the disease burden that diabetes creates in India, appropriate government interventions and combined efforts from all the stakeholders of the society are required (41). Clinicians may be targeted to facilitate the implementation of screening and early detection programmes, diabetes prevention, self-management counseling, and therapeutic management of diabetes in accordance with the appropriate local

guidelines form the backbone of controlling the predicted diabetes epidemic. Early screening and detection of pre-diabetes (especially in pregnant women and children and adults with BMI ≥25) may yield positive health outcomes in society (42). Continuing education programmes for general practitioners may provide the "clinical inertia" required to initiate programme adherence, and may be a major step in achieving target glycaemic levels and the prevention of disease complications. Aggressive clinical measures in terms of early insulin initiation combined with optimal doses of oral hypoglycaemic agents. The CDC estimates that in 2011 more than seven million people in the U.S. had diabetes and did not know it. Diabetes imposes a financial burden on both our healthcare system and the individuals living with the disease. The CDC estimates the cost of diabetes in the U.S. was $194 billion in 2011 and will increase to more than $250 billion in 2014(2).

Government policies may help in creating guidelines on diabetes management, funding community programmes for public awareness about the diabetes risk reduction, availability of medicines and diagnostic services to all sections of community (43). Efforts by various governments and agencies around the world to intervene in diabetes management have resulted in positive health outcomes for their communities. In the United States there are number of public and private funded programmes to prevent and manage diabetes that have been successful (44).

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