A Vis A Vis review study on Management of devastating metabolic disorder - *Diabetes mellitus*

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ABSTRACT

Diabetes mellitus is an endocrinological and/or metabolic disorder with an increasing global prevalence and incidence. High blood glucose levels are symptomatic of diabetes mellitus as a consequence of inadequate pancreatic insulin secretion or poor insulin-directed mobilization of glucose by target cells. *Diabetes mellitus* is aggravated by and associated with metabolic complications that can subsequently lead to premature death.

This review paper critically explores diabetes mellitus in terms of its historical perspective, biochemical basis, economic burden, management interventions along with the future perspectives.

This paper identify that the goal of diabetes management is to improve the quality of life and productivity of people living with diabetes. Management of diabetes entails the following components:
(i) Treatment of hyperglycemia
(ii) Treatment of hypertension and dyslipidaemias
(iii)Prevention and treatment of microvascular complications
(iv)Prevention and treatment of macrovascular complications.

This study predicts that there are two modalities of managing diabetes viz - *Non drug method (use of proper diet and physical activity) and - Use of Drugs e.g. diabetes tablets for lowering blood sugar and Insulin*. Whereas diabetes education goes hand in hand with these two methods)

Study finally concludes that life style management is apparently the cornerstone of management of diabetes mellitus. It is recognized as being an essential part of diabetes and cardiovascular disease prevention.

Keywords: *Diabetes mellitus, hyperglycemia, management, devastating metabolic disorder.*

INTRODUCTION

*Diabetes is a chronic disorder of carbohydrate, fat and protein metabolism characterized by increased fasting and postprandial blood sugar levels (**Gupta et al. 1984).***

According to *WHO (1999)*, diabetes is a metabolic disorder of multiple etiology characterized by chronic hyperglycaemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both. They also make clear that the effects of diabetes mellitus comprising long–term damage, dysfunction and failure of various organs. Notably, National health portal (2017) also states the same. Report elaborated in the portal states that diabetes mellitus is a condition associated with disturbance in the metabolism of carbohydrate, fat and protein, coupled with relative or absolute insulin deficiency.

In relation to diabetes, hyperglycemia refers to chronically high blood glucose levels. Hyperglycemia occurs when people with diabetes have too much sugar in their bloodstream. Hyperglycemia, the term for expressing high blood sugar, has been defined by the *World Health Organisation (2016)* as:

- Blood glucose levels greater than 7.0 mmol/L (126 mg/dl) when fasting
- Blood glucose levels greater than 11.0 mmol/L (200 mg/dl) 2 hours after meals

Although blood sugar levels exceeding 7 mmol/L for extended periods of time can start to cause damage to internal organs, symptoms may not develop until blood glucose levels exceed 11 mmol/L.

PREVALENCE

Diabetes is reaching as epidemic proportion across the globe. According to a report of *American Diabetes Association* released in year 2017, there are 382 million people affected with diabetes around the globe. Further, 316 million with impaired glucose tolerance are at high risk from the disease–an alarming number that is set to reach 471 million by 2035. Diabetes is on the rise all over the world and countries are struggling to keep up with the progression of this metabolic disorder (*ADA, 2017*). Although diabetes is often not recorded as the cause of death, globally, it is believed to be the fifth leading cause of death in 2000 after communicable diseases, cancer and injury (*Wild et al.* 2004). India ranked first with 31.4 million people followed by China

(20.8 million) and United State (17.7 million). The statistical data is going to be double by 2030 with expected number of 79.4 million people in India, 42.3 million people in China and 30.3 million people in USA *(NDEP, 2013; AIHW, 2013)*.

Prevalence of diabetes in Indian sub-continent countries showed that about one quarter of the population of urban region is affected in Bangladesh, Nepal, Bhutan and Sri-Lanka (*Anjana et al*. 2011). Preliminary study conducted by the Indian Council of Medical research (ICMR) revealed the statistical data, that the lower proportion of the population of Chandigarh (0.12 million), Jharkhand (0.96 million) and Uttar Pradesh (4.23 million) was affected in states of Northern India as compared to 9.2 million in Maharashtra and 4.8 million in Tamil Nadu (*Anjana et al*. 2011).

According to a forecast of National health portal (2017) it is estimated that by end of year 2035, 592 million people around the globe will be suffering from disease. A further 316 million people are currently at high risk of developing type 2 Diabetes, with the number expected to increase to almost 500 million within a generation. Another fact that was mentioned that, once affected, it needs long treatment, at time even

throughout life with possibility of several complications and this is part of the reason why diabetes mellitus is becoming more and more of a serious concern.

The prevalence of diabetes in Asian countries has increased from 9.6 percent in 2013 to 17.5 percent in 2018. The prevalence of diabetes is rising rapidly especially in the urban population in India. Since 2013 to 2018 a 10 fold increase has been observed from 2.2 percent to 22.1 percent. (*Indian Diabetes Association, 2018)*

According to a report published by *Indian Diabetes Association in year 2018,* India has nearly 33 million diabetic subjects today which is likely to go up to 57.2 million by the year 2025. The reasons for this escalation are due to changes in lifestyle; people living longer than before (ageing) and low birth weight could lead to diabetes during adulthood. Diabetes related complications are coronary artery disease, peripheral vascular disease, neuropathy, retinopathy, nephropathy, etc. People with diabetes are 25 times more likely to develop blindness, 17 times more likely to develop kidney disease, 30-40 times more likely to undergo amputation, two to four times more likely to develop myocardial infarction and twice as likely to suffer a stroke as non-diabetics.

Lifestyle modifications, inclusive of dietary changes, regular physical activity and weight reduction are indicated for prevention of diabetes *(Sidhu et al.2002).*

The prevalence of diabetes is increasing Globally. India has the maximum increase during the last few years. Type 2 diabetes mellitus is the commonest form of diabetes. The prevalence of type 2 diabetes mellitus is 2.4% in rural population and 11.6% in urban population. Prevalence of impaired glucose tolerance is also high in urban population. Subjects under 40 years of age have a higher prevalence of impaired glucose tolerance than diabetes. The important risk factors for high prevalence include obesity (especially central one) and Lifestyle changes due to rapid urbanization. The prevalence rate of diabetes type 2 among 10 countries is given in table 2.

- 46 million diabetics in India. The number of diabetics in the country is the highest in the world.

Table 1: Top 10 Countries estimated to have the highest numbers of people with Diabetes in 2000 -2030

Country	People with diabetes (million) 2000	People with diabetes (million) 2030
India	31.7	79.4
China	20.8	42.3
US	17.7	21.3
Indonesia	8.4	8.9
Japan	6.8	
Pakistan	5.2	11.1
Russian federation	4.6	
Brazil	4.6	
Italy	4.3	7.8
Bangladesh	3.2	6.7

According to World Health Organization Report, the "top three" countries are the same as those identified for 1995, INDIA, China and US.

- 60 % of World population does not do enough physical activity.
- 50% of diabetic patients worldwide are unaware that they have the disease.

CLASSIFICATION OF DIABETES

A major requirement for epidemiological and clinical research and for the clinical management of diabetes is an appropriate system of classification that provides a framework within which to identify and differentiate its various forms and stages. While there have been a number of sets of nomenclature and diagnostic criteria proposed for diabetes, no generally accepted systematic categorization existed until the NDDG classification system was published in 1979. Thus according to *WHO, 2018* diabetes can be classified into the following general categories:

1. Type I :- IDDM/Juvenile onset DM

2. Type II : -NIDDM/Maturity onset DM

3. Gestational Diabetes

4. Other types: – Diabetes associated with certain condition and syndrome such as drug induced or chemical induced, secondary to pancreatic disease, secondary to Endocrine disease.

Type 1 diabetes, also known as Insulin Dependent Diabetes Mellitus (IDDM), is due to an inadequate insulin secretion resulting from a large decrease in the number of beta-cells in the islets of Langerhans (*Eisenbarth*, 1986) and Type 2 diabetes, or Non- Insulin Dependent Diabetes Mellitus (NIDDM), is due to lack of insulin in target tissues (*Lillioja et al*.1988) i.e., insulin resistance that leads to impaired tissue glucose uptake and suppression of hepatic glucose production (Martin etal.,1992). Most of the pathological conditions of diabetes mellitus can be attributed to lack of one of the following three major effects of insulin

(i)- Decreased utilization of glucose by the body cells, with a resultant increase in blood glucose concentration

(ii)- Markedly increased mobilization of fats from the fat storage areas causing deposition of lipids in the vascular walls due to abnormal fat metabolism and resulting atherosclerosis and the formation of ketone bodies

(iii)- Depletion of protein in the tissues of the body. The overall effect is dehydration of the extracellular space, which then causes dehydration of the intracellular spaces as well (*ADA, 2013*).
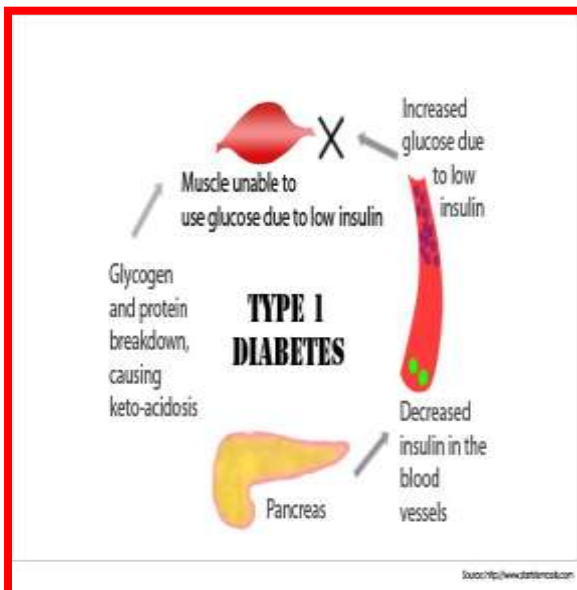
TABLE 2 PATHOPHYSIOLOGY OF TYPES OF DIABETES

| Pathophysiology	Type 1 Diabetes	Type 2 Diabetes
Etiology	Autoimmune	Peripheral resistance
Formerly known as	IDDM	NIDDM or "adult onset" diabetes
Age of onset	Younger	Older
Obesity	Rare	Common
FamilyHistory/Twin concordance	Rare	Common
HLA association	Yes	No
Ketosis	Yes	No
Insulin resistance	No	Yes
Endogenous insulin	No	Yes
Respond to Oral Agents	No	Yes
Metabolic liability	Labile	Not labile

FIGURE NO 1.1 SIGNS OF DIABETES
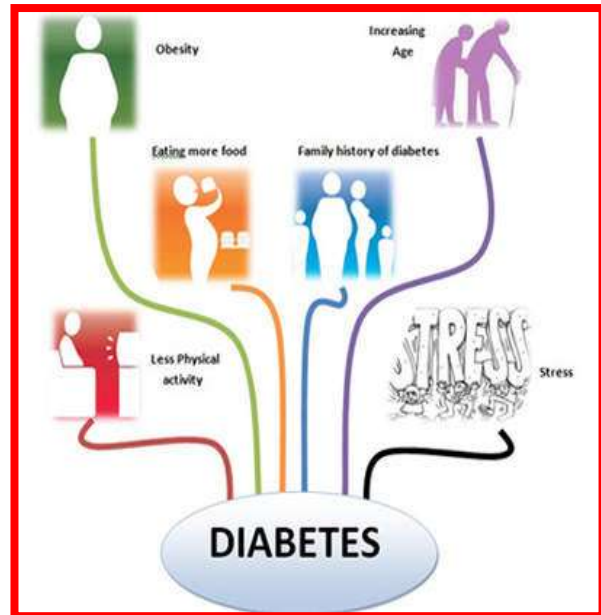
FIGURE NO 1.2. CAUSES OF DIABETES

FIGURE NO 1. 3 PHYSIOLOGY OF TYPE 1 DIABETES
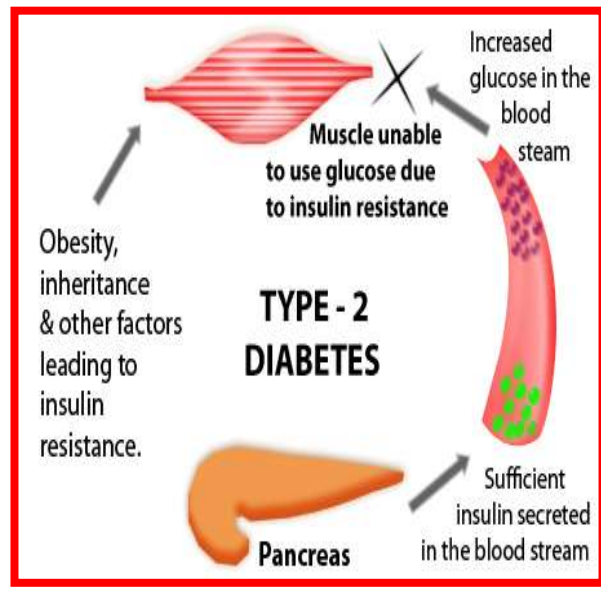
FIGURE NO. 1.4. PHYSIOLOGY OF TYPE 2 DIABETES

DIAGNOSIS OF DIABETES

American Diabetes Association Symptoms of marked hyperglycemia (2008) included polyuria, polydipsia, weight loss, sometimes with polyphagia, and blurred vision. Impairment of growth and susceptibility to certain infections may also accompany chronic hyperglycemia as the diagnosis aid of diabetes. They mentioned that hyperglycemia with ketoacidosis or the nonketotic hyperosmolar syndrome as acute

complications and long-term complications include retinopathy with potential loss of vision; nephropathy leading to renal failure; peripheral neuropathy with risk of foot ulcers, amputations, and Charcot joints; and autonomic neuropathy causing gastrointestinal, genitourinary, and cardiovascular symptoms and sexual dysfunction.

Similarly, *Jiva et.al (2009)* also explained that symptoms like fatigue, weight loss or weight gain, frequent urinary tract infections, blurred vision, excessive sweating, excessive thirst, excessive hunger, frequent urination in large quantity is the basic criteria for diagnosing the diabetes. Hereditary factors also play role in causing diabetes. They mentioned that factors that are often responsible for causing diabetes are excessive intake of foods which are difficult to digest, such as fried foods, creams, etc. Lack of exercise, mental stress and strain, excessive sleep, overeating and consequent obesity, excessive intake of sugar and refined carbohydrates, Overloading of proteins and fats can also lead to diabetes.

World Health Organization (WHO) recommendations Diabetes UK (2014) had given the diagnostic criteria published by the WHO in 2006. Diabetes UK describes the use of HbA1c testing in diagnosing diabetes. Notably, *Nathan et.al* 2014, *elucidated the same. He was a committee appointed by the American Diabetes Association, the European Association for the Study of Diabetes, and the International Diabetes Federation was convened in 2008 to consider the current and future means of diagnosing diabetes in non pregnant individuals. The report of the International Expert Committee represented the consensus view. The International Expert Committee considers the use of the A1C assay for the diagnosis of diabetes.*

Health care professionals as well as policy makers are well aware of the public health impact of diabetes. Diabetes is a silent disease – many sufferers, become aware that they have diabetes, only when they develop one of its life-threatening complications. Knowledge of diabetes mellitus can assist in early detection of the disease and reduce the incidence of complications. An understanding of the level of public awareness is helpful for health educators to plan for future programmes.

Diabetes imposes a high cost, for both the individual and health care system. The economic cost of diabetes continues to

rise because of increasing health care cost and aging population. It was found that the direct cost of diabetes to the patient was high in our country. And the cost per patient with or without complications worked out to be Rs. 20000 per annum in year 2017. It is also found that people with diabetes use more health care resources than those who do not have the condition. This excess expenditure is related to the high cost of treatment for late-developing diabetes complications, such as retinopathy or nephropathy as well as indirect costs resulting from lost work days or unrealized economic opportunity.

Direct costs to individuals and their families include medical care, drugs, insulin and other supplies. Patients may also have to bear other personal costs, such as increased payments for health, life and automobile insurance. Direct costs to the healthcare sector include hospital services, physician services, lab tests and the daily management of diabetes, like availability of products such as insulin, syringes, oral hypoglycemic agents and blood testing equipment. Costs range from relatively low-cost items, such as primary care consultations and hospital outpatient episodes, to very high cost items, such as long hospital inpatient stays for the treatment of complications.

Hospitalization for a diabetic patient works out to be very costly and may be even higher for patients with diabetes related complications. The high prevalence of diabetes in India poses a huge threat to the Indian economy. Low income, increased health care costs, complications to different organs and the psychological reaction in adjusting to new requirements of health care routine can cause stress in adopting a diabetes adjusted quality of life (DAQL)

RATIONALE OF STUDY

Creating awareness on all aspects of diabetes is primary. This can be achieved through creating public awareness; this may enable those with initial symptoms, and those at risk, to adopt remedial and preventive measures. The ideal treatment for diabetes such as treatment with Insulin therapy would allow the patient to lead a completely normal life, to remain not only symptom free but in good health, and to avoid the complications associated with long term diabetes.

Diabetes requires a lifelong management plan, and persons with diabetes have a central role in this plan. Insulin therapy and lifestyle modification is an opportunity for diabetics to take

charge of their health. Therefore, it is important to learn as much as possible about insulin therapy for diabetes and take an active role in making decisions about health care and treatment. A study conducted related to adherence/non adherence to diet restriction, 17 % stated frustration, 66 % had difficulty at social gatherings to recommend treatment, 645 of men and 325 of women patients were non adherent, and they cited lack of time or being lazy. The study also revealed that not all those who seek medical help follow advice and those who fail to adhere to regimen always find excuses.

Diabetes is now a worldwide epidemic. By the year 2025, more than three quarters of all persons with diabetes will reside in developing countries. India and China are leading this surge in diabetes. There are compelling reasons why aggressive efforts must be directed towards primary prevention of diabetes in developing countries. Once diabetes develops, the cost of caring for patients is prohibitive. Poorly managed diabetes leads to several complications, e.g., end stage renal failure, blindness, amputation and heart disease. Insulin therapy by self administration and lifestyle modification approaches are found to be more efficacious than expensive medications in

the prevention of diabetes complications. This is fortunate because Insulin therapy by self administration and lifestyle modification can be implemented locally, whereas medications often need to be imported at high cost. The first task is the education of all diabetics on Insulin therapy by self administration and lifestyle modification, urgent need for timely action to prevent the translation of diabetes complications through dietary modification, and increased physical activity. This would require careful planning.

Effective and good diabetes management by Insulin therapy by self administration and lifestyle modification helps to prevent or delay many of the complications. Effective management includes Insulin therapy by self administration and lifestyle modification measures such as a healthy diet, physical activity, and foot care, eye care, no smoking, avoiding alcohol, monitoring blood sugar level, and managing medication. Helping people with diabetes to acquire the knowledge and skills to manage their own condition is central to leading a full and healthy life.

STATEMENT OF THE PROBLEM

A Vis A Vis review study on Management of devastating metabolic disorder - Diabetes mellitus

RESULTS OF THE STUDY

MANAGEMENT OF DIABETES MELLITUS

Life style management is apparently the cornerstone of management of diabetes mellitus. It is recognized as being an essential part of diabetes and cardiovascular disease prevention. Meta-analyses demonstrate that lifestyle interventions, including diet and physical activity, led to a 63% reduction in diabetes incidence in those at high risk. Lifestyle modification programs have demonstrated encouraging improvement in risk factors for diabetes; however, the effect on diabetes incidence has not been reported (Rebecca *et al.,* 2009). The dietary management of diabetes mellitus is a complement of lifestyle management. It has a positive effect on long term health and quality of life. Dietary management aims at optimal metabolic control by establishing a balance between food intake, physical activity, and medication to avoid complications. In type 2 diabetes, the dietary objective is for improved glycemic and lipid levels and weight loss as appropriate (Piero *et al.,* 2006).

In spite of the underscored importance of lifestyle measures in diabetes therapy, most diabetics cannot escape the value of pharmacotherapy to achieve target glucose concentrations. Different oral hypoglycemic have been in use to aid in maintenance of blood glucose level at the requisite threshhold in diabetics through distinct mechanisms (Inzucchi, 2002). Sulfonylureas and the nonsulfonylurea secretagogues establish normoglycemia by upregulating endogenous insulin secretion; alpha-glucosidase inhibitors work by delaying intestinal carbohydrate absorption; thiazolidinediones (TZDs) maintain normoglycemia by enhancing insulin sensitivity primarily by increasing peripheral glucose disposal, and suppressing hepatic glucose production. Metformin works by decreasing hepatic gluconeogenesis while at times also increasing peripheral glucose mobilization and disposal (Curtis, 2007). Synthetic insulin injections are also a therapy against type I diabetes mellitus.

Curtis,(2007) reports that despite many effective oral hypoglycemic agents available to manage type 2 diabetes, 5% to 10% of the population with diabetes experience secondary failure. This bottleneck can be arrested if clinicians

understand the limitations of some therapies currently in use. Secondary failure arises as a result of deteriorating beta cell function, poor compliance to treatment, weight gain, reduced exercise, dietary changes, or illness. A major drawback associated with hypoglycemic agents is that they are expensive and harbor adverse effects on patients

Plant derived medications have also found immense use in the management of diabetes mellitus. Piero et al. (2012) notes that there is a new trend in the world to turn to phytodrugs to avoid the adverse effects associated with conventional hypoglycemic agents. Many plant species have been used to treat life-threatening diseases including diabetes mellitus. A World Health Organization (WHO) study shows that 80% of the world population solely relies on medicinal plants for their primary health care needs (Njagi et al., 2012).

To date, the catalogue of antidiabetic medicinal plants is growing at a pleasantly high rate particularly in the African continent. Perhaps this is advised by the economic situation in African, which has driven African diabetics to seek cheaper treatment and management options. This overreliance on antidiabetic medicinal plants has probably invoked scientists to bioassay these plants in an effort to elucidate more hypoglycemic medicinal plants. The antidiabetic potential of some medicinal plants extracts has been demonstrated in human and animal models of type II diabetes. However, more detailed research on the antidiabetic plants is inevitable to ameliorate the concerns of *in vivo* safety and efficacy (Piero *et al.*, 2012).
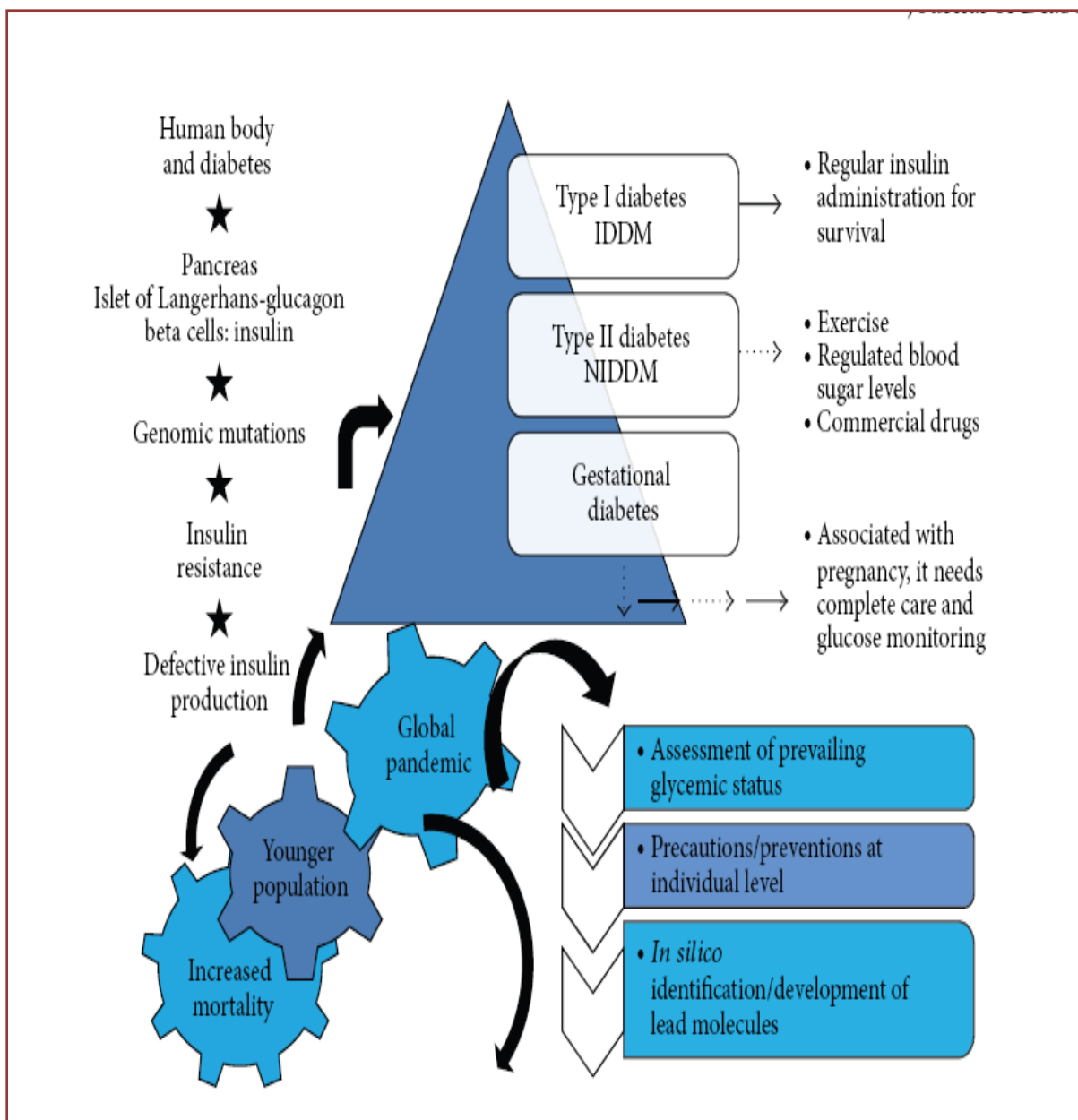
Figure 5 Proposed schematic representation of general occurrence and approaches in diabetes management

CONCLUSION

Diabetes highlights a growing epidemic imposing serious social economic crisis to the countries around the globe. Despite scientific breakthroughs, better healthcare facilities, and improved literacy rate, the disease continues to burden several sections, especially middle and low income countries. The present trends indicate the rise in premature death, posing a major threat to global development. Scientific and technological advances have witnessed the development of newer generation of drugs like

sulphonylureas, biguanides, alpha glucosidase inhibitors, and thiazolidinediones with significant efficacy in reducing hyperglycemia. Recent approaches in drug discovery have contributed to the development of new class of therapeutics like Incretin mimetics, Amylin analogues, GIP analogs, Peroxisome proliferator activated receptors, and dipeptidyl peptidase-4 inhibitor as targets for potential drugs in diabetes treatment. Subsequently, the identification and clinical investigation of bioactive substances from plants have revolutionized the research on drug discovery and lead identification for diabetes management. With a focus on the emerging trends, the review article explores the current statistical prevalence of the disease, discussing the benefits and limitations of the commercially available drugs. Additionally, the critical areas in clinical diabetology are discussed, with respect to prospects of statins, nanotechnology, and stem cell technology as next generation therapeutics and why the herbal formulations are consistently popular choice for diabetes medication and management

WHAT DOES THE FUTURE HOLD?

Currently, the management of type 2 diabetes focuses on glucose control via lowering of blood glucose (fasting and postprandial) and hemoglobin A(1c). The considered view is that the diabetes therapy should focus on delaying progression of the disease. Treatment options are supposed to be directed at the known pathogenetic disturbances of the disease. Recently, treatment and/or management strategies have been directed at the development of novel therapeutic options that are more efficacious in maintaining normoglycemia in type 2 diabetics and that provide durable glucose control (Defronzo, 2010).

The realization that diabetes mellitus is a "metabolic curse" should be a trigger for desire to seek understanding of the biochemical and molecular basis of this metabolic disorder. Such an understanding will inform efforts to elucidate more effective management interventions against diabetes mellitus. In this regard, more efficacious synthetic insulin with rapid actions, ability to traverse all body compartments, less adverse effects as well as longer durations of actions need to be designed. The oral hypoglycemic agents, which are apparently bedeviled by side effects, need to be optimized to mitigate these demerits.

Lifestyle management needs to be optimized to achieve the intended goal of lowering the glycemic index in diabetics.

Gene therapy will doubtlessly address the complications of diabetes mellitus. The pioneering gene therapy approach to diabetes mellitus was occasioned by the cloning of the insulin gene. The strategy was based on the premise that non-insulin producing cells could be manipulated to produce insulin using a suitable promoter and insulin gene construct. It was thought that these substitute cells could reclaim insulin production diabetics. Advances in molecular biology have enabled unraveling of the human genome. This milestone can be exploited in order to characterize the insulin gene for its subsequent use in management of diabetes. The immunological concerns underlying gene therapy can also be addressed by the current advances in molecular biology. However, irrespective of all these concerns, it is imperative to always farthom that the merits of gene therapy of diabetes exceed the demerits and present advantages as compared with conventional treatment before this approach could gain widespread acceptance in general medical practice.

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