Chapter 11

Principle of Management of Type 2 Diabetes: From Clinical, Public Health and Research Perspectives

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Additional information is available at the end of the chapter

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Abstract

Apart from stopping smoking, controlling hypertension and using statin, losing possible excess bodyweight and regular physical activity and exercise are the cornerstones in diabetes management. There is often need of controlling blood glucose immediately. Approach of '*dynamic dose management of medications likely to cause hypoglycemia*' helps to control high blood glucose immediately as and when required with sulfonylurea or insulin and to taper off their dose later. Anti-hyperglycemic medications which are unlikely to cause hypoglycemia are continued to control hyperglycemia. The diagnosis of gestational diabetes usually made at 24-28 weeks is applicable for clinical management of mother and child and for possible prevention of diabetes later in the mother. From the public health perspectives, however, protection of the susceptible *in utero* population from maternal malnutrition or clinical or subclinical hyperglycemia right from the time of conception itself also needs to be considered to control the diabetes epidemic at the population level. Campaigns and programmes for maintenance of optimal pre-pregnancy body weight as per the recommended body mass index of the respective populations along with regular physical activity and exercise during pregnancy are the essential measures available at hand to prevent the possibility of maternal hyperglycemia right from the early pregnancy.

Keywords: diabetes, CVD, hypertension, high blood pressure, physical activity, exercise, smoking, body mass index, ethnicity, hypoglycemia, acarbose, diabetes epidemiology, diabetes control, maternal health, pre-pregnancy weight

1. Introduction

There are now estimated 415 million adults aged 20–79 with diabetes worldwide and a further 318 million adults are estimated to have impaired glucose tolerance [1]. About half of the

3.7 million deaths due to diabetes and its complications occur before the age of 70 years [2]. Up to 80% of deaths in type 2 diabetes are cardiovascular diseases (CVDs) related. Persons with impaired glucose tolerance are also almost three times more likely to develop coronary heart disease and other major cardiovascular events than people with normal glucose tolerance. In fact, CVDs alone account for nearly 30% of all deaths worldwide and 27% in low-income and middle-income countries [3, 4]. Thus, in one hand, there is a need to prevent and treat diabetes, and on the other hand, considering various possible risk factors, the impaired glucose tolerance itself and CVDs have to be prevented both at individual and population levels.

This chapter will focus on the principles of management of type 2 diabetes at individual and population levels to consider while following the guidelines and managing diabetes and its epidemic. Management is defined as the act or skill of dealing with people or situations in a successful way [5]. The term management in the chapter covers clinical management, research and public health perspectives. Public health is the practice of preventing disease and promoting good health within groups of people, from small communities to entire countries [6]. Primary prevention requires a focus on individuals known to be at risk for disease, i.e. the high-risk strategy with interventions focused on high-risk group, for example on people with glucose intolerance. A large proportion of the reductions in coronary heart disease mortality experienced in many high-income nations since the 1960s have been ascribed to the interventions in people at elevated risk [7]. However, individuals with markedly elevated levels of risk factors are relatively uncommon in the population. The majority of CVD events occur in individuals with average or only mildly adverse levels of risk factors [7, 8]. Therefore, population-wide strategies are also essential. Health promotion and disease prevention strategies must embrace both high-risk and population strategies [7–10].

2. Prevention of CVDs and control of blood pressure (BP)

Seven modifiable well-known risk factors of atherosclerotic CVDs are high BP, glucose intolerance, physical inactivity, tobacco use, dyslipidemia, unhealthy diet and overweight/obesity (**Figure 1**).

2.1. High blood pressure (BP)

Hypertension is the most prevalent risk factor for development of cardiovascular and kidney disease. In 2008, worldwide, approximately 40% of adults aged 25 had been diagnosed with hypertension and its prevalence is predicted to increase by almost 60% in the next 2 decades [11, 12]. Hypertension is responsible for at least 45% of deaths due to heart disease and 51% of deaths due to stroke [11, 12]. High BP is the leading risk factor in the world especially in the non-industrialized countries [13]. In fact there is some increase in cardiovascular risk in patients with BP 120–140/80–90 (i.e. pre-hypertension) than in those with BP less than 120/80 (i.e. normal BP) even in the general population [14]. Untreated BP <120/<80 mmHg (i.e. normal

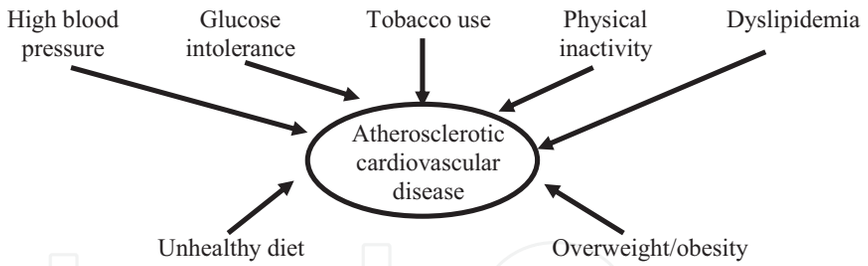

Figure 1. The seven modifiable risk factors of atherosclerotic cardiovascular disease.

BP) is considered as one of the ideal health factors for cardiovascular health [7, 8]. Programmes for controlling high BP in the industrialized countries achieved significant reduction in CVD mortality [7], and tobacco smoking including the second-hand smoke became the leading risk factor [13]. In many non-industrialized countries, such programmes have mostly not been accomplished. As a matter of fact in many such countries due to the inadequate network of the State supported rural and urban health centers/clinics, people often have limited access to blood pressure monitoring and management [15]. It is difficult for the people to regularly visit private clinics or to wait at the long queue in the free medical clinics of public hospitals. In such situations, the patients are more likely to visit hospitals late for crisis management only when the complications (like stroke, coronary heart diseases, kidney failure or pneumonia) develop [15].

2.2. Interaction of high blood pressure and glucose intolerance

Death rate due to CVD, even in the industrialized countries, seems to be on increase again particularly in the relatively younger population [8]. The emerging epidemic of glucose intolerance, another CVD risk factor, seems to be adding up and interplaying with high BP. Among more than 3000 Euro Heart Survey patients with acute and elective coronary heart diseases, only about one-fourth had normal plasma glucose by the WHO criteria [16]. If the American Diabetes Association classification with fasting plasma glucose >5.6 mmol/L (>100 mg/Dl) had also been considered, the proportion of patients with glucose intolerance would perhaps have been more, as reported in another study in patients with acute coronary insufficiency [17]. There are two pertinent points to note in the interaction between high BP and glucose intolerance.

Firstly, hypertension is relatively more common in people with diabetes, about two times more in one study [18], than in those with normal plasma glucose. More than 75% of adults with diabetes have blood pressure (BP) levels ≥130/80 mmHg or are using antihypertensive medication [12]. Secondly, the adverse effects of higher blood pressure are more in people with glucose intolerance than in those with normal blood glucose. Even among people with systolic BP between 120 and 139 mmHg (i.e. at pre-hypertension level), CV mortality rate is about three times more in those with diabetes than in those without diabetes. And the risk is similarly high in different systolic BP ranges from normal to high levels [19]. Mortality is indeed increased 7.2-fold when hypertension is present in patients with diabetes [12]. Lowering 4 mmHg of systolic BP is more effective in reducing cardiovascular events than

reducing 1 mmol/L of LDL cholesterol and is about four times more effective than lowering 0.9% of glycated hemoglobin (HbA1c), and thus, in diabetes, BP control is more efficacious and more easy than lowering glucose [20].

Clinical management perspective: The current guidelines recommend to treat hypertension in type 2 diabetes to an systolic BP target of 130–140 mmHg and a diastolic BP target of 80 mmHg and to consider the lower targets if the patients are younger or when additional CV risk factors or microvascular diseases are present [21]. In the studies, the number of antihypertensive drugs required to achieve the systolic blood pressure around 130–140 mmHg are often more than two and even more than three in many patients. Treatment of hypertension in patients with diabetes is lucidly reviewed in the position paper of American Society of Hypertension [12].

Public health perspective: In non-industrialized countries, there is urgent need of establishing the network of the State supported rural and particularly urban health centers/clinics with general practitioners (preferably well trained with residential training in General Practice after medical graduation). It is required (i) for the comprehensive longitudinal health care of the people with diabetes, hypertension, CVD and other conditions, (ii) for supervision of healthcare workers to implement various public health programs including that for hypertension and CVDs and (iii) to provide the State supported diagnostic facilities and antidiabetic, antihypertensive and other CVD drugs and antibiotics (then only it may be possible to restrict the over-the-counter sale of antibiotics and other drugs as the people otherwise would not have any access to such life-saving drugs) [15].

Research perspective: Study of the occurrence of CVD complications in the people with pre-hypertension level of BP and impaired glucose intolerance may indicate the different levels of HbA1c and BP to start antihypertensive treatment. The combined presence of the subclinical or borderline hypertension and glucose intolerance (as 'subclinical or borderline syndrome') may be another CVD risk factor, as a residual risk factor of CVDs, at the population level.

3. Promoting cessation of smoking and tobacco use

The health effects of tobacco use, including on CVD, and various public health measures to control it are well known [2, 10]. Harmful tobacco products also include smokeless tobacco like snuff, gutkha, gul, chimo, mawa, nass, pan masala, tambaku and others [22].

Clinical management perspective: The five A's framework (Ask, Advise, Assess, Assist, Arrange) has been developed to allow physicians to incorporate smoking cessation counseling into busy clinical practices [23]. Others have further added 'Assess again'. There are various pharmacological agents available to help patients quit smoking and tobacco use. However, before such products were available and even now hundreds of thousands of people including health professionals have had stopped tobacco use once they realized the possible complications to them. Physicians' priority, repeated advice and time spent on explaining its importance and its process of quitting play a crucial role for the motivation of the patients to quit tobacco use. Smokers who quit smoking abruptly ('Cold Turkey' method) have been reported to be successful than those who quit gradually [24]. However, the most important well-known point, to emphasize to the patients repeatedly, is that after stopping tobacco use whether abruptly or slowly, it should not be used even once; otherwise the habit is likely to be resumed.

4. Regular physical activity and exercise

Exercise is often classified as aerobic, strength (resistance) and flexibility exercise and each of them has their own utility and limitations. The common recommendation (e.g. 150 minutes

or more of moderate-to-vigorous intensity physical activity per week, spread over at least 3 days/week, with no more than 2 consecutive days without activity) is applicable to most adults and help to achieve cardiovascular fitness and other benefits. Brisk walking can be regularly included into the daily life. Two to three sessions/week of resistance exercise on non-consecutive days are also recommended [25]. Increased physical activity is effective in preventing diabetes, and the protective benefit is especially pronounced in persons at the highest risk for the disease [26]. At higher BMI, exercise is protective against diabetes and is dose-dependent. The prevention of diabetes and reduction of hyperglycemia in diabetes occur even without significant weight reduction [27]. American Diabetes Association recommends that prolonged sitting should be interrupted every 30 minutes for blood glucose benefits, particularly in adults with type 2 diabetes [25]. Possible physical activity even while seated (e.g. by leg exercise with or without sit down leg exercise machines) may also help. A more intensive physical activity program including at least 275 minutes per week may be needed to assist weight loss and avoid regain [21]. Higher levels of physical activity before pregnancy or in early pregnancy are associated with a significantly lower risk of developing gestational diabetes mellitus [28]. NICE guideline recommends women with gestational diabetes to take regular exercise (such as walking for 30 minutes after a meal) to improve blood glucose control [29]. **Figure 2** summarizes the potential benefits of regular physical activity and exercise in relation to diabetes.

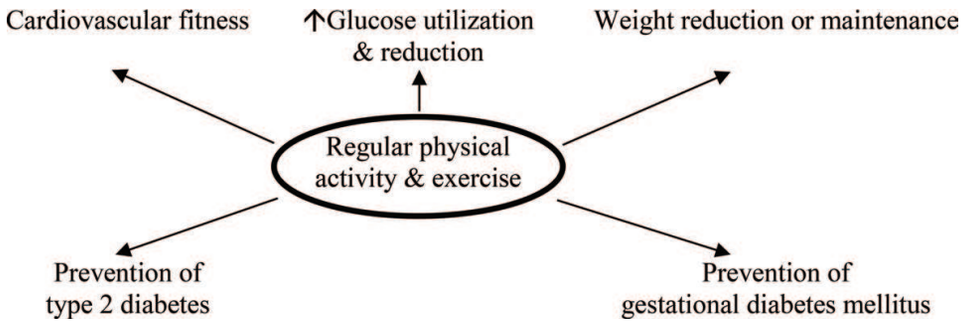

Figure 2. Potential benefits of regular physical activity and exercise in relation to diabetes.

Research perspective: Although type 2 diabetic subjects are insulin resistant, they are not resistant to the stimulatory effects of exercise on glucose utilization [30]. The local cellular and other metabolic adaptations could explain the increase in glucose utilization and improvement in the glucose tolerance in exercise and trained muscles. A major challenge has been to elucidate the molecules or cascade of molecules that act through insulin-independent, exercise-stimulated signaling pathway [30]. If such molecules produced during exercise are secreted in the blood and act like hormones in other tissues, organs, muscles and fat, study of the effect in the resting state by the reuse of serum of blood collected during exercise in the same person may give insight into such actions and the difference in the contents of resting and post-exercise sera may help to elucidate the molecules.

Research perspective: Many overweight older people with diabetes have knee osteoarthritis which may prevent them to walk freely. Exercises to strengthen the quadriceps—for example, quadriceps-setting exercise and straight-leg raises—are effective in reducing pain and improving function in patients with knee osteoarthritis. However, people often may not adhere to the recommended methods of quadriceps strengthening exercises. Regular exercise with a bicycle ergometer in such patients can have beneficial effects not only for knee osteoarthritis but also for diabetes and CVD [31].

5. Use of statin and antiplatelet therapy

The use of statin is the other core element to prevent the premature death and disability in diabetes. The mechanisms of beneficial effects of statins in CVD are not completely understood. Some beneficial effects appear to occur independently of lowering of LDL cholesterol. Thus, most trials of statins and CVD outcomes tested specific doses of statins against placebo or other statins rather than aiming for specific LDL cholesterol goals, suggesting that the initiation and intensification of statin therapy should be based on risk profile [25, 32]. Before starting statin, lipid profile should be required at least once; a fasting sample is not routinely needed [32]. Antiplatelet therapy in diabetes is generally recommended for those with history of CVD and dual antiplatelet therapy is reasonable for up to 1 year after an acute coronary syndrome [25, 32].

Research perspectives: Studies indicate that lower statin doses achieve lipid improvements in Chinese, Japanese and Koreans patients comparable with those observed with higher doses in Caucasians [33]. However as the mechanism of action of statins may not be just related to the lowering of LDL cholesterol, the relation of such observation with cardiovascular events need to be studied.

6. Body weight as per the recommended body mass index (BMI) for the respective populations

The WHO 1998 Consultation on Obesity, based on classifications used in a number of past studies on Europids, indicated BMI of 18.5–24.9 kg/m^2 as normal [34, 35]. A WHO expert consultation on BMI for Asian populations concluded that Asians generally have a higher percentage of body fat than white people of the same age, sex and BMI and that the proportion of Asian people with a high risk of diabetes and CVD is substantial at BMIs lower than the existing WHO 1998 cut-off point for overweight (>24.9 kg/m^2) [36]. The WHO [35], International Diabetes Federation and American Diabetes Association have recommended the upper limit of cut-off point of normal BMI for Asian people as 22.9 kg/m^2 [25, 35, 37]. Similar and variables recommendations for different non-Caucasian populations have been made in various other studies, including those conducted in the Westernized ones.

These recommendations are in agreement with the actual body mass index of the population. The adult mean BMI levels of 20–23 kg/m^2 are found among the general population in Africa and Asia, whereas levels of 25–27 kg/m^2 across North America and Europe in 2002 [10]. The WHO consultation on BMI for Asian populations identified further potential public health action points along the continuum of BMI and indicated that the earlier optimum population range (21–23 kg/m^2) gives some intuitive consistency for policy makers [36]. The risk of insulin resistance and diabetes in adult increases progressively upwards of a BMI of 20–22 kg/m^2 [10]. More than 80% of the people with diabetes live in low- and middle-income countries and nearly two thirds of diabetes globally are attributable to BMI above 21 kg/m^2 [10]. In general, the risk of insulin resistance and glucose intolerance appears to increase once BMI starts rising above the middle of the recommended BMI for the population.

Research perspectives: Compared with the BMI cut point of 30.0 kg/m^2 among Europeans, a similar glucose factor distribution is observed at corresponding BMI cut points of 21.0 kg/m^2 in South Asians, 20.6 kg/m^2 in Chinese and 21.8 kg/m^2 in Aboriginals in Canada [38]. The BMI cut points are, however, higher, for the lipid and blood pressure factors than for the glucose factor in South Asians, Chinese, and Aboriginals in the study [38] pointing out the need to study BMI cut points in different populations similarly considering the glucose, lipid and blood pressure factors separately.

7. Antihyperglycemic medications

Type 2 diabetes is a chronic metabolic condition characterized by insulin resistance and insufficient pancreatic insulin production from beta-cell, resulting in high blood glucose levels [39]. Difficulty in utilizing the available insulin increases the workload of beta-cell. While using antihyperglycemic medications, the issues that need to be considered are shown in **Figure 3**. A few pertinent points are further discussed below.

7.1. Reduction of insulin resistance and beta-cell workload

Beta-cell failure is central to the ultimate development and progression of type 2 diabetes and it antedates and predicts diabetes onset and progression [40]. Subjects with normal glucose tolerance with 2-hour plasma glucose 120–139 mg/dL may have already lost 50% of beta-cell function, whereas subjects with impaired glucose tolerance with 2-hour plasma glucose 180–199 mg/dL have lost up to 80% of beta-cell function. Thus, when the diagnosis of diabetes is made, the patient may have already lost 80% of their beta-cell function [41, 42]. The available clinical studies with appropriate protocols, however, indicate that existing therapy may not reverse or arrest progression of beta-cell dysfunction in type 2 diabetes [40]. Weight loss reduces insulin resistance and beta-cell workload and physical activity increases insulin utilization and also helps to reduce beta-cell workload and bodyweight. Both help to normalize the blood glucose and are also useful for cardiovascular health. Promotion of physical activity and exercise and loss of excess bodyweight for as long as possible are the cornerstones of management in type 2 diabetes. Medications favoring these two aspects are preferred for as long as possible.

7.2. Risk of hypoglycemia

Hypoglycemia can manifest in different ways (**Figure 4**). Insulin is a known cause of hypoglycemia. The risk of hypoglycemia associated with the use of other antihyperglycemic medications is given below [21]:

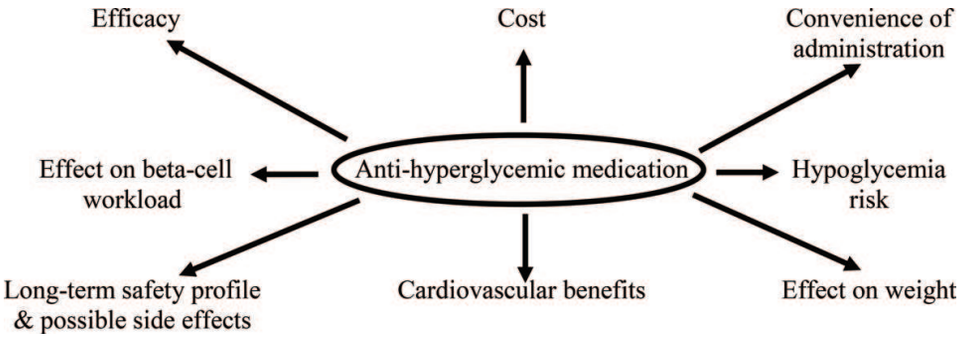

Figure 3. Factors to consider while prescribing antihyperglycemic medications in type 2 diabetes.

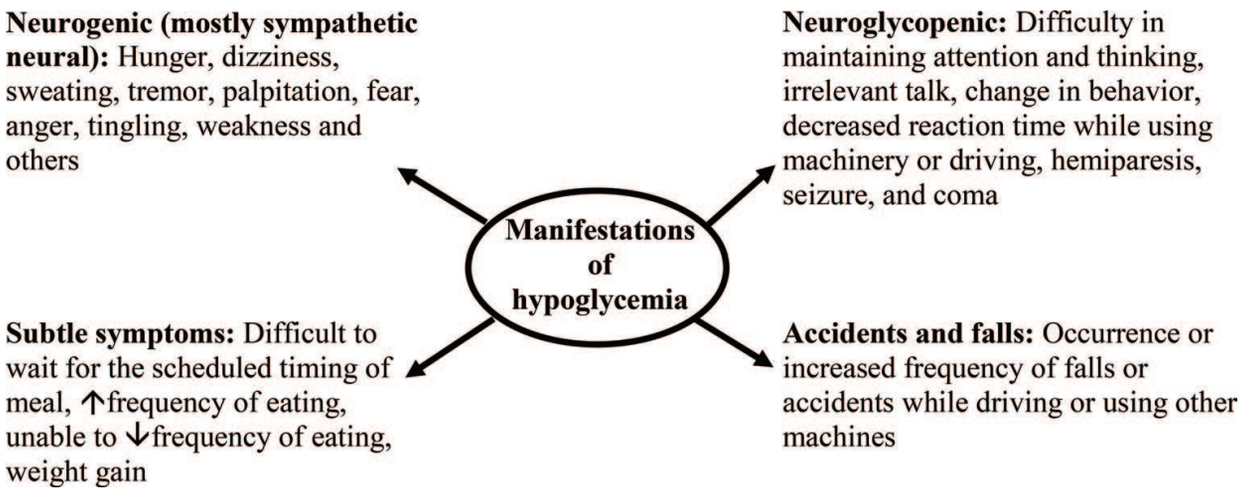

Figure 4. Manifestations of hypoglycemia. *Note:* The patient may not volunteer the information; the healthcare professionals have to ask the leading questions so that the dose of the medications likely to cause hypoglycemia, viz. insulin, sulfonylurea and repaglinides, can be appropriately reduced.

- Metformin, acarbose and other alpha-glucosidase inhibitors, dipeptidyl peptidase-4 inhibitor, glucagon-like peptide-1 receptor agonist and sodium-glucose cotransporter 2 inhibitors are associated with neutral risk of hypoglycemia.
- Sulfonylurea is associated with moderate-to-severe risk and repaglinide moderate risk of hypoglycemia [21].

The patients only on antihyperglycemic treatment unlikely to cause hypoglycemia can check their glycemic control with blood glucose fasting, 2-hour postprandial glucose and HbA1c estimation. If the patients are also on medications, like sulfonylurea, repaglinide and insulin, which can cause hypoglycemia, they need to check their blood glucose also at other time (e.g. before meals and exercise or later in the day or at night) considering the hypoglycemic symptoms and the maximum onset and duration of action of the drugs likely to cause hypoglycemia.

The popular guidelines cover detail aspects of different medications including the monitoring of glucose [21, 25, 39]. As acarbose, an alpha-glucosidase inhibitor, is increasingly used and has relatively longer safety profile, efficacy and other benefits, it can also be considered in the early phase of therapy in glucose intolerance. Four alpha-glucosidase inhibitors currently exist: acarbose, miglitol, voglibose and emiglitate [43]. Acarbose inhibits both alpha-amylase (which breaks down starch to disaccharides) and other alpha-glucosidase (which digests disaccharides), where as voglibose and miglitol inhibit the disaccharide-digesting enzymes well, but have no effect on the starch digesting enzyme alpha-amylase [44]. Acarbose and voglibose are minimally absorbed from the intestine and have very low bioavailability [44] with acarbose having less than 2% systemic availability [45]. Miglitol is almost completely absorbed from the upper part of the intestine [44]. Acarbose was first developed. Among the alpha-glucosidase inhibitors, acarbose is the most prescribed drug and most data and best-outcomes are obtained for it [43].

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7.3. Acarbose

Acarbose is an effective drug with relatively long safety profile having various cardiovascular and metabolic beneficial effects, it is not associated with hypoglycemia and it promotes weight loss [43–48]. Different meta-analysis, review articles and more than 350 studies have reported its efficacy (when used alone or in combination with other antihyperglycemic medications, including metformin), safety profile, cardiovascular, weight reduction, metabolic and other benefits [43–48]. Metformin or acarbose is recommended by International Diabetes Federation and American Association of Clinical Endocrinologist when the lifestyle modification strategy is not enough for prevention of type 2 diabetes [21, 49]. Acarbose can also be considered to be used as a first-line antihyperglycemic agent [46, 48].

Gastrointestinal side effects have been an issue with acarbose. The predominant gastrointestinal symptom associated with acarbose is flatulence; however, loose stools and/or abdominal discomfort have also been reported. The side effects occur maximally during the first 2 weeks of therapy and start decreasing. By 12 weeks, 13.7% report flatulence and 2.2% diarrhea, and a 5-year surveillance study of about 2000 patients with diabetes found that gastrointestinal side effects associated with acarbose were reported by only 3.9% of patients [45]. For administration and dose adjustment and for understanding its metabolic benefits, its unique mode of action, not just alpha-glucosidase inhibition, need to be considered.

- The effect of acarbose is to delay the digestion of starch and oligosaccharides in the small intestine so that the release and absorption of glucose takes place over a longer time across the length of the small intestine. In many individuals, alpha-glucosidases are most active in the upper small intestine, and as acarbose treatment continues, there is a compensatory increase in enzyme activity in the lower small intestine and gastrointestinal side effects decrease over time [45].

- Furthermore, exposure of the lower small intestine to undigested carbohydrate leads to an increased quantity and duration of glucagon-like peptide-1 (GLP-1) release [45]. Acarbose also potentiates the reduction of ghrelin [46], thus may help to increase satiety.

- Low glycemic foods are preferred in type 2 diabetes. Low glycemic index foods are created by different processing methods; alpha-glucosidase inhibitors mimic these compounds in that they decrease the glycemic index (as well as the glycemic load) of carbohydrate-rich foods [46].

- Acarbose acts by competitive inhibition of alpha-glucosidase, so it is given at the same time as the ingested carbohydrate [45]. When taken as a tablet, the usual available form, it is less effective than when consumed in powdered form; so it is better to chew the tablet with food than to swallow at the beginning of a meal [47].

- Acarbose blocks and slows the digestion of complex carbohydrate, like starch, and sucrose (table sugar) without affecting the absorption of monosaccharides like glucose and fructose (present in fruits) and disaccharide lactose (present in milk products), which is digested by beta-glucosidase [44–47]. Trials in some countries report a higher incidence of gastrointestinal symptoms when initiating the dose of acarbose [46]. It may be due to the dietary habit of the population using sugar-rich food or soft drinks with or after meals. In any case, while initiating

therapy with acarbose, starting with low dose (e.g. 25 mg or in a few cases still lower, once a day after dinner) and with slow stepwise-increasing dose over weeks avoiding the sugar-rich food or soft drinks with or after meals may help the patient to tolerate acarbose. Cochrane review reports that acarbose dosages higher than 50 mg three times daily offer no additional effect on HbA1c but more adverse effects instead. However, the fasting and post-load glucose may benefit from higher dosages [43].

Thus considering the benefits and safety of acarbose, it can be used in the treatment of diabetes next after metformin even if HbA1c is well controlled. With judicious initiation of the drug, most patients may be able to tolerate the drug. As in the case of metformin, those who tolerate the drug will be benefitted.

8. Principles of planning of antihyperglycemic therapy

Apart from various factors (**Figure 3**) to consider while prescribing antihyperglycemic medications, there are other principles to guide planning of antihyperglycemic therapy in type 2 diabetes.

8.1. Possible loss of excess bodyweight for as long as possible and regular physical activity and exercise: The cornerstones of therapy of diabetes

Loss of excess body weight and maintaining regular physical activity and exercise reduce insulin resistance and beta-cell workload and also benefit cardiovascular health and are thus the cornerstones of therapy of diabetes. The medications which support such aspects are preferred.

8.2. Requirement of combination therapy

Combination therapy, even in many newly diagnosed diabetic patients, is often required and it may also allow the use of submaximal doses of each antihyperglycemic medication resulting in fewer side effects [41, 42].

8.3. Need of gradual building up of the doses of metformin and acarbose

The doses of antihyperglycemic medications, particularly of metformin and acarbose having longer history of safety profile and other benefits, have to be built up slowly so that the patients tolerate the drugs; their maximum effect may take some time to be clinically evident.

8.4. 'Dynamic dose management of medications likely to cause hypoglycemia'

There is often need of controlling blood glucose immediately to prevent or treat acute complications [50]. Sulfonylurea and insulin act relatively fast. Insulin remains effective in all situations and it also helps to prevent ketosis. During the infection, other complications or

immobility of the patients or the initial stage of diagnosis, rapid control of high blood glucose may thus be required to be done as rescue therapy. However, sulfonylurea, repaglinide and insulin not only cause hypoglycemia but also prevent the patients to lose weight and may even cause weight gain. Normalizing blood glucose is important, but there are other factors to consider as well (**Figure 3**). Moreover, even if sulfonylurea is continued to control the blood glucose, the glucose-lowering effect of sulfonylurea by beta-cell stimulation is not durable and wane over some years [41, 42]. DeFronzo has pointed out that such focus on simply HbA1c reduction with continuous use of sulfonylurea may lead to '*treat to fail*' approach and thus underlying pathophysiology also needs to be considered [41, 42]. The aim in the management of hyperglycemia in type 2 diabetes is to normalize it for as long as possible with the help of antihyperglycemic medications avoiding hypoglycemia and helping the patient to continue regular physical activity and exercise and to reduce excess bodyweight for as long

Phases of therapy	**Diet, physical activity and exercise and weight plan**	**+**	**Regular use of antihyperglycemic medicines**	**±**	**Temporary use of other antihyperglycemic drugs likely to cause hypoglycemia***
1. Initiation of therapy	Recommended diet, reduction of excess body weight and regular physical activity and exercise	+	Gradually building up of metformin dose to the optimum level	±	Short-term temporary use of sulfonylurea or insulin to control hyperglycemia immediately as rescue therapy
2. Once the dose of metformin is optimum & tolerable, next phase of therapy with other 2nd to 4th drugs unlikely to cause hypoglycemia†,‡	Continue above diet, physical activity and exercise and weight plan	+	Addition of acarbose, pioglitazone, dipeptidyl peptidase-4 inhibitor, glucagon-like peptide-1 receptor agonist, sodium–glucose cotransporter 2 inhibitors	±	Short-term temporary use of sulfonylurea or insulin to control hyperglycemia immediately as rescue therapy
3. Regular hypoglycemic therapy	Continue diet and physical activity and exercise plan	+	Repaglinide, sulfonylurea or basal insulin with other drugs	±	Short-term temporary use insulin to control hyperglycemia immediately as rescue therapy
4. Long-term combination insulin therapy phase	Continue diet and physical activity and exercise plan	+	Combination insulin therapy with or without other drugs		

Note: The medications are used if not contraindicated and as per their effectiveness, tolerance by patients and local guidelines.

*'*Dynamic dose adjustment of medications likely to cause hypoglycemia*' aims to taper off the dosage of the drugs like sulfonylurea to continue normalization of HbA1c for long time with diet, regular physical activity and exercise and possible loss of excess bodyweight for as long as possible and with other drugs not likely to cause hypoglycemia.

†Even if HbA1c is well controlled, considering the long-term safety profile, mechanisms of action and negligible systemic absorption, acarbose can be added once the optimum dose of metformin is tolerated. Acarbose is started with low and slow stepwise-increasing dose over weeks or months to the optimum tolerable level. In patients only on antihyperglycemic drugs unlikely to cause hypoglycemia, they may have their major meals two times a day as per their convenience and custom. In such patients, the dose of acarbose can be gradually increased to the optimum tolerable level, e.g. 50–100 mg two times daily with the meals. Whatever the dose the patients tolerate, it is likely to be beneficial considering its unique mode of action and long-term safety profile.

‡Whether to add other new drug even if blood glucose is well controlled and which one to add as 3rd or 4th drug will depend on various factors as discussed in the text and on the guidelines of the local regulatory bodies.

Table 1. A suggested algorithm of antihyperglycemic therapy in type 2 diabetes.

as possible. Physical activity and exercise increases glucose utilization and reduces blood glucose. Thus, there is need of continuous effort to reduce the dose of sulfonylurea, repaglinide and insulin to the lowest possible level as the '*Dynamic dose management of medications likely to cause hypoglycemia*' letting the healthy lifestyle and other non-hypoglycemic antihyperglycemic drugs to maintain the blood glucose [50]. Patient education and guidance from family physicians, diabetes educators and other health care workers will help to achieve such dynamic dose management.

8.5. Long-term safety profile

Geoffrey Rose rightly highlighted 'Safety is paramount with long-term interventions' [9]. There is relatively longer history of safety profile with metformin and acarbose. They are preferred in the prevention and in the early phase of treatment of diabetes so that they can be safely continued for long time.

Based on such principles, a suggested approach of antihyperglycemic therapy is outlined in algorithm in **Table 1**.

Compared to the two agents prescribed separately, combination tablets reduce pill burden and help adherence of patients [49]. However due to the contrasting effect as well as the need of 'dynamic dose adjustment of medications likely to cause hypoglycemia' to the lowest possible dose and of gradual building of the dose of metformin for its continued maintenance at the optimum level, the formulation of fixed dose of combination of such drugs in a single tablet is irrational (**Table 2**) [50]. Availability of such fixed dose combination formulation in the market is likely to lead to the continued usage of sulfonylurea and suboptimal dosage of metformin even right from the time of diabetes diagnosis with all its effects in the patients.

	Metformin	**Sulfonylurea or repaglinide**
Hypoglycemia risk	Neutral	Moderate to severe
Effect on bodyweight	Slight loss	Gain
Major cardiovascular events	Beneficial	Generally neutral*
Principle of use	To maintain optimum dose	To keep the dose as minimum as possible to minimize hypoglycemia
Administration	Usually after meal	Usually before meal†
Dose adjustment with combination tablet	Difficult and the dose is likely to be suboptimal due to the fear of inducing hypoglycemia	Difficult and likely to cause hypoglycemia if the optimal dose of metformin is targeted or maintained

*Apart from the risk of effect of severe hypoglycemia on heart, it is also advised that use of the sulfonylurea types (glibenclamide, glipizide, glimepiride and others) that bind the sulfonylurea receptor-2 A and B should be avoided in high-risk patients suspected of having significant coronary artery disease [51].

†Sulfonylureas are often advised to be taken at least 15–20 minutes before a meal [51].

Table 2. The contrasting effect and uses of metformin and sulfonylurea and repaglinide making their fixed dose combination formulation irrational.

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9. Avoiding unnecessary medicines and products

There is no clear evidence that dietary supplementation with vitamins, minerals, herbs or spices can improve outcomes in people with diabetes who do not have underlying deficiencies, and there may be safety concerns regarding their long-term use [25]. Unnecessary medication or local herbal, traditional or plant products may increase the cost and/or number of tablets to be taken which can affect the adherence to the essential medicines. Any medications or various products are also some form of chemicals and can also cause side effects, affect different organ systems or interact with other medications [52]. It is a famous saying 'Everything under the sun, including the sun, can cause allergy or side-effects'. For example, peripheral edema may occur in up to 16% with pregabalin [53]; however, amlodipine, a useful and essential medicine for hypertension, may instead be inadvertently stopped due to its well-known association with peripheral edema. Symptoms like tingling, numbness or others may need to be investigated. However, if treatment does not change the course of the condition and if symptoms do not affect sleep or daily life of the patients, explanation and reassurance with the required follow-up may be preferred than using unnecessary medications.

Research perspectives: State may develop some support system (e.g. by making available research funds or by involving pharmaceutical companies or other donor agencies) to study the local herbal, traditional or plant products and to identify and isolate the active the pharmacological ingredient of such possible crude products [52].

10. Education to the patient and training of educators

Structured education is an integral part of diabetes care [39]. Lifestyle management is a fundamental aspect of diabetes care and includes diabetes self-management education, diabetes self-management support, nutrition therapy, physical activity, smoking cessation counseling and psychosocial care [25]. Nurses and other healthcare professionals requires adequate training and certification to work in the health system to fill the gap between medical professionals and patients and thus between the available scientific knowledge and effective application by the patients [50].

Public health perspectives: For the training in the management and education of people with diabetes, the nurses and other healthcare professionals (with minimum of 2 years of professional practice experience) should have at least 1000 hours of practice experience in diabetes self-management education along with various educational activities [54]. In the non-industrialized countries, it may thus entail 1 year of working under the supervision of physicians (as a sort of residential training) in the daily diabetes and other outdoor and indoor services providing care and education to the patients fulfilling the other training requirements (like logbook recordings of case history records, procedure and academic activities, assignments and assessments) [50, 55]. To incorporate such trained personnel in the local health system, the terminology of certification of such training should match with the nomenclatures of other existing healthcare workers and with the various intervention programs being planned and/or implemented [55].

11. Programmes to control diabetes epidemic

There are extensive work done and literature available regarding the diabetes epidemiology, healthy lifestyle, primary prevention of diabetes and effects of gestational diabetes and *in utero* malnutrition and hyperglycemia. Many of them have been cited in the various publications referred in this chapter [1–3, 7, 10, 25, 27, 29, 32, 39, 49, 56, 57, 67, 68]. In this section, the focus is on briefly highlighting the urgent priority public health programmes required to control the diabetes epidemic. The perspectives on controlling the diabetes epidemic in the population as a whole, not just primary prevention of diabetes in individuals, and the implementations of the required programmes are the dire needs today.

11.1. Factors fueling the diabetes epidemic

The epidemic of glucose intolerance in the world is relatively a new phenomenon starting since the latter half of twentieth century and the initial rise in diabetes prevalence has occurred differently in various populations in the world [56, 57]. For example, gradual rise in diabetes prevalence has occurred in Europids in Europe, Canada and the USA since around 1940s with increasing sedentary life, obesity and aging with about a third of their population over 50 years of age. On the top of similar gradual rise, the migrant or urbanized Asian-Indian, Arab, African, Chinese and Hispanic people faced the rapid rise of diabetes prevalence since around 1970s mostly due to the rapid transition in the nutritional status of population leading to dissociation in metabolic states of fetal life (associated with nutritional want) and adult life (with nutritional surfeit) of people. The indigenous people of the USA, Canada, Australia and Pacific region also faced the rapid rise in diabetes prevalence (due to the rapid transition in their nutritional status) since around 1940s and subsequently further faced the accelerated rise mostly due to the addition of the factor of maternal hyperglycemia during pregnancy affecting the *in utero* life of the offspring [56].

Such variations in the rise in diabetes prevalence in different populations can just be ascribed to the effect of ethnic variations leading to a sense of fatalism. The concept of ethnicity does provide self-identification with cultural traditions and social identity and boundaries between groups, but it has dynamic nature [58]. Ethnicity is a sort of surrogate marker for multiple environmental and genetic factors (though genetics playing a relatively small part), in disease causation and for public health policy [56, 59, 60]. In terms of the scientific approach and public health policy, ethnic variations in the prevalence of any disease or condition should lead the humankind to search for such environmental or genetic factors [59]. The different pattern of initial rise in diabetes prevalence in various populations in the world, thus, appears to be related to the various proportions of three groups of risk factors present in different populations. Thus, the three groups of such possible factors to consider are [56]:

- obesity, sedentary life and aging;

- the rapid transition in the nutritional status of population leading to dissociation in metabolic states of fetal life (associated with nutritional want) and adult life (with nutritional surfeit) of people (this factor of *in utero* undernutrition appears to limit the range of normal body mass index in adult life in such population and even in the individual person of any population group) and
- maternal hyperglycemia during pregnancy affecting the *in utero* life of the offspring.

Whatever may be the differences of the initial rise in diabetes prevalence in the world and its pathogenesis, the fact remains that diabetes epidemic is now increasingly affecting the younger and younger population. There is, thus, the need to consider all possible factors to control the epidemic of diabetes in all the populations.

11.2. Healthy diet and weight and regular physical activity and exercise at the population level

Healthy diet with proportionate intake of nutrients, body weight as per the recommended body mass index for the population and regular physical activity and exercise are applicable to general population and people with impaired glucose intolerance, diabetes and CVDs [3, 10, 21, 25, 32, 39, 56].

Public health perspectives: Campaigns and programmes are required to make the people, housewives and children well aware of the recommended bodyweight (as required for the respective population) and the recommendations regarding the daily intake of plain water, fruit, vegetables, salt, sugar, fat (with adequate proportion of mono- and poly-unsaturated and saturated fatty acid) and other nutrient avoiding the trans-fatty acid. Multisectoral population-based approaches, including trade and agricultural policies and the workplace-, school- and other setting-based interventions, for healthy diet and physical activity and exercise need to be considered [2, 3, 10, 56].

Public health perspectives: Pedestrians, cyclists and public transport passengers are the top three hierarchy groups recommended while developing transport and traffic strategies [61]. It is also essential to have campaigns and support system to develop various physical activity and exercise programmes at the community, school and various workplace levels like regular walking, games and sports, marathon running, aerobic dance and others [2, 3, 10, 56].

11.3. Prevention of maternal and childhood malnutrition

Taking a life-course perspective is essential for preventing type 2 diabetes, as it is for many health conditions [2]. Firstborn offspring in the resource poor settings may be at increased risk of glucose intolerance due to the likelihood of possible maternal malnutrition during the first pregnancy as compared to that in later pregnancy [56, 62]. Adequate nutrition and micro- and macronutrient supply before and during pregnancy are the steps to reduce the risk of *in utero* malnutrition and its ill effects [27]. Good nutrition during infancy and childhood and adequate physical activity among children are important for the development of a healthy child and an adult [27].

11.4. Maintenance of optimal pre-pregnancy bodyweight: the key programme required

The diagnosis of gestational diabetes mellitus (GDM) usually made at 24–28 weeks is applicable for the clinical management of the women and their children during and after pregnancy and it may also be useful for the mothers for primary prevention of later development of diabetes. From further public health perspectives to avoid any possible long-term *in utero* effect, prevention of subclinical maternal hyperglycemia right from the time of conception needs to be considered [56]. The sedentary lifestyle, obesity and glucose intolerance affecting relatively younger population are increasing in the community. The risk of maternal hyperglycemia during pregnancy has thus increased (**Figure 5**) [56]. The relative risk of developing overt GDM over the age of 35 years is 2.57 [63]. However, significant increase in the risk of overt GDM is reported even at age >25 years as compared to that in lower age [64].

The exact 'safe' normal level of maternal plasma glucose to prevent relative hyperglycemia *in utero* for fetus appears difficult to define. To find out such level, long period of follow-up is required after birth of offspring with exposure to different levels of maternal plasma glucose correlating with other risk factors [56, 57]. The normal value of neonatal plasma glucose may give some insight. However, the limits of normal plasma glucose defining neonatal hypoglycemia in infants are arbitrary. Neonatal glucose concentrations may decrease after birth, to as low as 30 mg/dL during the first 1–2 hours after birth, and then increase to higher and relatively more stable concentrations, generally above 45 mg/dL by 12 hours after birth [65, 66]. Later, it will gradually rise to adult levels.

Considering the risks of the macrosomia development, the safe normal level of fasting plasma glucose during pregnancy appears to be below 80 mg/dL (4.4 mmol/L), perhaps

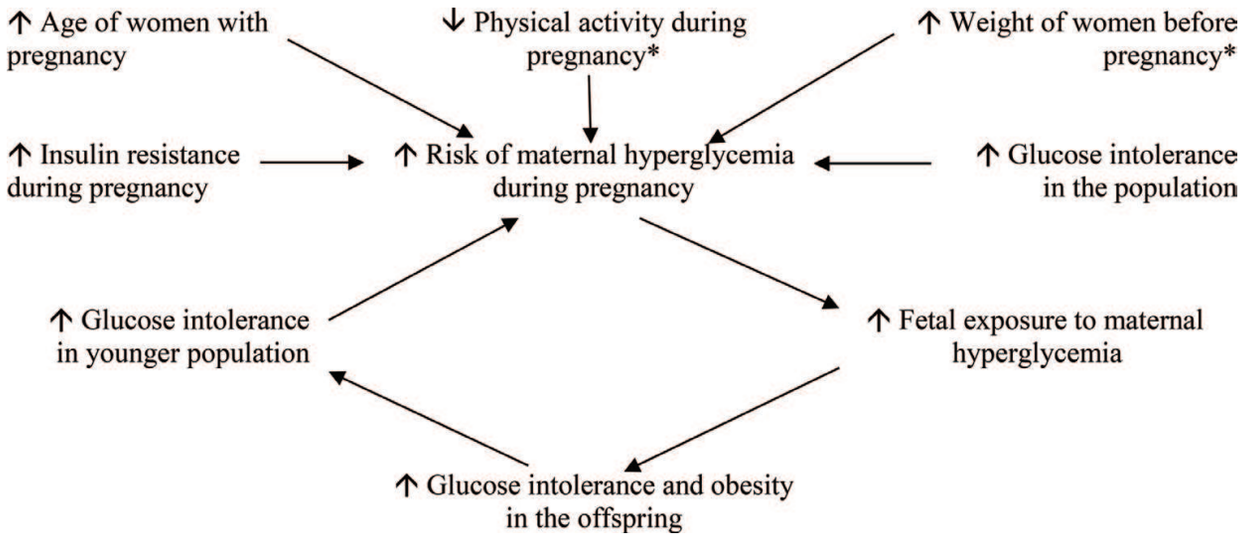

Figure 5. A vicious circle of glucose intolerance in younger population and maternal hyperglycemia during pregnancy. *The two preventable factors from the public health and clinical management perspectives. (Figure published with minor modification with kind permission from *JNMA*2009;48;173 [56]).

even below 75 mg/dL (4.2 mmol/L) [67, 68]. Macrosomia is to a great extent measurable but the fetal programming due to relative maternal hyperglycemia is difficult to assess and is obviously likely to be affected earlier than the overt macrosomia. Weeks 3–8 encompass organogenesis and major malformations in infants of diabetic mother occur during these periods [69]. So to protect the fetus from any possible effect of maternal hyperglycemia, blood glucose during the whole duration, including the early stage, of pregnancy has to be within the safe normal level [56, 57]. As discussed earlier that even in non-pregnant state, the risk of insulin resistance and diabetes in adult increases progressively upwards of a BMI of 20–22 kg/m^2 and more than 80% of the people with diabetes live in low- and middle-income countries and nearly two thirds of diabetes globally are attributable to BMI above 21 kg/m^2 [10]. Considering the inherent insulin resistance during pregnancy and increasing age of mother, the pre-pregnancy bodyweight should preferably around or below the middle of the recommended BMI for the population [56]. In Finland with predominant Europid population, the mean pre-pregnancy BMI of women were 21.9 and 23.7 kg/m^2 in 1960s and 2000, respectively [70]. If it increases to higher level, as in many other populations, the risk of glucose intolerance during pregnancy may also increase. Women who had a child gains extra weight than women who remained nulliparous [71] and the second and subsequent offspring were anticipated about a decade earlier to have increased risk of *in utero* exposure to the maternal clinical or sub-clinical hyperglycemia due to the increased weight of mothers [56]. A recent study indeed reported increased risk of GDM with increasing weight gain from first to second pregnancy [72]. In summary, campaign and programmes for maintenance of optimal pre-pregnancy body weight as per the recommended body mass index of the respective populations along with regular physical activity and exercise during pregnancy are the essential measures available at hand to prevent the possibility of maternal hyperglycemia right from the early pregnancy and are the urgent priority to control diabetes epidemic.

Research perspective: Long-term follow-up study of offspring with exposure to different levels of maternal plasma glucose correlating with other risk factors can be conducted. Possible risk of obesity and early glucose intolerance in both female and male offspring due to the *in utero* hyperglycemia could also be due to the involvement of mitochondrial DNA. Exposure of mitochondrial DNA to reactive oxygen species (ROS) can lead to mitochondrial mutation [73]. Glucose excursions can lead to the formation of ROS, such as superoxide, which leads to oxidative stress in the body [74] and acute hyperglycemia can lead to oxidative stress with increase in the markers of oxidative damage [75–77]. Such oxidative stress due to high glucose level for the fetus during pregnancy can thus be postulated to lead to oxidative damage to fetal mitochondrial DNA and the offspring in this way may later be at increased risk of obesity and glucose intolerance. Superoxide anions, markers of oxidative damage and mediators of subclinical inflammation can be analyzed in the fetal, amniotic and/or maternal samples. If it is such mitochondrial inheritance as postulated, the affected female offspring would transmit the disease to all their children, and affected male offspring, however, would not transmit the disease to their children. The possibility of such pattern can be studied in the populations with high prevalence of type 2 diabetes in young age.

Public health perspectives: Examples of prevention and control programmes in the communicable diseases as a model for similar strategies required at individual and population levels for diabetes epidemic are summarized [78] in **Table 3**. Control programme to protect the other susceptible populations (**Table 3**) is the dire need today to control diabetes epidemic.

	Examples in the communicable disease	Examples in diabetes[†]
Prevention programmes for individuals	• Immunization • Personal protective measures • Chemoprophylaxis	• Population-wide and primary prevention programs with healthy food, physical activity and exercise and weight reduction interventions to prevent impaired glucose tolerance and diabetes • Campaign and programmes to help achieve the body mass index by the people as recommended to the respective populations
Control programmes to protect the other susceptible populations[*]	• Isolation • Quarantine • Vector control (e.g. mosquito control for various diseases, cyclops control for guinea worm, chicken and poultry culling for avian influenza) • Treatment of case (e.g. tuberculosis) and carrier	Campaign and programmes for • Maintenance of optimal pre-pregnancy body weight, as per the recommended body mass index of the respective populations • Nutritional support for the girls and women of childbearing age in rural and poorer sections of the societies

*The vulnerable populations to be protected by the control programme of diabetes include the offspring of malnourished or overweight mothers during their *in utero* life.

[†]National and international health and diabetes agencies should clearly spell out the control programmes, with appropriate budget allocation, for the control of diabetes epidemic.

Table 3. Examples of prevention and control programmes in the communicable diseases as a model for similar strategies for individuals and susceptible populations in diabetes epidemic (table published with minor modification) [78].

12. Conclusion

Adequate control of blood pressure, use of statin, cessation of tobacco use, regular physical activity and exercise and possible loss of excess bodyweight for as long as possible are the core management aspects in diabetes. Judicious use of antihyperglycemic drugs requires consideration of various factors, especially hypoglycemia and effect on bodyweight and cardiovascular events. The aim should also be to achieve normalization of HbA1c for long time by loss of excess bodyweight for as long as possible, regular physical activity and exercise and using regularly the antihyperglycemic medications not having the risk of hypoglycemia. 'Dynamic dose adjustment of medications likely to cause hypoglycemia' helps to apply such principles by temporary use of sulfonylurea or insulin as rescue therapy. Apart from such clinical management and various research aspects, there are public health approaches to be considered as the top priority for the control of diabetes epidemic in the population. The diagnosis of gestational diabetes usually made at 24–28 weeks is applicable for the clinical management of mother and child and for possible primary prevention of diabetes later in the mother. From the public health perspectives, however, protection of the susceptible *in utero* population from maternal malnutrition or clinical or subclinical hyperglycemia right from the time of conception itself is particularly required to control diabetes epidemic at the population level. There is urgent need of campaigns and programmes for maintenance of optimal pre-pregnancy body weight, as per the recommended body mass index for the respective populations.

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