

**Review Article****AN UPDATES ON DIABETIC CONDITION IN RESPECT TO INDIAN AND GLOBAL POPULATION**

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**ABSTRACT**

The prevalence of diabetes is rapidly increasing globally at an alarming rate and become a major healthcare problem. In India it is estimated that 66.8 million people suffering from diabetes, representing the largest number of any country in the world. The rising burden of diabetes has affected the healthcare sector in India. Chronic diabetes condition includes type 1 diabetes and types 2 diabetes causes high blood sugar levels due to deficiency of insulin. The types of diabetes and diabetic complication such as impairment of the immune system, periodontal disease, retinopathy, nephropathy, somatic and autonomic neuropathy, cardiovascular diseases. Minor changes in lifestyle can greatly reduce the chances of this disease. In order to avoid this condition are should be taken regarding the adjustable factors that influence its development-lifestyle and dietary habits. Proper blood testing, treatment, and lifestyle changes, healthy eating strategy, walking, exercise and other physical activities have valuable effects on human health and prevention or treatment of diabetes.

**1. Introduction**

Diabetes is a very common health problem across the world and even becomes a major public health problem in India. Diabetes has a vast impact on quality of life and an individual's subjective perception of physical, emotional and social well-being[1]. Diabetes mellitus (DM) or simply diabetes is a group of metabolic diseases in which a person has high blood sugar level due to the body does not produce enough insulin or body cells do not respond to the insulin produced by the pancreas. It is found to damage many body systems particularly blood vessels, eye, kidney, heart, and nerves[2]. The high bloodsugar produces the symptoms of frequent urination (polyuria), increased thirst (polydipsia), and increase hunger (polyphagia)[3].

Diabetes has been divided into three types namely i.e., Type 1 DM or insulin-dependent diabetes mellitus in which body fails to produce insulin, and presently requires the person to inject insulin this is also known as "juvenile diabetes". Type 2 DM or non-insulin-dependent diabetes mellitus (NIDDM) results from insulin resistance, a condition in which cells fails to use insulin properly, with or without an absolute insulin deficiency and this type of diabetes were previously referred to as "adult onset diabetes". The third types of diabetes are gestational diabetes which occurs during pregnancy the blood sugar level increase and after giving birth it disappears sometimes may lead to the development of type 2 DM 4,5].

Pharmacotherapy for the management of diabetes mellitus includes insulin and oral hypoglycemic agents. Different types of hypoglycemic agents such as biguanides and sulfonylureas are also available for treatment of diabetes and none of these medications is ideal due to their toxic side effects and a

decrease of response is observed sometimes in their prolonged use. These types of drug acts by either increasing the secretion of insulin from the pancreas or reducing plasma glucose concentrations by increasing glucose uptake and decreasing gluconeogenesis[6].

**1.1 Epidemiology**

The prevalence of diabetes is swiftly increasing over the globally at an alarming rate. According to the International Federation of Diabetes, 415 million adults around the world are suffering from diabetes, and it is estimated that the numbers will reach around 642 million by the year 2040[7]. The first World Health Organization (WHO) global report on diabetes demonstrates that the number of adults living with diabetes has almost increased to 422 million adults since 1980[8].

Globally the prevalence of adult diabetes population was 9.8% in men and 9.2% in women observed in 2008, which was reported as 8.3% and 7.5% in 1980[9]. Diabetes has become one of the leading causes of premature illness and deaths in most countries, mainly through the increased risk of cardiovascular disease which is responsible for over 50% of deaths in the population with diabetes. Although diabetes is sometimes considered major concern for developed nations. The life from premature death among persons with diabetes is greatest in developing countries[10]. About 80% of the total adult diabetes population are in low- or middle-income countries[7]. India leads the World and stands at the second position after China, with 69 million persons affected by diabetes present a disconcerting challenge to the sustainable

development of the nation as almost every tenth adult (9.3%) in India is estimated to be affected by diabetes. The WHO estimated every 26 per 100,000 persons die due to diabetes in India though it declined marginally and for males increased between 2000 and 2012[10].

A clinical study in India indicates that more than 50% of people with diabetes have poor glycemic control, uncontrolled hypertension, and dyslipidemia and a large percentage have diabetic vascular complications[11]. Another study on Indian data shows that common risk factors such as greater duration of diabetes, hypertension, poor metabolic control, smoking, obesity, and dyslipidemia are more likely to develop diabetic complications[12].

Several studies on DM showed a rising trend in the prevalence of diabetes across different parts of India. The first national study on the prevalence of type 2 diabetes based on clinical data (blood glucose level >170 mg/dl) in India was done by the Indian Council Medical Research estimated diabetes prevalence of 2.1% in urban and 1.5% in the rural area in 1972–1975. A national rural diabetes survey estimated 2.8% of diabetes (based on the WHO 1985 criteria) in 1989–1991[13]. Subsequent studies used the WHO 1999 standard estimate of a high prevalence of diabetes ranging in rural area from 10% in Goa[14] to 19.8 in Karnataka[15] and in an urban area from 9.3% in Mumbai to 19.5% in Ernakulam[16]. However, due to lack of clinical data at large scale, available studies provided estimates of DM for the rural, or urban area of selected states or districts and many studies used the different measure to define DM[10].

The prevalence of DM in India and its states are also available in national health surveys based on the self-reported criterion that is respondents reported that they were diagnosed by doctor or others and are available in national health surveys[17]. SAGE (2013) reported 1.9% among 15–49 and 6.9 among 50 above age persons have diabetes. For the first time, large-scale national level surveys namely district level household and facility survey (DLHS-4, 2012–2013) and Annual Health Survey (AHS, 2014) provide clinical data that includes glucose level results of blood sample tested for adults above age 18 years[18].

Reports from both the surveys provide diabetes prevalence at district and state level. However, both reports adopted a different measure to define diabetes. DLHS-4 reports consider blood glucose level between 140 and 160 mg/dl for prediabetes and >160 mg/dl for moderate to high level of diabetes and AHS provide three estimates for  $\geq 110$  mg/dl,  $\geq 130$  and  $\geq 150$  level of blood glucose. Both surveys collected fasting blood sample from individuals; however, DLHS-4 data also include result from a random blood sample although it collected only one blood sample from each individual (either fasting or random) [10].

It is manifested from the above literature review that there is an urgent need to access the increasing burden of diabetes and its associated risk factors using the recent available large-scale clinical surveys in India[9]. Therefore, the present paper aims to provide the comparable prevalence rates DM for all covered states and districts in India using the WHO 1999 standard. In the developing countries including India, a higher proportion

of diabetes is undiagnosed. Therefore, the present study examines the risk factors of newly diagnosed and self-reported (previously diagnosed) DM in select states of India[10].

## 1.2 Economic Burden of Diabetes Mellitus

The current and future economic burden of the disease on the health system can assist decision makers to understand the magnitude of the problem, prioritize research efforts, and plan resource allocation to properly manage the condition. Disease cost estimates also help prioritize interventions, which must be done in the face of limited health care resources in our country. The International Federation has estimated that globally there are 415 million people with diabetes in 2015 and is predicted to increase to 642 million by 2040[19].

318 million people are estimated to have impaired glucose tolerance and 20.9 million live births are affected by some form of hyperglycemia in pregnancy, of which 85.1% are due to gestational diabetes. People with type 2 diabetes are rising in every country, but more than 80% live in low and middle – income countries such as India, Bangladesh, Bhutan, Pakistan, Sri Lanka, Philippines, and Indonesia[19].

A recently reported Indian Council of Medical Research - India Diabetes (ICMR-INDIAB) study conducted in four different zones of rural and urban India showed that the occurrence of diabetes and prediabetes are higher compared to previous studies. The inter-state variations in prevalence, ranging from 4.3% in Bihar, 10.4% in Tamil Nadu and 13.6% in Chandigarh[20].

In a clinical survey, the total yearly cost of care for 50 patients of the sample population was 14,508 rupees (263.78 euros). The largest percentage of the total cost was made up of direct costs (68%), followed by indirect costs (28.76%) and provider's costs (2.8%). Drug costs were elevated. Total treatment cost was extensively higher in those who were more educated, those who visited the hospital more frequently, and those receiving a greater number of drugs[21,22].

A clinical study in Indian patients by Ramachandran et al analyzed the urban-rural spending on diabetes. The study indicated that the economic burden of diabetes care on families in growing countries is raising rapidly, even after accounting for inflation. The yearly family income was higher in urban subjects [rupees (Rs) 100,000 or \$2,273] than in the rural subjects (Rs 36,000 or \$818) ( $P < 0.001$ ). Total median overheads on health care were Rs 10,000 (\$227) in urban and Rs 6,260 (\$142) in rural ( $P < 0.001$ ) subjects. Treatment costs improved with duration of diabetes, the presence of complications, hospitalization, surgery, insulin therapy, and urban setting[21]. For example, expenditure proportionately enlarged with the number of complications. Expenditure on the treatment of complications different significantly between the populations[23]. Another survey reported on the economic burden of DM in urban Indians, the average monthly income of the sample was Rs. 20,000 out of which Rs.735 (3.6%) was spent on direct cost and Rs. 329 (1.4%) was spent on indirect cost, which is approximately close to the findings of this study with mean direct and indirect cost of INR 687.5 and INR 348.75 per month[24].

To know the pathogenesis, complications, and testing of various therapeutic agents appropriate experimental models are needed. Diabetes animal models can be obtained through unexpectedly chemical induced or dietary or surgical manipulations. In recent trends, large numbers of new genetically modified animal models including transgenic, generalize and tissue-specific knockout mice have been used for the screening of antidiabetic drugs[25].

Since the initial result in 1943 of alloxan-induced  $\beta$ -cell necrosis in rabbits has been used for inducing experimental diabetes till so far. Alloxan is a uric acid derivative that acts by selectively destroying the pancreatic beta islets leading to insulin deficiency, hyperglycemia, and ketosis. Because of its low stability, relatively very shorter half-life and acidic nature of the solution and mostly intravenous route preferred for administration[26].

Like alloxan, streptozotocin causes hyperglycemia mainly by its straight cytotoxic action on the pancreatic beta cells. In streptozotocin, nitrosourea moiety is liable for beta cell toxicity, while deoxyglucose moiety facilitates move across the cell membrane. Like alloxan, the attachment of free radicals generation and resulting alteration of endogenous scavengers of these reactive species have been reported in streptozotocin-induced diabetes. There are various types of Type 2 antidiabetic screening animal model used for the screening of drug such as spontaneous or genetically derived diabetic animals, Diet/nutrition induced diabetic animals, chemically induced diabetic animals, surgical diabetic animals, transgenic/knock-out diabetic animal models[27].

### 1.3 Physiological investigation

#### A. Diabetic Retinopathy

Diabetic retinopathy occurs when diabetes damages the tiny blood vessel inside the retina, light-sensitive tissue at the back of the eye. The version condition occurs as; Microaneurysms, Hemorrhage, Hard exudates, Cotton wool spots, and Venous loops[28]. The following stages induced during diabetes retinopathy mentioned below:

- Non-proliferative stage: This stage also known as 'No apparent retinopathy'. There is no diabetes fundus change.
- Mild non-proliferative stage: The presence of a few microaneurysms (capillary wall dilation)
- Moderate non-proliferative stage: The presence of multiple microaneurysms, intraretinal hemorrhage or venous beading that do not reach the severity of the standard photograph.
- Severe non-proliferative stage: The presence of cotton wool spots (accumulation of axoplasmic debris related to capillary non-perfusion), venous beading and intraretinal microvascular hemorrhage.
- Proliferative diabetic retinopathy: It is characterized by neovascularization of the disc, neovascularization of the retina, neovascularization of iris, neovascularization of the angle, vitreous hemorrhage or tractional retinal detachment[29].

#### B. Diabetic Nephropathy

Diabetic Nephropathy (DN) or diabetic kidney disease is a syndrome characterized by the presence of pathological quantities of urine albumin excretion, diabetic glomerular lesions, and loss of glomerular filtration rate (GFR) in diabetics[30]. Its four classifications according to glomerular lesions, along with a separate scoring system for tubular, interstitial, and vascular lesions[31]. The following stage induces during diabetic nephropathy mention below:

- Pre-nephropathy: Presence of macroalbuminuria.
- Incipient nephropathy: Presence of low but normal amount of urine albumin, referred to as microalbuminuria (persistent albuminuria at level 30-299 mg/24 hours).
- Overt nephropathy: Presence persistent albuminuria at level  $\geq 300$  mg/24 hours develops after many years in type 1 diabetes but may be present at the time of diagnosis of type 2 diabetes.
- Kidney Failure: It has been redefining in all cases as a GFR less than 30ml/min/1.73m<sup>2</sup>.
- Dialysis therapy: Any status on continued dialysis therapy[32].

#### C. Diabetic Neuropathy

Diabetic neuropathy occurs when there is an imbalance between nerve fiber damage and repair. The nerve-damaging process preferentially affects autonomic and distal sensory fibers, leading to the progressive loss of sensation[33]. Nerve damage may be directly induced by the accumulation of intracellular glucose and its increased flux through the polyol pathway (with aldose reductase as the rate-limiting enzyme), the consequences of which include the production of glycating sugars and advanced glycation end-products (AGE), enhanced oxidative damage and protein kinase C activation[34]. The following stages induce during diabetic neuropathy mention below:

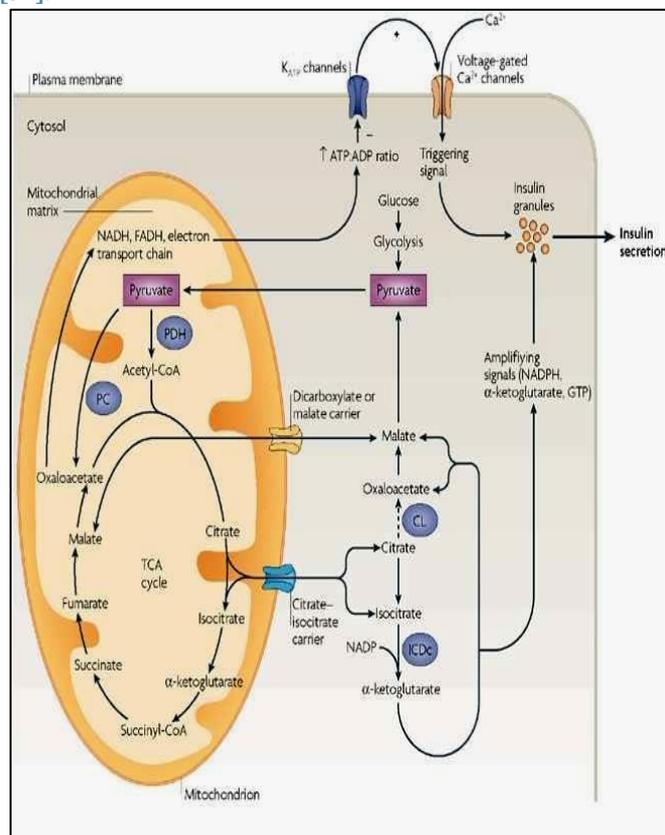
- No neuropathy: In this stage any evidence of neuropathy was not observed.
- Subclinical neuropathy: In this stage no signs or symptoms of the neuropathic problem but abnormal quantitative neurologic function tests.
- Clinical neuropathy: Findings of signs and symptoms consistent with diabetic neuropathy.
- End-stage: Debilitating neuropathy. In this stage, people have an abnormal gait, cannot walk on their heels, or foot ulcer[35].

#### 1.4 Pathophysiology

Diabetes mellitus (DM) is a set of related diseases in which the body cannot normalize the amount of sugar (specifically, glucose) in the blood. The blood delivers glucose to deliver the body with energy to perform all of a person's daily activities. The liver changes the food a person eats into glucose. The glucose is then released into the bloodstream. In a healthy person, the blood glucose level is keeping up by several hormones, primarily insulin[36]. Insulin is formed by the pancreas, a small organ between the stomach and liver. The pancreas also makes other important enzymes released straight into the gut that helps digest food.

Insulin allows glucose to move out of the blood into cells through the body where it is used for fuel. People suffered diabetes either do not generate enough insulin (type 1 diabetes) or cannot use insulin properly (type 2 diabetes), or both (which occurs with several forms of diabetes).

In diabetes, glucose in the blood cannot move well into cells, so blood glucose levels remain high. This not only starves all the cells that need the glucose for fuel but also harms certain organs and tissues exposed to the high glucose levels (Fig. 1) [37].



**Figure No. 1:** Mechanism of insulin release in normal pancreatic beta cells[38]

### 1.5 Types of diabetes

#### A. Type 1 diabetes

Type 1 diabetes is an autoimmune disease in which the  $\beta$ -cells of the pancreas do not generate sufficient insulin, a hormone which helps use blood sugar (glucose) for energy[39]. The cells become be malnourished of energy and there will be excess of glucose in the blood[40]. This is then followed by life-threatening situation of hypoglycemia, low blood sugar, and hyperglycemia, high blood sugar[41]. When hypoglycemia develops, cells do not acquire enough glucose and patients suffer from confusion, loss of consciousness, and coma. Even death can result when the brain is depressed of glucose for too long[42].

Hyperglycemia and prolonged absence of insulin may lead to ketoacidosis, which is the accumulation of ketones in the blood when the body uses fat for energy instead of glucose[43]. This is because fatty acids cannot be converted into glucose at a steady state. Ketones invent the blood acidic

and slow down all body functions. This also leads to a coma and ultimately death[44].

#### B. Type 2 diabetes

Type 2 diabetes mellitus is a complex endocrine and metabolic disorder[45]. The interaction between some genetic and environmental factors results in a heterogeneous and progressive disorder with changeable degrees of insulin resistance and pancreatic  $\beta$ -cell dysfunction[46]. Overweight and obesity are major contributors to the improvement of insulin resistance and impaired glucose tolerance[47]. When  $\beta$  cells have not longer able to produce sufficient insulin to overcome insulin resistance, impaired glucose tolerance progresses to type-2 diabetes[48,49]. Abnormalities in other hormones such as reduced secretion of the incretin glucagon-like peptide 1 (GLP-1), hyperglucagonaemia, and increasing concentrations of other counter-regulatory hormones also contribute to insulin resistance, decrease insulin secretion, and hyperglycemia in type 2 diabetes[50,51]. Overweight and obesity provide to insulin resistance through several pathways, including an imbalance in the concentrations of hormones (e.g., increased leptin, reduced adiponectin, and increased glucagon), improved concentrations of cytokines (e.g., tumour necrosis factor  $\alpha$ , interleukin 6), suppressors of cytokine signalling (e.g., suppressor of cytokine signaling), other inflammatory signals, and possibly retinol-binding protein[52,55].

Concurrent alterations in  $\beta$ -cell function often consist of a period of compensatory hyperinsulinaemia with abnormal secretory dynamics[56]. When insulin secretion is no longer enough to overcome insulin resistance, glucose intolerance progresses to type 2 diabetes[57]. The decline in  $\beta$ -cell function seems to involve chronic hyperglycemia (glucotoxicity), chronic exposure to non-esterified fatty acids (lipotoxicity), oxidative stress, inflammation, and amyloid formation[58]. Patients with type 2 diabetes usually have pancreatic  $\alpha$ -cell dysfunction that results in increased (or nonsuppressed) glucagon secretion in the presence of hyperglycemia and probably reduced prandial GLP-1 secretion[59].

#### C. Gestational diabetes

Gestational diabetes mellitus (GDM) is defined as any irregular carbohydrate intolerance that begins or is first know during pregnancy[60]. It does not exclude the possibility that unidentified glucose intolerance has preceded the pregnant state. GDM complicates around 7% of pregnancy, which accounts for more than 2,00,000 cases per year[61]. The clinical significance of GDM lies in the fact that it is related to significant maternal and fetal morbidity.

#### Role of Beta Cell in Autoimmune Diabetes

T cells activated by antigens initiate in pancreatic  $\beta$  cells cause type-1 diabetes. T-cell activation results in the synthesis of cell-surface and secreted molecules usually used by the immune system to neutralize invading microorganisms. In type 1 diabetes, these immune effector mechanisms result in  $\beta$ -cell death. CD4 (T helper) and CD8 (cytotoxic) T cells and

macrophages are established within the ‘insulinitis’ lesion of affected humans and mice. Type-1 diabetes in humans has been relocated by bone marrow transplantation, but dependence on individual cell types is unlikely to be properly proven[62].

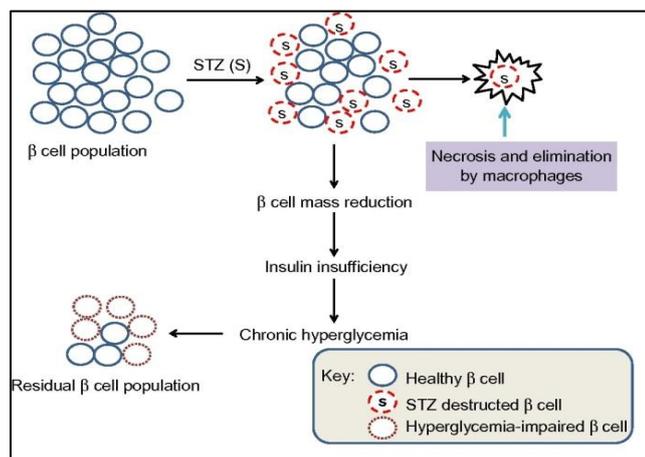
Both CD4 and CD8 T-cell clones have been depicted that is capable of causing diabetes when injected into non-diabetic recipient mice. We have revealed that CD8 T cells directly recognize  $\beta$  cells [via peptides bound to cell surface major histocompatibility complex (MHC) class I proteins], but CD4 T cells are unlikely to distinguish  $\beta$  cells directly because they do not express MHC class II proteins, which are required for recognition by CD4 T cells. It is more expected that CD4 T cells know as local antigen-presenting cells (APCs), including dendritic cells, macrophages or  $\beta$  cells. CD4 T-cell dependent  $\beta$ -cell death then lead indirectly, without antigen-specific relationsbetween CD4 T cells and  $\beta$  cells. As well as individually able to kill  $\beta$  cells in a CD8 T-cell independent manner, CD4 T cells take part in the activation of CD8 T cells by activating APCs[63].

APC activation by CD4 T cells involves CD4 ligand exchanges and most likely takes place in draining lymph nodes.  $\beta$ -cell death might also play a role in the introduction of  $\beta$ -cell autoimmunity. Although inconclusive, this is suggested by the requirement for CD8 T cells and evidence that the cell death receptor FAS might be necessary for the initiation of insulinitis[64].

### 1.6 Chemically induce diabetes in animal

Chemical agents which produce diabetes (diabetogenic agent) can be classified into three categories, and consist of agents that: specifically damage  $\beta$ - cell, cause provisionalinhibition of insulin production and/ or secretion and diminish the metabolic effect of insulin in the target tissue[65,66]. The five major diabetogenic agents are:

**1. Streptozotocin:** It is naturally occurring chemical. It is used to produce Type1 and Type2 diabetes in animals. The dose which administrated to induce diabetes in an animal is low dose is 45 or 55mg/kg i.p this induce type 2 diabetes and high dose is 120mg/kg i.p this induce type1 diabetes[67].



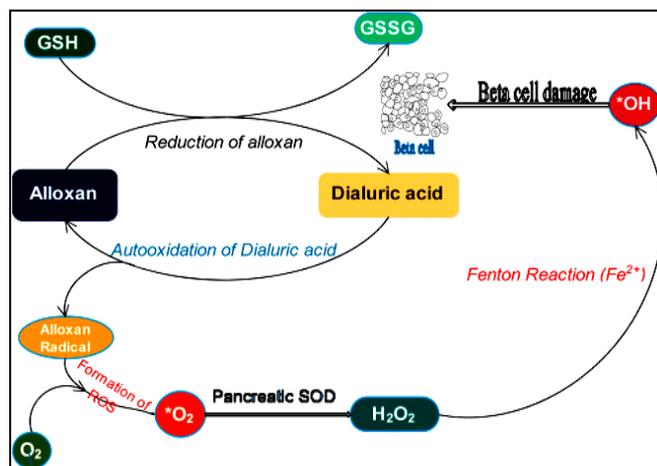
**Fig. 2:** Scheme showing the partial destruction of a  $\beta$  cell population by STZ and reduction in  $\beta$  cell mass that induces insulin insufficiency and chronic hyperglycemia.

**Action:** The streptozotocin enters the pancreatic cell via a glucose transporter-GLUT2 (Glucose transporter 2) and causes alkylation of DNA. Further STZ induces activation of polyadenosine diphosphate ribosylation and nitric oxide release, as a result of STZ action, pancreatic  $\beta$ -cells are destroyed by necrosis and finally induced insulin-dependent diabetes (Fig. 2[68,69]).

**Notes:** While STZ-destroyed  $\beta$  cells undergo necrosis and elimination by macrophages, the surviving or residual  $\beta$  cells are exposed to persistent hyperglycemia that can impair mitochondrial function in the residual  $\beta$  cell population[70].

**2. Alloxan:** Alloxan is a most prominent chemical compound used in diabetogenic research. It is used for induction of Type 1 diabetes and causes selective necrosis of the  $\beta$ - cells of pancreatic islets[71]. The dose which administrated to induce diabetes in the animal are low dose is 44 mg/kg and high dose is 200mg/kg.

**Action:** Alloxan action in the pancreas is preceded by its quick uptake by pancreatic beta cells. Moreover, in pancreatic beta cells, the reduction process occurs in the occurrence of reducing agents like reduced glutathione (GSH), cysteine, ascorbate and protein-bound sulfhydryl (-SH) groups. Alloxan reacts with two -SH groups in the sugar binding site of glucokinase and consequences in inactivation of the enzyme[72,73]. As a result, dialuric acid is formed which is then re-oxidized back to alloxan establishing a redox cycle and generates reactive oxygen species (ROS) and superoxide radicals[74,75]. The superoxide radicals release ferric ions from ferritin and reduce them to ferrous and ferric ions and also go through dismutation to yield hydrogen peroxide ( $H_2O_2$ ). As a result, highly reactive hydroxyl radicals are formed in the presence of ferrous and  $H_2O_2$ . Another mechanism that has been reported is the outcome of ROS on the DNA of pancreatic islets. In the beta cells, alloxan causes DNA fragmentation and damage.



**Figure No. 3:** Formation of ROS through redox cycling of alloxan[78]

Antioxidants like superoxide dismutase, catalase and the non-enzymatic scavengers of hydroxyl radicals have been found to protect against alloxan toxicity[76]. In addition cytosolic free elevated  $Ca^{2+}$  has also been reported to represent an important

step in the diabetogenic action of alloxan. The calcium influx results from the ability of alloxan to open voltage-dependent calcium channels and improve calcium entry into pancreatic cells.

The increased concentration of  $Ca^{2+}$  Streptozotocin (STZ) ion further contributes to suprphysiological insulin release that along with ROS eventually causes damage of beta cells of pancreatic islets (Fig. 3)[77].

**3. Dithizone:** Dithizone induced the sign of diabetes in cats, rabbits, golden hamsters and in mice. It induces type2 diabetes. The dose which administrated to induce diabetes in the animal are low dose is 55 mg/kg and high dose is 150mg/kg[79].

**Action:** A Zinc-chelating agent such as dithizone is caused by diabetes in laboratory animals. Dithizone has abilities to permeate membranes and to complex zinc inside liposomes with the release of protons, that can enhance diabetogenicity. When such complexing agents are supplementary to lipid vesicles at pH 6 containing entrapped zinc ions, they acidify the inside of these vesicles. Such proton release occurs within the zinc-containing insulin storage granules of pancreatic beta-cells; solubilization of insulin would be induced which leads to osmotic stress and eventually the granule rupture and finally, diabetes is induced[80].

**4. Gold thioglucose:** Gold thioglucose is diabetogenic compound, which is induced hyperphagia and rigorous obesity-induced Type -2 diabetes.

**Action:** Gold thioglucose developed obesity persuade diabetes in genetically normal mouse strains. Gold thioglucose treated DBA/2 (Dilute Brown Non- Agouti), C57BLKs, and BDF1 mice increase weight rapidly and significantly increase non-fasting plasma glucose level within 8- 12 weeks. These mice showed impaired insulin secretion, mainly in the early phase after a glucose load and reduced insulin content in pancreatic islets[81].

**5. Monosodium glutamate:** Monosodium glutamate induces Type -2 diabetes without polyphagia.

**Action:** Monosodium glutamate causes a very large insulin retort after ingestion. It is developed glycosuria in both male and female mice but not provoke polyphagia. Within 29 weeks level of glucose concentration in blood, total cholesterol and triglyceride were higher[82].

**1.7 Clinical Investigation**

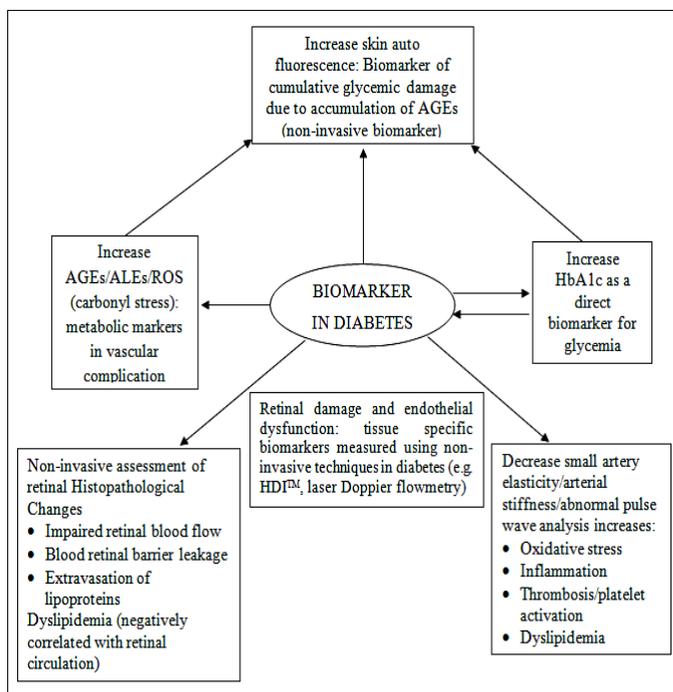
The clinical diagnosis of diabetes is often prompted by symptoms such as increased thirst and urine volume, and weight loss. High levels of glucosuria are usually present. A single blood glucose inference of diagnostic value indicated > or =200mg/dl at random, or > or =140mg/dl at fasting in specimens of venous plasma. Only if blood glucose values lie in the uncertain range (i.e., between the level that establishes diabetes) need an oral glucose tolerance test (OGTT) be considered in order to establish the diagnosis status. Diagnostic interpretation of the 75g OGTT retort is performed

by the criteria of the expert committee of the Japan Diabetic Society. Glycated hemoglobin (HbA1c, HbA1) is widely used as a cumulative approximation of the mean blood glucose concentration over the preceding one approximately two months. Reference ranges of HbA1c are 4 approximately 6%. Labile glycohemoglobin frequently influences the estimate.

Fructosamine and glycated albumin are also used as means of calculating the degree of control. These facts divulge the mean blood glucose concentration over the preceding 2 weeks. 1.5-Anhydroglucitol in blood is deliberated as a means of diagnosis and control evaluation of diabetes. Microalbuminuria is broadly measured for early detection of diabetic nephropathy. Other microproteinuria such as urinary transferring and IgG are assayed for the same purpose[83].

**2. Biomarkers**

The term biomarker instead called a molecular marker or a signature molecule requires clear definition and must be distinguished from risk factor. A biomarker has been distinguished as a biological molecule found in blood, other bodily fluids, or tissue which represents a sign of a normal or abnormal process of a condition or disease[84,85].



**Fig.4;** Biomarkers in diabetes: HbA1c, endothelium, skin, and retina. AGEs 5 advanced glycation endproducts; ALEs 5 lipoxidation end-products; HbA1c 5 hemoglobin A1c; HDI 5 hypertension diagnostics; ROS 5 reactive oxygen species[88].

A biomarker may be used to see how well the body responds to an action for a disease or condition. In diabetes, elevated HbA1c is a consequence of an (often) asymptomatic underlying disease state, namely hyperglycemia[86]. Glycation of hemoglobin, in itself, without functional consequence, ie, it does not directly cause disease, and so HbA1c may most accurately be described as a direct biomarker for glycemia over 6 to 8 weeks before the test. Additionally, since maintain hyperglycemia is well established as a risk factor for microvascular complications of diabetes,

HbA1c may also be measured as a biomarker for a risk factor, ie, a marker of risk for diabetic retinopathy, nephropathy, and other vascular complications[87]. In this last example, the vascular complications do not cause the increase of HbA1c, nor is glycated hemoglobin a direct participant in the causal pathway for vascular disease, so HbA1c and indirect biomarker (Fig. 4)[88].

### 3. Conclusion

Now a day's diabetes complication is increasing day by day. Diabetes is a pancreatic disease that is caused by the imbalance of the insulin hormone. It occurs when the body produces very little or no insulin or when the body does not respond properly to insulin. Diabetes has been shown to increase the risk in other organs such as kidney, eye and many more which lead to an increase in the variety of diseases. Some of them are Diabetic retinopathy leads to damage in the eye. Diabetic nephropathy is a clinical syndrome and leading to a relentless decline in the glomerular filtration rate(GFR) and elevated arterial blood pressure. Diabetic neuropathy is a leading cause of chronic renal failure. Epidemiologic research supports increases in prevalence and economic burden. The advances in therapy over the past 50 years have provided a remarkable selection of choice so that treatment can be modified for each patient, but even with expert teams of dietician and diabetes educators, most patients need drug therapy, maybe multiple-drug therapy, to accomplish optional HbA1c targets. It is most important to control blood glucose level by continue monitoring to avoid complication. In the future, we may admit that drugs are needed to allocate us to lead modern lifestyles without increasing our risk of diabetes. The main aim of this review is to spread the detailed knowledge of the mechanism, pathophysiology, and management of diabetes to control this disease.

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### Conflict of interest

The author declares no potential conflict of interest concerning the authorship or publication of this review article.

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