# Treat to Target - Type 2 Diabetes Mellitus

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## ABSTRACT

Diabetes causes profound alterations in both micro and macrovascular tree affecting virtually every organ in the body due to hyperglycemia and the associated comorbid conditions such as hypertension and dyslipidemia. In order to reduce the impact of diabetes on the individual not only focus for management should be on maintaining quality of life and prevention of its acute complications, but more importantly attempt to reduce the mortality and morbidity due to micro and macrovascular complications. Since diabetes management is complex, both healthcare providers and the diabetic individuals should be aware of the various targets to be achieved. The currently recommended target of <7% glycated hemoglobin level itself is a challenge and this is likely to be reduced to 6.5% in the future. To achieve this goal the first step is non-pharmacologic measures (diet, exercise and lifestyle modifications) and when these fail, various pharmacological agents should be considered. Control of blood pressure (<130/80 mm Hg) is equally if not more important to prevent macrovascular complications. Angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, diuretics, cardioselective beta-blockers, and calcium-channel blockers are effective antihypertensive agents in Type 2 diabetes. However, combinations of these agents are frequently required to reduce risk for renal and cardiovascular events. Lipid management aimed at lowering LDL cholesterol (<100 mg/dl) and triglyceride levels (< 150 mg/dl) and raising HDL cholesterol (>40 mg/dl), has been shown to decrease macrovascular disease and mortality. Statins are the first drug of choice, also consideration can be given to combining a fibrate or nicotinic acid. In addition, education, self-monitoring of blood glucose and integrated therapeutic intervention are vital components in the treatment of Type 2 diabetes.

## INTRODUCTION

With the global rise in its incidence and prevalence rates, Type 2 diabetes is becoming a major public health problem for healthcare providers, since it is associated with serious micro and macrovascular complications leading to substantial morbidity and mortality. Type 2 diabetes constitutes over 95% of the total diabetic population.[1] The current numbers of people with diabetes globally and among Indians, the leading country with highest number of diabetes are ~171 million and ~32 million respectively. These numbers are projected to increase significantly to ~366 million worldwide and to ~80 million in Indians by the year 2030.[2] While significant morbidity occurring due to microvascular complications (retinopathy, nephropathy and neuropathy), macrovascular complications [cardiovascular disease(CVD) and strokes] are the major cause of morbidity and mortality in Type 2 diabetes.[3] In Indians the prevalence of microvascular complications, retinopathy, neuropathy and microalbuminuria among Type 2 diabetic subjects has been reported to be 19%,[4] 17.5%[5] and 26.3%,[6] respectively, while the prevalence of macrovascular complications, coronary artery disease and peripheral vascular disease was 21.4%[7] and 6.3%[8] respectively.

Thus, to reduce the impact of Type 2 diabetes, the primary objectives for management should be focused on i) maintaining quality of life as little affected by the disease as possible, ii) prevention of its acute complications, and iii) curbing increased mortality and morbidity due to macrovascular complications, as well microangiopathic organ damage.[9] Studies have shown that an intensified and goal-oriented strategy to the treatment of Type 2 diabetes targeting at strict glycemic control is sufficient to prevent microvascular complications while a multifaceted approach that addresses all major risk factors, including dyslipidemia and hypertension is needed to prevent macrovascular complications.[10,11] Landmark intervention trials have clearly documented that aggressive treatment of these metabolic consequences is beneficial in improving diabetes outcomes and delaying the onset of complications, thereby reducing the economic burden and loss of quality life.

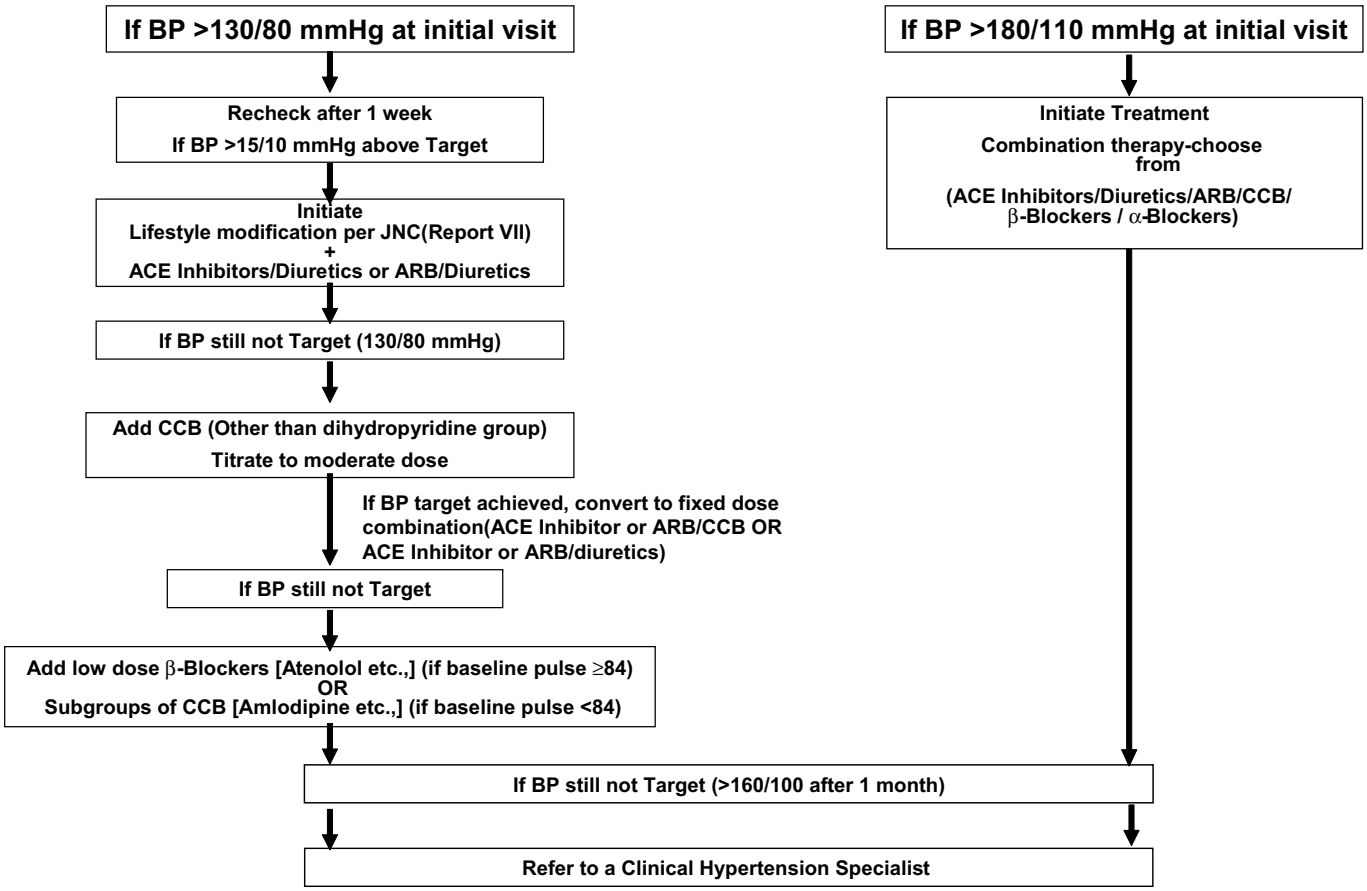


**Fig. 1:** Algorithm suggested for hypertensive diabetic patients without documented preexisting problems (e.g., angina, arrhythmia, heart failure) to achieve blood pressure target by minimum invasive strategies.
BP-Blood pressure; JNC- Joint National Committee; ACE - Angiotensin-converting enzyme ; ARB- Angiotensin receptor blocker; CCB- Calcium Channel Blocker.

**Table 1 : Targets for Adults with Type 2 Diabetes**

| Metabolic Outcomes | Target Values |
|---|---|
| **Glycemic control**[12] | |
| Glycated hemoglobin (HbA1c) | < 7% |
| Preprandial plasma glucose | 90-130 mg/dl |
| Postprandial plasma glucose | <180 mg/dl |
| **Blood pressure control**[13] | <130/80 mmHg |
| **Lipid control**[14] | |
| Total cholesterol | <200 mg/dl |
| Low density lipoprotein cholesterol | <100 mg/dl |
| High density lipoprotein Cholesterol | >40 mg/dl |
| Triglyceride | <150 mg/dl |

## TARGETS FOR MANAGEMENT OF DIABETES

Diabetes management is complex and requires that many issues to be addressed beyond glycemic control. The management plan should be individualized and diabetes self-management education should form an integral component.[12] Both the healthcare providers and the diabetic individuals should be aware of the targets of the metabolic consequences including hyperglycemia, hypertension and dyslipidemia to achieve positive long-term diabetes outcomes (Table 1).[12-14]

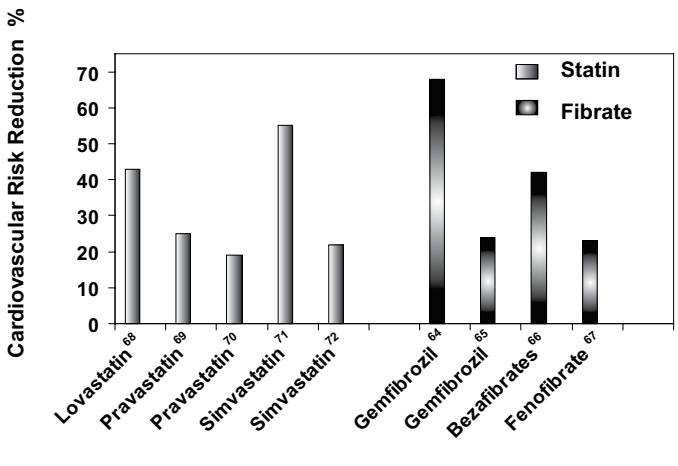


**Fig. 2:** Lipid lowering agents and cardiovascular risk reduction in Type 2 diabetic individuals

### Targets for glycemic control

Glycemic control is fundamental to the management of diabetes. Three hallmark studies on glycemic control in diabetes including the Diabetes Complications and Control Trial (DCCT), the United Kingdom Prospective Diabetes Study (UKPDS) and Kumamoto study[15-17] have clearly documented the beneficial

**Table 2 : Glycemic Control and Risk Reduction of Microangiopathy in Intervention Studies**

| Intervention Studies (Follow up) | Type of DM/ Number Studied | Eye | Kidney | Nerve |
|---|---|---|---|---|
| **DCCT [15] (6.5 yrs)** | Type 1 (n=1441) | 63% | 54% | 60% |
| **UKPDS [16] (10 yrs)** | Type 2 (n=5102) | 21% | 34% | - |
| **Kumamoto [17] (8 yrs)** | Type 2 (n=110) | 69% | 70% | 57% |

**Table 3 : Recommended Target Blood Pressure and First-Line Therapy in Diabetic Individuals to Reduce Cardiovascular Risk**

| Recommended by | Year | Target blood pressure (mm Hg) | First-line therapy |
|---|---|---|---|
| American Diabetic Association (ADA)[20] | 2004 | <130/80 | ACE Inhibitors/ARB |
| Canadian Hypertension Education Program[54] | 2004 | <130/80 | ACE Inhibitors /Angiotensin receptor antagonists |
| British Hypertension Society[55] | 2004 | <130/80 | ACE Inhibitors |
| Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC)[13] | 2003 | <130/80 | ACE Inhibitors |
| World Health Organization (WHO) - International Society of Hypertension[56] | 1999 | <130/85 | ACE Inhibitors |

ACE- Angiotensin-converting enzyme; ARB- Angiotensin receptor blocker

**Table 4 : Management of Dyslipidemia in Diabetic Adults**

| LIPID FRACTIONS | MANAGEMENT | | |
|---|---|---|---|
| | | Drugs | |
| | | First Choice | Others |
| ↓ LDL cholesterol | Lifestyle interventions | Statins | Resins, cholesterol absorption inhibitor or niacin |
| ↑ HDL cholesterol | Lifestyle interventions | Nicotinic acid or fibrates | - |
| ↓ Triglyceride | Lifestyle interventions, glycemic control | Fibric acid derivative | Niacin, high-dose statins |
| Combined hyperlipidemia | Glycemic control | High-dose statin | Combination of statin and fibrates or niacin |

effects of glycemic control in preventing microvascular complications (Table 2). In general, all trials demonstrated a 30 to 35% reduction in microvascular complications per 1% absolute reduction of glycated hemoglobin (HbA1c). However, in the UKPDS cohort receiving intensive treatment, demonstrated a significant (14%) reduction in macrovascular complications for every 1% reduction in HbA1c.[18]

Primarily, the glycemic control should be monitored by periodic measurement of HbA1c levels, the "gold standard" for assessing glycemic control in patients with Type 1and Type 2 diabetes[15-17] and the secondary assessments should include regular measurement of both fasting preprandial and postprandial glucose levels. The recommended targets for glycemic control according to the American Diabetes Association (ADA) are a preprandial blood glucose level of 90–130 mg/dl and a HbA1c level of <7% (with a level of >8% requiring additional measures)- the best determinant of glycemic exposure.[12] The American College of Endocrinology has adopted a more aggressive strategy by designating an HbA1c level of 6.5% as both a target and action level.[19]

More stringent target (HbA1C <6%) can be considered in individual patients, however, the absolute risk and advantages of lower targets are not well documented. Thus, in individuals who have premeal glucose values within target but who are not meeting HbA1C targets, consideration of monitoring postprandial glucose (PPG) 1–2 hours after the beginning of the meal and treatment aimed at reducing PPG values <180 mg/dl may lower A1C. The Kumamoto study done on 110 Japanese Type 2 diabetic subjects who were either on multiple insulin injection or conventional insulin injection therapy concluded that the glycemic threshold to prevent the onset and progression of diabetic microvascular complications were HbA1c < 6.5%, fasting plasma glucose concentration < 110 mg/dl, and 2-h postprandial plasma glucose concentration < 180 mg/dl.[17]

## Targets for blood pressure control

Hypertension is common among patients with Type 2 diabetes mellitus (~20-60%).[20] It has been hypothesized that both Type 2 diabetes and hypertension have common pathogenic mechanisms, thus increasing their risk of cardiovascular morbidity and also at a considerable risk of renal impairment and end-stage renal disease.[21] Results from clinical studies emphasize the need for tight blood pressure control in diabetic individuals. Three studies, the Hypertension Optimal Treatment (HOT) study,[22] the UKPDS,[23] and the Appropriate Blood Pressure Control in Diabetes (ABCD) trial,[24] specifically compared the effects of randomly assigning participants to different blood pressure targets on cardiovascular outcomes and have demonstrated the benefit (reduction of CHD events, stroke, and nephropathy) of lowering blood pressure to <140 mmHg systolic and <80 mmHg diastolic in diabetic individuals. Based on these and other studies the targets for tight blood pressure control in Type 2

diabetic individuals recommended by ADA and Joint National Committee (JNC) VII is <130/80 mmHg.[20,13]

The National Institutes of Health (NIH) has reported that for every 10-mm Hg reduction in systolic blood pressure (SBP) there is a 12% reduction in the risk for any complication related to diabetes[25] and the UKPDS study, demonstrated that for each 10-mmHg decrease in mean SBP, reductions in risk of 12% for any complication related to diabetes, 15% for deaths related to diabetes, 11% for myocardial infarction, and 13% for microvascular complications could be seen.[23] In the HOT study, a four-point difference in diastolic blood pressure(DBP), from 85 to 81 mm Hg, resulted in a 50% decrease in risk for CVD in patients with diabetes.[22] Whether achieving lower levels than the recommended target would further decrease the risk is an unanswered question, but may perhaps be answered by clinical trials now in progress.

### Targets for lipid control

Type 2 diabetic individuals have a higher prevalence of lipid abnormalities that contributes to increased rates of CVD.[12,26,27] Fagot-Campagna et al,[28] reported that among individuals with diabetes 97% had at least one lipid abnormality. The most common pattern of dyslipidemia in Type 2 diabetes individuals is increased triglyceride levels and decreased HDL cholesterol levels.[29] Lipid control plays a major role in preventing macrovascular disease. Several intervention studies have very clearly demonstrated the positive benefits of lipid control in preventing cardiovascular disease.[30] In addition, dyslipidaemia, particularly increased serum cholesterol and LDL cholesterol has been shown to be associated with diabetic retinopathy especially hard exudates in macula[31] and it also hastens the decline in glomerular filtration rate and progression of albuminuria to overt nephropathy.[32]

The current National Cholesterol Education Program (NCEP)/ Adult Treatment Panel (ATP) III guidelines recommendation for adults with diabetes are presented in Table 1. For women, it has been suggested that the HDL target be increased by 10 mg/dl.[14] The recent NCEP III update[33] recommends a very low LDL level ( < 70 mg/dl) for patients with diabetes plus CVD. In situations where the triglycerides are elevated and the calculated LDL is no longer accurate, they have recommended the non-HDL-cholesterol as the appropriate target, with values 30 mg/dl higher than the LDL-cholesterol targets cited.[33]

## TREATMENT FOR ACHIEVING TARGETS

### Glycemic control

Tight glycemic control is fundamental, to achieve near-normal glycemic control to delay or prevent the development of diabetic complications. The goals to achieve the target are a) nonpharmacologic measures and b) pharmacological therapy. Improvement in glycemic control can be achieved through dietary modification and regular exercise. A recent meta-analysis of randomized controlled trials of diabetes patient education observed a net reduction of 0.32% in HbA1c among intervention groups vs control.[34] The analysis concluded that interventions that included a face-to-face delivery, cognitive reframing teaching method, and exercise content were more likely to improve glycemic control.

Pharmacological strategies should be introduced when diet, exercise and lifestyle modifications fail to achieve good control. A number of oral antidiabetic agents and insulin are currently available for the treatment of Type 2 diabetes that target fasting and postprandial plasma glucose levels to improve glycemic control. Alone or in combination, these agents have enhanced the clinical approaches to treating diabetes.[35] As far as anti-hyperglycemic effect is concerned, no one category of antidiabetic agent is preferred over another[36] and each of the drug categories lead to a similar reduction in HbA1c excluding nateglinide and α-glucosidase inhibitors (AGIs).[37]

The UKPDS showed that intensive control of hyperglycaemia with sulfonylurea (SU) or insulin did not significantly reduce the risk of myocardial infarction or stroke.[16] However, subgroup analysis of obese patients (n=342) suggested that metformin therapy reduced the risk of myocardial infarction.[38] Thus, metformin is the drug of first choice in overweight patients with Type 2 diabetes.

In due course glycemic control becomes more difficult, even with maximum monotherapy. UKPDS demonstrated that monotherapy with SU, metformin, or insulin eventually fails, in about 50% by 3 years after diagnosis, and about 75% by 9 years, and hence multiple therapies were essential.[39] Most individuals require combination therapy as diabetes progresses.[40] The combination of SU and metformin has proven effective in many studies.[41,42] Garber et al[43] showed that initial treatment with glibenclamide/metformin improved glycemic control compared to either glibenclamide or metformin monotherapy. Combination therapy of thiazolidinediones (TZDs) and SU has also considerably improved HBA1c and fasting blood sugar levels.[44] A non-SU supplemented in patients inadequately controlled with a TZD has also been successful.[45] In addition, various studies have demonstrated that early addition of insulin when SU therapy is inadequate has also been effective in glycemic control.[46,47]

Hyperglycemia increases glycation of proteins resulting in advanced glycation end-products (AGE). AGE per se can trigger the atherosclerotic process, in addition, as the arterial wall components also get glycated, this leads to arterial stiffness and thence to vascular disorders. It could be proposed that glycemic control reduces non-enzymatic glycation, which in turn could reduce the occurrence of cardiovascular events in Type 2 diabetes. Several studies on antidiabetic agents, particularly TZDs have shown beneficial reduction in cardiovascular risk factors like LDL, fibrinogen, inflammatory markers and pre-clinical atherosclerotic markers.[48,49] The results of the DIGAMI (Diabetes Mellitus Insulin-Glucose Infusion in Acute Myocardial Infarction) trial demonstrated that 24 hour acute treatment with intravenous insulin, glucose, and potassium followed by tight blood sugar control with aggressive treatment with subcutaneous insulin reduced mortality by 29% in one year.[50] However, Mathew et al[51] reported contrary results stating that among diabetic patients who underwent successful percutaneous coronary intervention, patients treated with insulin had worse survival.

### Blood pressure control

Blood pressure control must be a priority in the management of individuals with hypertension and Type 2 diabetes. Angiotensin-

converting enzyme (ACE) inhibitors, angiotensin-receptor blockers (ARBs), diuretics, beta-adrenoceptor blockers, and calcium-channel blockers are effective antihypertensive agents in Type 2 diabetes.[52,53] Recent studies indicate that the choice of antihypertensive agent is also important. Combinations of these agents are frequently required to reach the target blood pressure of <130/80 mm Hg and also reduce risk for renal and cardiovascular events in diabetic individuals.[52] Patients with a SBP of 130–139 mmHg or a DBP of 80–89 mmHg should be given for a maximum of three months lifestyle and behavioral therapy alone and if targets are not achieved, then should be treated with pharmacological agents that block the renin-angiotensin system.[20] Table 3 presents the recommended target blood pressure and first-line therapy in diabetic individuals to reduce cardiovascular risk.[13,20,54-56] Studies including the recent Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) have concluded that thiazide-type diuretics are superior in preventing one or more major forms of CVD.[57,58]

The cardioprotective effect of ACE inhibitors and their benefit in the management of hypertension in diabetic individuals have been demonstrated in the ABCD,[24] Heart Outcomes Prevention Evaluation [HOPE],[59] Captopril Prevention Project [CAPP],[60] Fosinopril Versus Amlodipine Cardiovascular Events Randomized Trial [FACET][61] and Swedish Trial in Old Patients with Hypertension-2 [STOP-2][62] studies. The HOPE study showed that using the ACE inhibitor ramipril in individuals who already had a blood pressure of 139/79 further reduced CVD death by 37%.[57] In UKPDS it was concluded that treatment with either ACE inhibitors or β blockers substantially reduced the risk of death and complications due to diabetes.[23] The algorithm for management of hypertension in diabetic individuals is depicted in figure 1.

### Lipid control

Lipid management aimed at lowering LDL cholesterol, raising HDL cholesterol, and lowering triglyceride levels has been shown to decrease macrovascular disease and mortality in Type 2 diabetic patients, particularly in those who have previously had cardiovascular events. Table 4 presents the management strategies to be followed in diabetic adults to achieve targets.

As a first step, to achieve lipid targets, lifestyle intervention including Medical Nutrition Therapy (MNT), increased physical activity, weight loss, and smoking cessation should be initiated. MNT should be tailored made and centered on the reduction of saturated fat, cholesterol, and trans-unsaturated fat intake. In patients with very high triglycerides and blood glucose levels, glycemic control may be beneficial in modifying plasma lipid levels. When lifestyle modifications and improved glycemic control fail, then pharmacological therapy can be instituted. The first priority of pharmacological therapy is to lower LDL cholesterol to a target goal of <100 mg/dl for which statins are the drugs of choice.[14] However, in patients with clinical CVD and LDL >100 mg/dl, both lifestyle intervention and pharmacological agents should be initiated.[12] A reduction in LDL levels of at least 30% to 40% beyond dietary therapy should be achieved if feasible.[33] Maximum MNT is recommended for a reduction of LDL cholesterol by 15–25 mg/dl in patients with CVD by the American Heart Association.[63] Another class of drugs, the fibrates has been shown to markedly reduce triglycerides and moderately elevate HDL cholesterol and thereby reduce cardiovascular events.[64-67]

More than 50 clinical trails have supported the clinical benefit of cholesterol management and its risk reduction in cardiovascular disease in patients with diabetes. Figure 2 shows the risk reduction of cardiovascular events in diabetic subjects from various trials.[64-72] The role of simvastatin in reducing mortality rates was shown in the 4S trial conducted on 4444 subjects[71] while both the CARE[69] and LIPID[70] studies demonstrated the effect of pravastatin and simvastatin in increasing survival. Niacin is the most effective drug for increasing HDL levels but can significantly raise blood glucose at a high dose. Grundy et al[73] have demonstrated that low doses of extended-release niacin has significant benefit with regards to LDL, HDL, and triglyceride levels and complemented by modest changes in glucose that are generally amenable to adjustment of diabetes therapy. One can also combine a fibrate or nicotinic acid with an LDL-lowering drug (statins), when a diabetic patient has high triglyceride or low HDL levels.[33]

## CONCLUSION

Thus, to reduce the morbidity and mortality due to diabetes, aggressive treatment for metabolic targets including hyperglycemia, hypertension and hyperlipidemia is essential. For a number of reasons, diabetic individuals and their health care providers do not achieve the desired targets of treatment for which additional actions including enhanced diabetes education, initiation of or increase in self-monitoring of blood glucose (SMBG), integrated therapeutic intervention, frequent interaction between patient and healthcare provider, and referral to a diabetologist are vital components in the management of Type 2 diabetes.

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