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Transforming the Diabetes Therapy Paradigm

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ABSTRACT

A combination of lifestyle modifications and drug therapy is required for diabetic patients in order to achieve and maintain long-term good metabolic control. The risk of macrovascular and microvascular problems is considerably reduced by achieving near-normal glycated haemoglobin levels. For the treatment of type 2 diabetes mellitus (T2DM), various medications, both oral and injectable, are currently available. The need of maintaining good glycaemic control is emphasized in treatment algorithms intended to slow the onset or progression of diabetes complications. The objective of this review is to provide an update on the advantages and disadvantages of various medicines used to treat T2DM, both now and in the future. The first course of action should emphasize a change in lifestyle. Furthermore, lifestyle changes have been proved to be beneficial, even though they frequently result in long-term complications for many people because of issues like metabolic illnesses, joint and bone disorders, cardio-vascular diseases, hypertension, obesity, violence, and other issues that can be caused on by an unhealthy lifestyle. Doctors should be knowledgeable about the various types of diabetes medications currently available so they may choose the ones that are the most productive, secure, and patient-friendly. For the majority of patients, metformin continues to be the drug of choice. Depending on the features of each patient, second-line therapy choices or other alternative therapies should be tailored. The treatments for T2DM patients are reviewed in this article, with a focus on medications that have been on the market for less than ten years.

INTRODUCTION

According to the U.K. Prospective Diabetes Study (UKPDS) findings, treatment of type 2 diabetes should include intensive efforts to lower blood glucose levels as near to normal. With publication of the UKPDS results, the American Diabetes Association issued this advice (1). The recommendation was quickly included into official guidelines across all of the world (2). They consistently advise setting an A1C target of 7.0%. However, due to a risk reduction that was only marginally statistically significant (16%, P <0.052), the results of the UKPDS remained ambiguous with regard to cardiovascular (CV) problems.

However, a recent meta-analysis of randomized trials in type 2 diabetes (3) estimated a 19% decrease in the incidence of any kind of macrovascular incident linked with improved long-term glycemic control, supporting the UKPDS findings. Moreover, type 1 diabetic individuals have

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shown a substantial correlation between glucose management and micro- and macrovascular disease (4,5).

Previous large-scale intervention experiments have been hampered. 10,000 people with type 2 diabetes, vascular disease, or multiple CV risk factors were randomly assigned in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial to either an intensive treatment programme aiming for normal blood glucose levels and an A1C of 6% or a standard treatment program aiming for an A1C of between 7 and 7.9%. Due to excess mortality (hazard ratio [HR] 1.22, 95% CI 1.01-1.46; P <0.04) and a lack of a significant decline in the primary outcome, which is a composite of nonfatal myocardial infarction, nonfatal stroke, or death from CV causes (HR 0.90, 0.78-1.04; P <0.16), the intensive blood glucose arm was prematurely stopped (6).

Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE), the largest-ever study of the strategy of intensive glucose control, included 11,140 high-risk type 2 diabetic patients. After a median 5-year follow-up, there was no evidence that major CV event reduction occurred when A1C was lowered to 6.5% (HR 0.94, 0.84-1.06; P <0.32). (7). The Veterans Administration Diabetes Study has shown similar outcomes (8). It is noteworthy that all three trials included patients with long-term diabetes, and in two of the studies, participants with prior CV events were included, leaving the significance of achieving and maintaining good glycemic control from the time of diabetes diagnosis unaltered (or at least uncertain). The outcomes of the UKPDS's 10-year follow-up provide evidence in favour of this viewpoint (9).

The risk for microvascular complications, myocardial infarction, and all-cause mortality was significantly reduced in patients who initially received rigorous treatment, despite the early elimination of glycemic differences. There are hardly many people with newly diagnosed type 2 diabetes who reach and, more critically, maintain their glycemic target. No particular information is available, although the average A1C in the UKPDS, which included only newly diagnosed type 2 diabetic individuals without a history of cardiovascular events, was 7%. However, this threshold number was not kept constant for 4 years (1), and more current data showed that 50% of this patient population is at target (10).

Thus, an early and effective intervention that is also adaptable enough to provide long-term metabolic control is necessary for the effective treatment of type 2 diabetes. Strategies that recognise and go around present restrictions should be developed in order to establish new paradigms of therapy.

INADEQUATE DIET AND EXERCISE PROGRAMS

As recently verified by the European Association for the Study of Diabetes/American Diabetes Association treatment algorithm (11), diet and exercise continue to be the cornerstone of type 2 diabetes treatment. However, for lifestyle adjustment to be successful, it requires long-term

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adherence. The first significant clinical research measuring the long-term health effects of intensive lifestyle intervention in 5,145 overweight or obese individuals with type 2 diabetes is called Look AHEAD (Action for Health in Diabetes) (12). Follow-up is ongoing and will continue for 11.5 years to see whether long-term weight loss accomplished with diet, exercise, and behaviour adjustment will lower CV morbidity and death.

At one year, participants' body weight reduced by 8.6%, their A1C target levels climbed from 46 to 73%, and their percentage of those meeting the recommended levels for blood sugar, blood pressure, and cholesterol doubled (from 10 to 23.6%) (12). The subsequent follow-up will confirm whether these initial positive effects will be sustained over time and whether they will be converted into a CV benefit. The Diabetes Prevention Program (13) and Diabetes Prevention study revealed a 58% reduction in the conversion rate to overt diabetes, making the effects of lifestyle changes for the prevention of type 2 diabetes more apparent in the interim. These changes included losing a small amount of weight and increasing physical activity to prevent or delay type 2 diabetes. (14; Figure 1). But even with these impressive outcomes, implementing similar programs in the entire population is still difficult and, at least initially, expensive enough to necessitate deliberate political action.

Figure 1. Physical activity and healthy diet for Prevention of Diabetes

LIMITED PHARMACOLOGICAL ARMOURY

The ideal antidiabetic drug should regulate plasma glucose profiles, reduce side effects, and shield against the emergence of micro- and macrovascular problems. Of course, there is no such agent at this time, and it is unlikely that there will be one in the near or medium term. There is no shortage of antidiabetic medications, and more are on the way (15; Figure 2). Even though each of these medications has advantages and disadvantages, none of them is likely to provide long-term, reliable excellent glycemic control. Although the UKPDS experience is just with conventional antidiabetic drugs, it has provided a significant lesson.

Regardless of the medication first administered to the patient, glycemic control ultimately crossed the desired line. Alternatively, you might ask if there are any treatments that have

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longer-lasting effects. Recently, this problem was addressed in A Diabetes Outcome Progression Study (ADOPT). In this trial, the cumulative incidence of monotherapy failure at 5 years was lowest with rosiglitazone (15%, P <0.001) and was greatest with glyburide (34%; P <0.001) (16). Rosiglitazone's greater longevity has been explained by simultaneous improvements in the two primary pathogenetic pathways of type 2 diabetes, namely insulin resistance and β-cells activity.

Glitazones have been asserted to maintain β-cells function. Loss of β-cells function is the primary factor contributing to the degradation of glucose tolerance and glycemic control (17,18, Figure 3). In light of preclinical research showing that these medications can maintain β-cells function and mass, a great deal of interest has been developed in the development of glucagonlike peptide (GLP-1) analogues and dipeptidyl peptidase-4 inhibitors (19). It would be foolish to anticipate the golden cure at this time; rather, it would be wiser to learn how to employ the present pharmacologic instruments more effectively. These intriguing but preliminary findings need clinical confirmation.

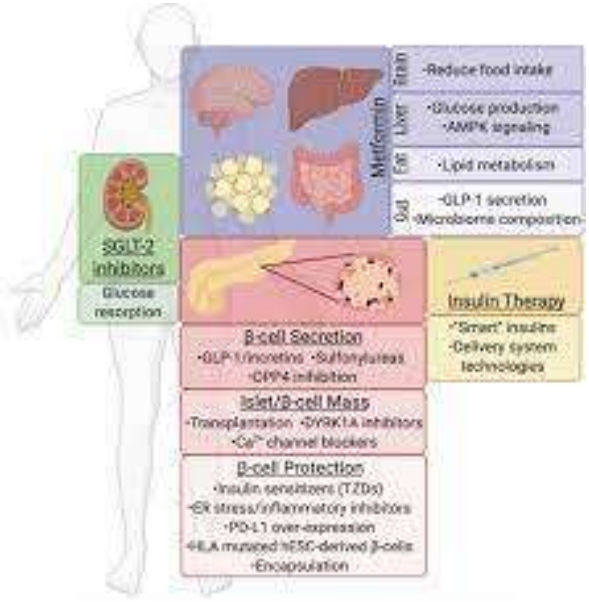

Figure 2: New Treatment for Diabetes

Treatments for type 2 diabetes currently focus on boosting insulin availability (either directly or indirectly through substances that encourage insulin secretion), enhancing insulin sensitivity, delaying the delivery and absorption of carbohydrates from the gastrointestinal tract, or boosting urine glucose excretion. By raising urine glucose excretion, sodium-glucose co-transporter 2 (SGLT2) inhibitors lower blood sugar levels. In patients with type 2 diabetes, SGLT2 inhibitors enhance the renal excretion of glucose and consequently only slightly lower elevated blood glucose levels. The filtered load of glucose and the osmotic diuresis brought on by this therapy limit the capacity to reduce blood glucose and glycated haemoglobin (A1C) levels. SGLT2

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inhibitors only reduce blood glucose levels by preventing the reabsorption of filtered glucose, which decreases as blood glucose levels rise (19).

The most recent class of oral anti-hyperglycemic medications to receive FDA approval for the treatment of diabetes mellitus are SGLT2 inhibitors. Significant changes have been made in this class of drugs' safety and effectiveness during the past year. Most people with type 2 diabetes are not thought to benefit from SGLT2 inhibitors as their first line of treatment. Most individuals with type 2 diabetes should start their treatment with metformin, weight loss, exercise, and dietary changes (19). These drugs present an exciting choice for patients throughout the course of type 2 diabetes naturally as well as a potential supplemental therapy for type 1 diabetes under close monitoring due to their new mechanism of action. Although using SGLT2 inhibitors has a wide range of side effects, including recently discovered episodes of ketoacidosis, this class may be a viable choice in the properly chosen patient (19).

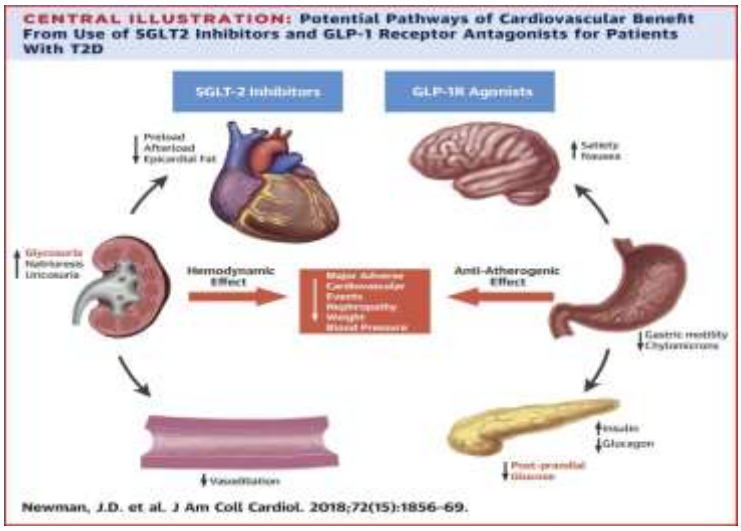

Figure 3: Potential Pathways of Cardiovascular Benefit From Use of SGLT2 Inhibitors and GLP-1 Receptor Antagonists for Patients With T2D

ECONOMIC MANAGEMENT

For type 2 diabetes, the stepwise approach is typically used to manage glycemic control. Upon diagnosis, a single oral antidiabetic drug is usually started and gradually increased to the maximum indicated dose before combination therapy is commenced. This cautious approach, nevertheless, has a number of disadvantages. Instead, a proactive strategy and therapy tailored to the person through rigorous selection among the various drugs can improve patient care (20). Although diet and exercise have been shown in numerous clinical studies to be useful in avoiding diabetes and slowing the progression of the disease (13,14), these regimens are challenging to follow and seldom result in glycemic control.

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Pharmacologic methods, therefore, become a crucial part of managing diabetes together with lifestyle changes, to the point where a recent American Diabetes Association/European Association for the Research of Diabetes agreement suggested nutritional therapy be started along with metformin (11). The latter is virtually universally acknowledged as the preferred drug, but failure is anticipated. In the UKPDS, the cumulative rate of failure in obese patients randomly assigned to metformin after 9 years of monotherapy was 87% (21). In ADOPT, the percentage of metformin failure throughout the course of five years was 21% (16), and at four and five and a half years, the rate of metformin secondary failure was 35.5% and 38%, respectively.

These studies, which all showed that clinical practice exhibits unacceptable treatment inertia, used various definitions of failure. For patients using metformin or sulfonylurea monotherapy, the average period between reaching an A1C action point of 8% and switching to, or adding, a second oral antidiabetic drug was 14.5 or 20.5 months, respectively, according to an analysis of the 1994–2002 Kaiser Permanente Northwest database (24). "Clinicians should change glucose-lowering therapies in type 2 diabetes much sooner or adopt treatments that are less likely to fail," the analysis's authors concluded (24).

The American Society of Clinical Endocrinologists and the Global Partnership of Effective Diabetes Management (20) also support this viewpoint (25). The more recent American Diabetes Association/European Association for the Study of Diabetes consensus statement, which supports more intensive and earlier use of combination therapy and the introduction of insulin therapy if glycemic control is not achieved, adopts a similar strategy, calling for individualized therapeutic choices to be taken into account as soon as A1C exceeds a threshold of 7.0% (11; Figure 4). Several studies have demonstrated how early use of submaximal combination dosages of medicines might enhance glycemic control without causing barely detectable adverse effects (26,27).

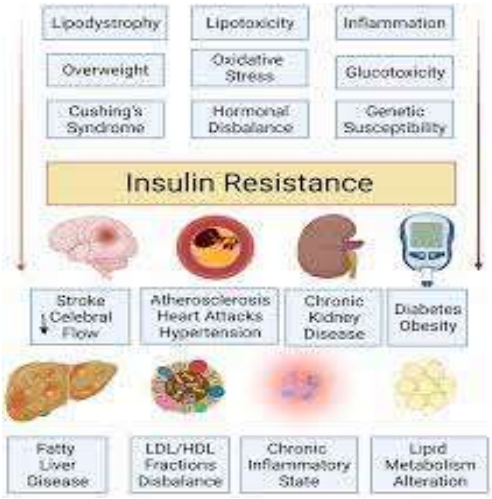

Figure 4: Resistance of Insulin Therapy

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In addition to better efficacy, the logical treatment approach to the many pathogenetic pathways underlying hyperglycemia and its progression should be taken into account when considering the use of numerous medications. In particular, the primary role of the gradual decrease of β-cells function, as explained below, should be fully taken into account.

Using a more intensive early intervention may increase the likelihood of experiencing adverse effects compared to more lenient treatment techniques. Moreover, patient compliance with the antihyperglycemic medication may be impacted by adverse effects. The efficacy-to-safety ratio of a medicine is the best indicator of its profile, however, this ratio can change depending on the dosage. Metformin is an example of a typical situation (28). When the dose is increased from 500 to 2,000 mg/day, a progressive decrease in A1C is seen; however, there is no further improvement in glycemic control at this dosage. On the other hand, a steady increase in the dose of metformin is linked to a rise in the number of patients who experience gastrointestinal distress. As previously indicated, early combination therapy enables the use of hypoglycemic medicines at a submaximal dose, lowering the likelihood of side effects.

Patients in the EMPIRE study (26) were randomized to receive either 2,000 mg/day of metformin or 1,000 mg/day of metformin + 8 mg/day of rosiglitazone. The number of patients who stopped treatment due to gastrointestinal-related adverse events was significantly lower with combination therapy (all gastrointestinal events 3.1 vs. 6.8%; diarrhea 1.6 vs. 4.2%; abdominal pain 1.0 vs. 2.3%), even though there was no discernible difference in A1C after 4 months of treatment. In contrast, glitazones and metformin have a reduced incidence of edema and body weight gain compared to glitazones and sulfonylureas and insulin.

Dipeptidyl peptidase-4 inhibitors and GLP-1 analogues have an intriguing safety profile connected to body weight loss or neutrality (18), but when these drugs are coupled with sulfonylureas, the danger of hypoglycemia, which is virtually nonexistent with monotherapy, becomes a concern. In the context of intense therapy started at the time of type 2 diabetes diagnosis, hypoglycemia is in fact the main issue.

The U.K. Hypoglycemia Study Group recently examined the incidence of hypoglycemia in these patients and found that even with early insulin use, the frequency of hypoglycemia was typically comparable to that seen in patients receiving sulfonylurea therapy and significantly less frequent than during the first five years of treatment in type 1 diabetes. By carefully choosing a course of therapy, this low rate of hypoglycemia in type 2 diabetes may be further decreased. As a result, hypoglycemia is not linked to the use of insulin sensitizers, its frequency is very low with incretin-based therapy, and both the use of fast-acting and long-acting insulin analogues has been linked to less hypoglycemic incidents (30).

LOW COMPLIANCE

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Unexpected adverse occurrences and a patient's inability to handle them may compromise their sense of dependability and commitment to their treatment. Physicians frequently experience a sense of frustration when patients don't comply. Yet, adherence is arbitrary and challenging to measure accurately. Patients may also underestimate the severity of their condition due to the absence of symptoms or a lack of faith in the immediate or long-term advantages of treatment, especially those with minor metabolic control changes. It is crucial for doctors to work to get their patients to comply with their orders.

More time would need to be spent on patient education and education reinforcement so that patients would understand the seriousness of the disease and the significance of adhering to the recommended course of therapy. Just 35% of patients in the survey by Browne et al. (31), less than 10% of patients on sulfonylureas understood the danger of hypoglycemia, and only 20% of patients taking metformin were aware of potential gastrointestinal side effects. Even medical professionals including doctors, nurses, and pharmacists lacked some understanding. Over 50% of respondents correctly responded to questions about the dosage, mode of action, and side effects of oral antidiabetic medications (31). These findings highlight the value of ongoing education and information consistency from primary and secondary team members, but they may also be the cause of medical inertia. A recent theory (32), known as "clinical myopia," proposes that failing to recognize the long-term advantages of treatment intensification may be a common mechanism underpinning both patient non-adherence and physician clinical inertia.

Given the need for multifactorial management, polypharmacy might add extra strain to the patient's life. Oral fixed-combination tablets are becoming more widely available, and studies from the literature suggest that using these combinations instead of a single medicine tablet may improve therapy adherence (33).

PHYSIOPATHOLOGY IN RELATION

In instance, insulin resistance and diminished cell activity are two pathogenetic pathways that coexist with type 2 diabetes in this complex disease (34). 85% of patients have insulin resistance, which is characterised by reduced insulin-mediated glucose absorption in insulin-dependent tissues (mostly skeletal muscle) and inadequate hepatic glucose production suppression. Due to an improper acceleration of gluconeogenesis, the latter is mostly to blame for elevated fasting plasma glucose levels. Along with being an independent CV disease risk factor, insulin resistance is tightly connected to a number of other CV disease risk factors (35,36).

Early alterations in insulin sensitivity in type 2 diabetes-risk individuals are already connected to severe β-cell destruction. A small alteration in glucose resistance is associated with a detectable loss in cell mass and function, even within nondiagnostic boundaries (37). Furthermore, the rate of progression from normal glucose tolerance to diabetes is set by the steady loss of β-cells] mass and function. Therapy aimed at correcting pathogenetic defects that are already evident in pre-diabetes hence ensures continuous glycemic control. This pathophysiological context led

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DeFronzo to suggest in his Banting Medal Lecture (38) that triple therapy should be started as soon as feasible rather than using a stepwise strategy based solely on A1C targeting.

Metformin will be used to enhance insulin action on the liver, pioglitazone to enhance peripheral insulin action, and GLP-1analogs (or dipeptidyl peptidase-4 inhibitors) to enhance β-cells function and, potentially, preserve β-cells mass, in accordance with this proposal, the effects of which will be tested in a randomized trial. The fact that none of the three medications carry a risk for hypoglycemia makes the treatment intriguing because it seems safe enough to be utilized in the early stages of the disease. Moreover, the anti-obesity effects of metformin and GLP-1 analogs may stop glitazone-mediated body weight gain.

Although logical and intriguing, this plan needs to be evaluated with appropriate clinical trials before being put into action. This should happen before any preliminary confirmation of efficacy and safety is taken into account. In conclusion, current pharmacopoeia enables, at least theoretically, the preservation of long-term glycemic control by facilitating a reasonable treatment approach aiming at reversal of the changes responsible for the increasing worsening of glucose homeostasis.

SYSTEM OF SUBOPTIMAL HEALTH CARE

It is improbable that type 2 diabetes can be managed effectively and sustainably with solely logical treatment. A systematic multidisciplinary approach is indicated by factors like education, motivation, avoidance of the occurrence of micro- and macrovascular problems, and the development of comorbidities. A multidisciplinary team made up of primary care doctors, diabetologists, diabetes educators, nutritionists, pharmacists, podiatrists, and other specialists should ideally help the patients. Any new educational, diagnostic, and therapeutic requirement should be quickly addressed by this interdisciplinary team.

Evidence are available to support the idea that such an approach greatly improves glycemic control, hospitalisation, and patients' quality of life (39). Since it has frequently been demonstrated that it not only improves metabolic control but also results in more cost-effective intervention, ongoing education is also crucial for diabetes management (40). Economical limitations may make it difficult to implement these strategies, but it is important to recognise that increasing the number of people who achieve good glycemic control depends on involving the patient in the diabetes care team. Each member of the diabetes team should understand how important it is to help patients take charge of their health.

MODIFICATION OF THE PARADIGM

A shift in diabetes therapy is necessary due to the rise in type 2 diabetes cases, the remaining uneven therapeutic response, and the burden of micro- and macrovascular consequences. Only by conquering the numerous obstacles impeding our capacity to provide good long-term

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glycemic management to as many patients as feasible can such change be achievable. Some of these constraints were attempted to be outlined in earlier parts. Whilst many more might be included, our list might already be sufficient.

The most prevalent phenotypic characteristic of type 2 diabetes is obesity, which has a direct impact on the likelihood of achieving prolonged glycemic control. Regrettably, there are still no proven anti-obesity medications, even after the use of endocannabinoid receptor antagonists was discontinued (41). The fact that type 2 diabetes is currently on the rise as a result of obesity is an even more important point, and combating obesity is a key duty in the effort to prevent this disease. Sadly, this strategy is not likely to be resolved at the personal level.

Instead, as stated by Simpson et al. (42), a more all-encompassing strategy should be used by implementing lifestyle modification strategies targeted at the community, addressing young generations by incorporating formal and structured educational programmes into the school curricula, and by exposing children to the devastation and mayhem of illnesses. All of this calls for cultural and political choices, such as treating metabolic poisoning, or high calorie fat content in food, with the same tax penalty strategy utilised for other health-harming elements, like cigarettes, alcohol, and carbon emissions.

As soon as fasting plasma glucose reaches 125 mg/dl, diabetes is identified. Just going over that line does not indicate that we have "mild diabetes disease." There is no such thing as "mild diabetes," just diabetes with all of the associated risks for complications, which pose a real harm to the patients' quality of life and life expectancy. Consequently, it is essential to quickly restore and maintain glycemic control at or near normal levels for as long as feasible. The diabetologist should be knowledgeable about the benefits and drawbacks of the current therapy techniques in order to accomplish this goal. This is required in order to integrate these approaches logically and optimise them. In order to do this, a proactive strategy should be taken from the moment of diagnosis, as recommended by a recent consensus statement from the American Association of Clinical Endocrinologists: "adopt an uncompromising insistence on treatment to target" (25). When such insistence is put into practise, adverse occurrences can be a cause for concern, but as with the previous point, deliberate use of agents in combination can lower this risk.

Without a close working relationship between the diabetes patient and the healthcare team, there is no hope of maintaining positive outcomes. Both parties should participate in an ongoing, reciprocal educational programme that includes information verification and update, and every effort should be taken to ensure effective communication. The creation of a diabetic team seems to be crucial for this goal. Although it may be tiny due to financial restrictions, it is imperative that the medical staff adhere to clear management practises and set well-defined goals.

Three key "innovations" are crucial to the shift in the therapy paradigm, nevertheless. The first is that we have the capabilities now to target treatment towards reversing the mechanisms causing the disease to evolve. The justification for early intensive combination therapy is based on the

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understanding that modifications are already present in those with mild disturbances of glucose tolerance and that allowing hyperglycemia to develop can only make those mechanisms worse. Second, insulin action in peripheral tissue should be improved, hepatic glucose generation should be suppressed better β-cells function should be supported at the time of diagnosis, even if the glucose parameter is just marginally above diagnostic criteria, and third, glycemic control is the main, though not only, aim of such a strategy. Hence, an improved CV risk profile might be anticipated when insulin resistance is reduced.

One of the main tasks in the management of type 2 diabetes continues to be the prevention of CV morbidity and death. Hence, a comprehensive strategy is required, as indicated by the findings of the Steno-2 investigations (43,44). In terms of vascular complications and a lower risk of death from CV causes, an intensified multifactorial intervention with strict glucose control, the use of renin-angiotensin system blockers, aspirin, and lipid-lowering medicines, as well as behaviour modification, has long-lasting positive benefits (43,44). Although this strategy might be highly successful, it might be difficult to put into practise in the diabetic community.

Controlling blood glucose, blood pressure, and cholesterol levels has been shown to lower the risk of vascular disease in type 2 diabetic patients; however, it is unclear how well these risk factors are currently controlled in the general population. The number of people meeting goal values for all of the aforementioned risk factors is still unsatisfactory, according to analysis of the National Health and Nutrition Examination Survey (NHANES) database in the United States, and it doesn't change noticeably over time (45). It is clear that even while a trend in the right direction may be discernible, only 13.2% of patients in the NHANES 1999–2004 study met the suggested targets for A1C level 7%, blood pressure 130/80 mmHg, and total cholesterol 200 mg/dl (5.18 mmol/l). More public health initiatives are therefore required to reduce CV risk factors in diabetics, but other treatments should also be sought.

As diabetes has been identified as a CV risk factor comparable (46), preventing diabetes may be the only viable option. Several studies have demonstrated that altering one's lifestyle can effectively stop high-risk groups from developing type 2 diabetes (47). Although it is unknown if diabetes prevention measures may ultimately stop diabetic vascular problems from developing, all CV risk variables are positively impacted.

Lastly, a significant cultural and practical effort must be done in order to meet the growing health demand of type 2 diabetic patients. As already mandated by the diabetic community: "Diabetes must be prevented sooner and detected earlier (48)," a change in the paradigm of treatment is required. All forms of diabetes must thereafter be controlled much more aggressively once they have been diagnosed (49).

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