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Milieu of Diabetes in the 2nd Decade of 21st Century

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Abstract

Diabetes mellitus, a multifactorial pathology, is a growing health problem in developed and developing countries of the modern world. Genetic, ethnic, health, dietary habit, sedentary potential, gestational abnormality in addition to other environmental stress factors are the potential stimuli for precipitating diabetic patho-physiology. The chemistry of diabetes and its milieu are multi-directional and cross-connectable. Diabetes is inter-related to hypertension, obesity, atherosclerosis, cardio-arterial disease, stroke and cancer. All these diseases can be transformed from its own pathology to other through some common axle which is still unknown. Advances in modern medicine and biotechnology are in prudent use in global research to strip up the cellular mechanism and its exploitation to bring remedies of these metabolic diseases. The probes of genetic engineering and drug modelling to find less side effects with the advents of information technology, abolition of abnormal genetic messages by DNA/RNA interference and organ grafting with regenerative prostheses by stem cell exploration are among some of the delicate devices to encounter the enmities orchestrated by the inter-locks of these dreadful diseases. This review sieves the prevailing scenario of the disease and its interventions standing in the house of advancements in second decade of this 21st century.

Keywords: Diabetes mellitus; Dyslipidemia; Insulin; Pancreatic β cells; Insulin receptor

Introduction

Diabetes Mellitus is probably one of the oldest diseases known to man. It was first reported in Egyptian manuscript about 3000 years ago [1]. Only an extensive research in the spring of 1921 by Frederick Banting with his hypothesis that a specific part of the pancreas produce a substance that could treat diabetes led the discovery of the first true miracle drug "Insulin". In January 1922, the purified isolate from pancreas (bovine Insulin) was tested by Banting, after a safe pre-trial on himself, on first human patient ---- a 14 year old child Leonard Thompson. In August 15th, 1922 the first adolescent girl Elizabeth Hughes, the youngest daughter of the then famous US-politician and New York Governor, was treated with insulin by Banting. Elizabeth lived long till old by the management of Insulin injection. A clear distinction between two varieties, *viz.* Type-1 and Type-2 diabetes mellitus (DM), was finally made in 1936 [2].

The insulin independent diabetes mellitus, which is most commonly known as Type-2 DM, is characterized by hyperglycemia, insulin resistance and relative insulin deficiency [3]. It results from interaction between genetic, environment and behavioural risk factors [4,5].

Type 1 diabetes mellitus is a chronic autoimmune disease precipitating in genetically susceptible individuals in collaboration with unknown environmental factors [6]. The body's immune system selectively destroys the insulin producing pancreatic β cells, resulting in insulin deficiency and hyperglycemia. People with type 2 DM is increasing with time in every country of the world [7].

- Over 250 million people are estimated to have diabetes throughout the world.
- 80% of them are from countries where mainly the low and middle income groups exist.

While over-nutrition and lack of exercise contribute to these trends, prevalence of type-2diabetes has increased along with chemical production.

There were approximately 5,00,000 children aged under 15 years suffered with type-1 diabetes around the world in 2013 [8].

18% of diabetic patients die from Coronary Artery Disease (CAD) ----- an outcome of a study conducted in Joslin Clinic in Boston between 1956 and 1968 [9]. Diabetes is associated with dyslipidemia, although the exact mechanisms are not entirely cleared so far [10-12].

Elevated plasma levels of free cholesterol and Low Density Lipoprotein (LDL) cholesterol are among the predisposed factors found responsible for an increased incidence of coronary heart disease in diabetes [13-14].

There are several reasons to suspect that the abnormal milieu in diabetes mellitus might adversely affect the metabolic curb of LDL. Firstly, the increased cholesterol synthesis [15] and cholesterol esterifying capacity [16] and relative enrichment of LDL with triglycerides [17], suggest an abnormality in the formation of VLDL, its conversion to LDL or both. It is also shown that increased VLDL-apoB100 secretion and greater conversion of VLDL to LDL than a normal individual are apparently the fundamental defects to initiate atherosclerosis in diabetic subjects [18].

Secondly, Lack of insulin action in diabetes, whether type-1 DM or type-2 DM. It impairs the receptor mediated uptake and catabolism of LDL, as it is documented in cultured cells in vitro [19-20]. The third reason is, the non-enzymatic glycosylation of LDL apo-B, which if occurs in vivo, could affect the catabolic rate and the metabolic fate of LDL [21].

Insulin is known to regulate multiple biological activities [22-26], resulting in enhanced glucose transport and maintenance of adequate blood glucose levels [27-30]. Transcription of LDL receptor mRNA and expression of LDL receptor are shown to be increased by insulin [31]. Though the exact mechanism is not known, sterol is found to be the ultimate regulator of LDL receptor even in presence of insulin [32]. As a cell surface protein, LDL receptor plays a major role in the clearance of plasma cholesterol and maintenance of intracellular cholesterol homeostasis [33] in most cell types, except RBC, and in all possible physiological conditions, except diabetes mellitus. LDL receptor expression remains depressed in diabetes mellitus because of inactivity of insulin on receptor mRNA transcription [34]. These studies provide clues for developing hyperlipidemia in diabetes.

Furthermore, diabetes is characterised by the inactivities of Insulin Receptor (IR), either through absolute deficiency of insulin (type 1 diabetes) or by transcriptional/ translational/post-translational abnormality of the receptor protein itself (type-2 diabetes). Some recent studies in the present decade also throw light on the mechanism of co-association of IR and LDLR as a normal physiological phenomenon but require insulin for their separation so that individual receptor can perform its assigned biological function [35-37]. These reports mainly tried to focus the non-functionality of LDL receptor in both Type-1 and Type-2 diabetes by the lack of insulin action either for its own deficiency or its receptor's insufficiency.

Besides bio-chemical reasons, diabetes is also a prey by many other physiological abnormalities like hypertension, obesity, too much work related stress, improper safety limits in developing countries as well as modern life style lacking physical exercise which have been most profoundly stemmed in the awake of 2nd decade of 21st century ---- the time to ascend the ambitious world to cope the advanced technology. Even more recently, the association of type-2 diabetes mellitus and increase risk of cancer is a cause of concern in the present decade as hyperinsulinemia appears to be an independent and one of the key mediators in this process [38].

Present decade of 21st century and Multifactorial origin of Type-1 and Type-2 DM

Type 1 diabetes mellitus (T1DM)

Apart from any simple pattern of inheritance, T1DM appears to be a complex multifactorial disease [39]. Children and adolescents are often the victims with classic trio symptoms *viz.* polydypsia, polyphagia and polyuria, along with overt hyperglycemia which needs for immediate exogenous insulin replacement therapy.

In mid-1980's, a classical model for natural history of T1DM proposes the induction of β-cell autoimmunity by putative environmental trigger in genetically susceptible subjects with a fixed number of β cells. This results in a progressive and predicable loss in insulin secretary function.

However, the concept of this classical model has been modified in recent past [40]. It suggests an extended life span of pancreatic β cells in many subjects with T1DM over an extended period to time (i.e. never reaching zero) [41]. It is also a growing question on the degree of β cell destruction for the symptomatic onset of T1DM. Studies have suggested that 40%-50% β-cell viability may be present at the onset of hyperglycemia [42] depending on many other related factors *viz.* subject age, body mass index, physical activity etc. This may explain the reason of long persistence of insulin secretary function in persons with T1DM despite having a persistent autoimmunity.

Loss of first-phase insulin response is usually followed by a period of glucose intolerance and a period of clinically "silent" diabetes (Figure 1) [43]. The subject relating the β cell loss in pre-diabetic state is also now a matter of considerable debate. Persisting relapsing/remitting like autoimmunity over a period of time has been projected as the cause for symptomatic onset of the disorder confirming the disease stage (Figure 2).

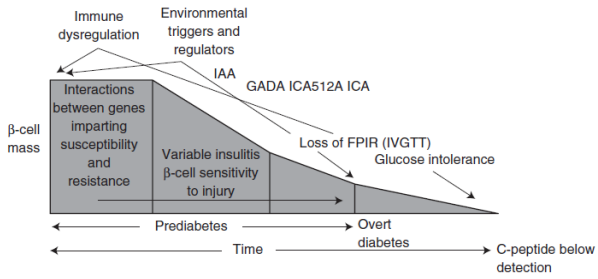

Figure 1: Model of the pathogenesis and natural history of type 1 diabetes.

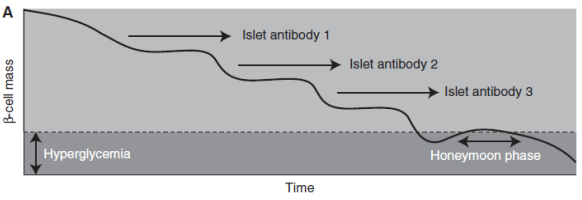

Figure 2: Model for type 1 diabetes as a relapsing-remitting disease.

Autoimmunity in T1DM [44,45] has been identified typically by the presence of autoantibodies to islet and/or β-cell antigens. Though the presence of these auto-antibodies is usually found at the time of diagnosis, they can often be detected long before the disease becomes clinically evident [46]. A list containing more than two dozen islet autoantibody in T1DM has been reported. Some of them are most prevalent and best characterised e.g. autoantibodies to glutamic acid decarboxylase (GADAs), insulin autoantibodies (IAAs), autoantibodies to transmembrane tyrosine phosphatase (IA2As) and against the ZnT8 molecule (ZnT8As).The potential also remains for other autoantibody/autoantigen combinations [47,48].

Besides autoantibodies, reports on precipitation of diabetes by islet autoreactive T cells are also prevalent. The discovery of imogen-38 and islet-specific glucose-6-phosphatase catalytic subunit-related protein (IGRP) as b-cell autoantigens has been made with the approach to identify CD4 T-cell targets in T1DM, although the data on existing humoral immune response is still lacking [49-52]. Also a third approach following the selective expression of β-cell with help of complementary DNA (cDNA) subtraction libraries and microarrays [51,53,54] has been considered to identify β-cell autoantigens in T1DM. In retrospect, proteins that were initially identified through their stimulation of autoimmune responses (imogen-38, IGRP, IA-2, and IA-2ß) were confirmed by these experiments. New candidates

were also identified that subsequently proved to be potentially relevant with the immunopathogenesis in Type-1 diabetes, such as ICA69 and most recently the zinc transporter 8 (ZnT8) [55].

Following decades of efforts to unravel the enigma of T1DM genetics, nearly 50 loci so far, have been associated with susceptibility to the disease [56-58]. The first T1DM susceptibility locus identified the Human Leucocyte Antigen complex (HLA), which provided the greatest contribution (i.e. 60%) to the overall genetic susceptibility.

Variable number of tandem repeats (VNTR) has been mapped in T1DM in the upstream to the insulin gene. Shorter repeats confer higher risk, with longer repeats conferring lower risk [59].

A non-HLA gene associated with T1DM is CTLA-4 (cytotoxic T lymphocyte associated-4) [60]. This gene plays an important role in the regulation of T-cell functionality and hence, overall immune responsiveness. Specific genes (PTPN22, CD25 etc.) were found having support on immune responsiveness in T1DM [57].

List of environmental triggers and regulators of disease process in T1DM remain under considerable debate. It is likely that through continued efforts and multicentre screening programs, the specific environmental factors associated with the disease development will be identified. E.g. association between toxic doses of nitrosamine compounds can cause diabetes through the generation of free radicals [61]. Historically, infectious agents have been the most frequently noted environmental factors that influences T1DM [62] e.g. relationship between β-cell autoantibody and enteroviral infections [63] etc. Polymorphisms in Vit-D metabolism have also been implicated [64]. Very recently, cross-reactivity between the β-cell specific protein (insulin) and α-casein (present in milk) has been marked as interesting potential for molecular mimicry [65].

Though environmental factors indict induction of both Type-1 and Type-2 DM, a genetic predisposition has been found to be more obvious as part of the indictment of Type-1 type; whereas the stress from progressive environmental change is more responsible to transform a normal subject into the abnormalities of Type-2 variety and thus a major culprit with the modernized life style getting immanent with the beginning of this 21st century.

Type 2 Diabetes Mellitus (T2DM)

Xinli Jiang et al. [66] and Mathers [67] have minutely sketched the impact of Type-2 diabetes with early life risk factors including nutrition. The impact of early life epigenetics with increased susceptibility of the disease has also been shown in these observations (Figure 3).

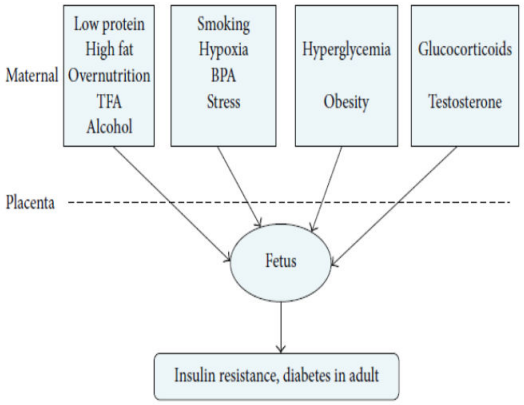

Figure 3: The impact of early life epigenetics in type-2 diabetes mellitus.

The following is the quote from their report --------- "The associations between maternal malnutrition, low protein diet, and T2DM have been widely studied. Increased oxidative stress and fibrosis [68], decreased HNF4a expression with increased DNA methylation in P2 promoters [69], defected mitochondriogenesis and mitochondria dysfunction [70], and increased cell differentiation instead of proliferation [71] were found in β cell of adult animal offspring whose mothers were under low protein diet during pregnancy. These may cause β-cell dysfunction and consequently increase the incidence of T2DM in postnatal life" (Figure 4).

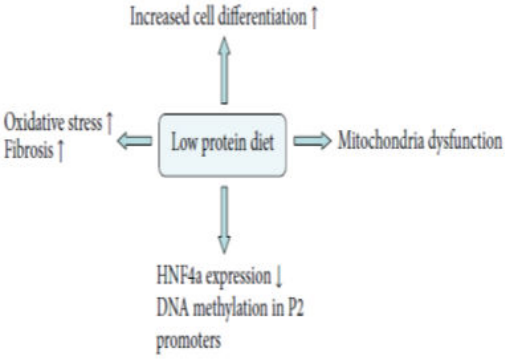

Figure 4: Affected parameters by low protein diet.

Postnatal maternal environment is also shown to be a major effector on the metabolic template in the adulthood of the offspring. Model experiments in animals have shown that obesity and insulin resistance in adult offspring may an outcome of the influence of mothers in stress [72], obesity [73], and exposed to nicotine [74] during lactating period (Figure 5).

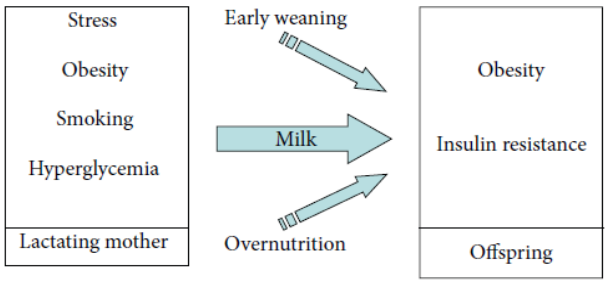

Figure 5: Interfering parameters of lactating mother towards development of insulin resistance in her offspring.

Other environmental factors like aging, obesity, insufficient energy consumption, alcohol drinking, smoking etc. are independent risk factors of the pathogenesis of diabetes. Industrialization, scientific development and economic growth (the glittering triode of this 21st century) facilitates easy life style with less use of body exercise. Lack of exercise induces visceral fat obesity which can indulge insulin resistance when accompanied by decreased muscle mass [75]. The world in this 21st century is fully wild to encounter all possible scientific challenges and exploits earthen ores, atomic resources; mechanical or magnetic super powers and synthetic advancement to make human life smooth, handy and colourful. This exploitation disturbs natural balance and develops more environmental pollution of various kind viz. toxic dust, ultrasonic/supersonic sound, magnetic vicinity, electronic overplay, heavy metals toxicity, toxic gaseous pollution from carbon, sulphur, nitrogen etc. Exposure to such pollutants is simultaneously polluting intravascular circulation initiating many metabolic imbalance and disorders. Among these, diabetes is a prior one. 21st century has also opened a rat race between developed and developing countries to fulfil similar goals. To achieve the goal with economic lag, the competitors in developing countries in many occasions fail to fulfil the safety measures. A major default health injury from workplace hazard ultimately victimise the labourer with several stresses or unhealed damage of nerve, muscle, blood vessel and especially atherosclerotic stroke and heart muscle infarction. Atherosclerosis is one of the major routes for insulin receptor dysfunction. The reports in 2011-2014 have shown [35-37] an intense association between receptors of LDL and insulin. To keep these receptors functional, this association is a major block. An atherosclerotic cell remains full with cholesterol and thus makes LDL receptor non-functional not only by its scanty expression but also with its affirmed adherence with insulin receptor. A bound insulin receptor thus becomes inactive to share its own ligand (insulin) intending the development of diabetic abnormality. This association between the two receptors i.e. insulin receptor and LDL receptor, in presence and absence of insulin is shown in (Figure 6.) The intracellular association between the two receptors has been confirmed by electron microscopic study (Figure 7).

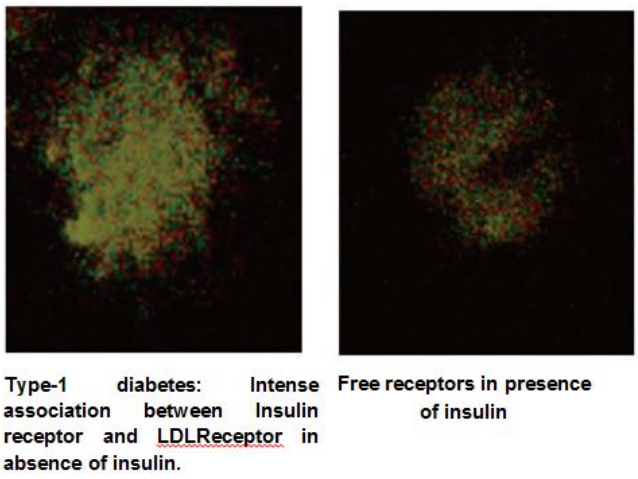

Figure 6: Confocal microscopy images showing association between insulin receptor and LDL receptor in absence of insulin in image 1 and in presence of insulin in image 2 in type-1 diabetes mellitus. Confocal Microscopy: Green: Insulin receptor; Red: LDL receptor. Yellow: Receptor-receptor overlapping (Association).

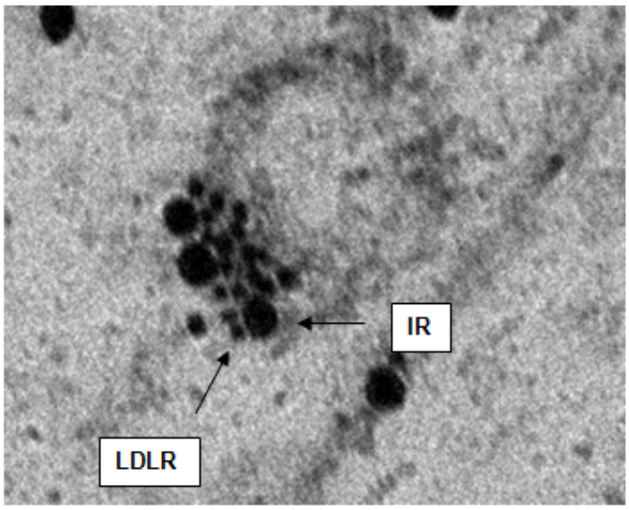

Figure 7: Electron Microscopy: Association of IR and LDLR in transport vesicle. Large gold particle: IR, Small gold particle: LDLR.

Relation of insulin resistance with genetic and environmental factors has become inevitable with the excogitation of the molecular mechanism for insulin action. It is reported that about 30% genetic factors [75] are responsible in the occurrence of the pathology of diabetes mellitus. Besides insulin receptor and insulin receptor substrate (IRS)-1 gene polymorphism that directly affect insulin signals; polymorphism of thrifty other genes among which β3 adrenergic receptor gene and the uncoupling protein (UCP) gene were found associated with visceral obesity which promote insulin resistance. Glucolipotoxicity and inflammatory mediators are also the factors involved in the associated mechanism for impaired insulin secretion and its post signalling impairment [10]. Also the impairment

of candidate genes e.g. glucokinase genes, mitochondrial genes and insulin receptor genes are involved in the impaired insulin action. Recently a genome wide association study (GWAS), has identified the mutation in KCNQ1 gene related to insulin secretion abnormality as an important disease susceptibility gene associated with the pathogenesis of diabetes in Asian ethnic groups [76]. Latest attention has been focussed on the involvement of adipokines (adipocyte-derived bioactive substances) in insulin resistance. While TNF-α, leptin, resistin and free fatty acids act to increase resistance, adiponectin acts to improve resistance [75].

Advances in our understanding of the physiology of nutrient regulation and of diabetes pathogenesis, generates a constantly expanding list of genes that can act as candidates for a role in typical multifactorial type 2 diabetes [77].

Diabetes and atherosclerosis

Cardiovascular disease (CVD), occurs more often in people with diabetes and not only that, it follows a more aggressive course with worst outcome than in non- diabetic subjects.

Epidemiological data shows that type 2 diabetes is associated with more than a twofold increased risk of cardiovascular death. In type-1 diabetes, despite the fact that the CVD rate is significantly lower compared with type-2 diabetes, their relative risk of coronary heart mortality is seven fold larger than in matched counterparts without the disease [78].

Complications in diabetes can be divided into Microvascular and Macrovascular complications. Microvascular complications like neuropathy, nephropathy and retinopathy are well characterised with respective treatment strategies but there is a growing evidence of severe macrovascular abnormalities even though they constitute more than 90% of the cases with type 2 diabetes mellitus and still need more stringent evaluation. These include diseases of coronary arteries, peripheral arteries and carotid vessels.

Coronary artery disease (CAD)

Diabetic patients having 2-4 fold increased risk of CAD [79] have shown serious casualties of morbidity and mortality when suffered from atherosclerosis related heart abnormalities. In terms of prognosis after Myocardial Infarction (MI), patients with diabetes suffer from increased rates of re-infarction, congestive heart failure and death. Not only that, the 5 year mortality rate following MI may be as high as 50% for diabetic patients, which is more than double that of non-diabetic patients [80].

Peripheral Arterial Disease (PAD)

Incidence of PAD in diabetics is 2-4 times more as compared to normal subjects with severity directly correlating with duration of diabetes and extent of glucose control [81,82]. Symptoms of PAD more commonly present as intermittent claudication and amputation in patients with diabetes.

Cerebrovascular disease

It mainly presents as stroke and the incidence is 3 times more in patients of diabetes mellitus than the matched controls [83]. Moreover the risk of stroke related dementia and overall stroke related mortality is seen to be more in diabetic patients [84].

Pathophysiology of Atherosclerosis in Diabetes Mellitus

Diabetes Mellitus is associated with arterial dysfunction in general which is a consequence of abnormal metabolic state which in turn affects multiple cell type independently viz. endothelial cells, smooth muscle cells and platelets as well. The inner layer of all the blood vessels in the body is covered by single layer of endothelial cells which functions to regulate the blood flow, provide adequate nutrients from the blood to tissues, coagulation functions and leukocyte diapedesis [85].

Diabetes impairs endothelial functions especially affecting the bioavailability of endothelial derived nitric oxide whose major function is to cause vasodilation (Figure 8) [86-89]. Not only decreased vasodilation but there is also increased vasoconstriction in diabetes due to increased production of endothelin-1, an activator of endothelin-A receptors on vascular smooth muscle cells. Other changes which occur are that endothelial cells elaborate cytokines in diabetics, which decrease the de-novo synthesis of collagen by vascular smooth muscle cells and increased production of matrix metalloproteins that cause collagen breakdown thus affecting the tensile strength of blood vessels [90,91].

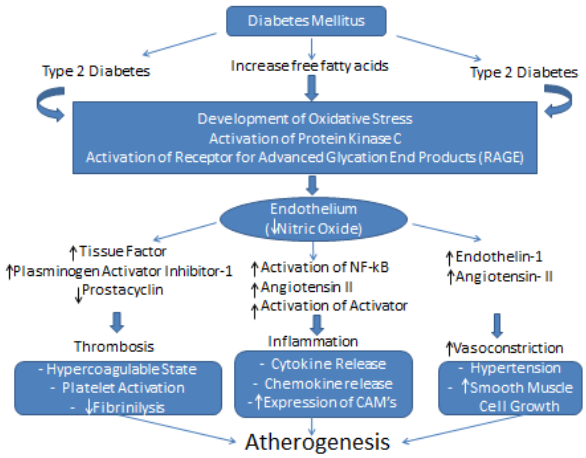

Figure 8: Adverse metabolic effects within the endothelial cell in type 1 and type-2 diabetes mellitus.

Similarly, changes in vascular smooth muscle cells and platelets, exacerbate the progression of atherosclerosis and plaque rupture in diabetes [92,93]. The enhanced thrombotic potential characteristics associated with diabetic subjects also are in part due to impaired coagulation profile of the patients leading to formation and persistence of thrombi.

Low nitric oxide with increased concentration of endothelin-1 and angiotensin-II increases vascular tone and vascular smooth muscle growth and migration. Activation of transcription factors like nuclear factor (NF-kB) and activator protein-1 induces transcription of inflammatory gene with the liberation of leukocyte-attracting chemokines and inflammatory cytokines and augmented expression of cellular adhesion molecules. Increased production of tissue factor and plasmin activator inhibitor-1 creates a prothrombotic environment whereas on the other hand, decreased endothelium derived nitric oxide

and prostacyclin favours platelet activation and finally thrombosis and atheroma formation.

Beginning of this 21st century has witnessed the new facet of diabetic reasons and insulin abnormalities. Six new genetic loci on different chromosomes have been identified as markers for maintenance of glucose and/or insulin metabolism. Hepatocyte nuclear factor (HNF)-1α gene on chromosome 12 and glucokinase gene on chromosome 7p are two most provocative entities that serve as glucose sensor and are responsible in developing hyperglycemia on their mutations but do not disturb normal insulin secretion. Less common forms have been found for the mutations of genes of other transcription factors e.g. HNF-4α, HNF-1β, insulin promoter factor (IPF)-1, and NeuroD1 [94-103].

Besides nuclear genome, point mutations in mitochondrial DNA have been found also to be associated with diabetic syndrome. The most common mutation occurs at position 3,243 in the tRNAleucine gene, leading to an A-to-G transition.

Genetic abnormalities have been identified in families having inability to convert pro-insulin to insulin as an autosomal dominant pattern with mild glucose intolerance. In fact a new level of concept has been reported in recent past for diabetes related atherosclerosis. Onset of atherosclerosis in diabetes has been found to be more responsible on the insulin action on its own receptor. A default co-adherence between insulin receptor and LDL receptor keeps insulin and LDL receptors inactive and binding of insulin only activates them by making them available in free functional mode [35-36]. So effectiveness and availability of insulin is more important over glucose level for a system to keep LDL receptor functional and devoid of atherosclerotic interference. At the end of first decade of this century the consciousness on cardiometabolic risk management in diabetic subjects in developing countries has been reviewed with new thought-provoking findings from laboratory- and population-based research studies [104].These reviews helped to resolve controversies, dilemmas and conflicting impulses in most clinicians as well as well-informed patients.

Thus, throughout the last decade, the perception of diabetes has developed from a focus on hyperglycemia and abnormal insulin levels to include generalised metabolic abnormalities including dyslipidemia, hypertension and disordered coagulation profile in these patients which make them more prone to develop atherosclerosis as compared to non-diabetic subjects.

Diabetes and Hypertension

Hypertension and Type-2 diabetes are two very common chronic diseases and are found inter-related in most of the affairs. A major mass of general population are affected by both two symptoms worldwide. Since in most cases the same subject is found affected by both the events; predisposing common factors have been presumed as the causative factors which have been viewed also from genetic and environmental angles.

In the genome scans of thousands of individuals, it is seen that genetic variations in the genes encoding angiotensinogen, adrenomedullin, apolipoprotein and α-adducin have been associated in the pathology of hypertension, diabetes, dyslipidemia and obesity, which together are all components of metabolic syndrome [105-108]. Some studies also depict the role of Single Nucleotide Polymorphism (SNPs) in the etiologic role of diabetes and hypertension [109-112].

Besides genetic studies, the uterine life period and lifestyle in adulthood particularly the choice of diet may influence the predisposition of these symptoms. Gestational diabetes, fetal malnutrition and high birth weight may also be considered as predisposing factors that can prone the fetus to develop cardiometabolic syndrome in adulthood [113-115]. Apart from these, unhealthy lifestyle pattern include high intake of sodium, unsaturated fats, smoking, alcohol and lack of physical activity. All these are examples of environmental factors of different origins.

Obesity and nature of physical inactivity are the leading factors which predispose an individual to both diseases. Obesity is mainly the precipitated result from the dysfunction of feeding centre in the hypothalamus, leading to the imbalance in food intake and energy expenditure. Genetic predispositions is noted largely to be a reason behind developing obesity [116,117]. Individuals with abdominal obesity are more prone to develop metabolic impairments leading to lipid abnormalities, elevation of blood pressure and glucose levels which in due course of time will manifest the pathology of hypertension and diabetes, which normally share a common etiology.

Apart from obesity, some other common pathways, which the two diseases share, are insulin resistance, inflammation, oxidative and mental stresses [118]. Insulin resistance, predicts type-2 diabetes mellitus, and also has a role on the development of hypertension [119].

Emerging reports suggests that insulin resistance is associated with impairment of insulin signalling pathways, leading to functional abnormalities of differently expressed cytokines, growth factors and peptides and overproduction of VLDL [120]. Insulin resistance is also associated with impaired fibrinolysis that leads to the induction of pro-thrombotic state in these patients, thus predisposing them to increased risk of cardiovascular events [121,122].

It is reported that the signalling of insulin receptor (glucose regulator) and leptin receptor (energy regulator) shares common cytoplasmic signalling cascades, e.g. p110, p85, PI3K, to transmit intracellular signals on their interactions with cognate receptors [123,124]. This cross down-regulation develops competition between the two receptors and could lock these signal relaying nodes for prolonged time at the behest of the receptor having comparatively stronger ligand-receptor interaction. Repeated response of such phenomenon makes the other receptor resistant to its own ligand and develops pathogenicity. Hence diabetes and obesity interlocks each other with receptor resistance and increase of hypertension from their metabolic abnormalities.

Finally, inflammation is another consequence of insulin resistance, and is a result of relative deficiency of anti-inflammatory cytokines (e.g. Adiponectin) and over-production of pro-inflammatory cytokines (e.g. IL-6, TNF and CRP) [125]. Report shows that cytokines like TNFα, IGF1 and IL-6 share common nodes in their signalling cascades with insulin [124].

Oxidative stress as a key of the underlying molecular mechanism in diabetes and hypertension has been realised from gene regulatory network analysis. The role of local renin-angiotensin-aldosterone cascade has shown its intimacy in oxidative stress developing mechanism. Angiotensin II, produced in the same cascade, is largely responsible to trigger vascular inflammation and oxidative stress [126].

The induced physiologic and psychological disturbances from modern lifestyle indulge chronic mental stress which indirectly initiates diabetes and hypertension [127-130].

Endoplasmic reticulum (ER) stress related suicidal death of pancreatic β-cell can develop insulin resistance. Intermediates of unfolded protein response (UPR) signalling pathway play dual roles within pancreatic β-cells imposing as beneficial regulators under physiological conditions but, ironically triggers of β-cell dysfunction and apoptosis under situations of chronic stress.

Novel findings indicate that besides immense capacity of synthesis and secretion of insulin, pancreatic β-cell is also its Achilles heel and is vulnerable to chronic high glucose and fatty acids that commit to β-cell failure in type-2 diabetes. Obesity and insulin resistance in type-2 diabetes is also linked with ER stress. High fat diet and obesity even induce ER stress in liver, which deregulates insulin signalling via c-Jun N-terminal kinase activation. In vitro experiments suggest that cytokine-induced β-cell death can also occur from induced ER stress. Thus, the cytokines like IL-1β and interferon-y, which mediates β-cell loss in type 1 diabetes, can also induce severe ER stress by NO-mediated depletion of ER calcium and inhibition of ER chaperones. This hampers β-cell defence and amplifies the pro-apoptotic pathways. A comprehensive understanding of the signals for regulating ER stress in β-cells may show the avenue for the design of novel therapies to combat β-cell loss in diabetes [131]. ER stress as one mechanism that links immune response with nutrients and thus sensing the patho-physiology of atherosclerosis and its complications, often presented together with obesity and insulin resistance persuaded pathogenicity of type-2 diabetes [132].

On an average about 30% of all newly synthesized proteins gets degraded, presumably because of improper folding and non-functionality. Stress perturbed synthesis of proteins have enormous chances of having misfolded conformation and thus potentially inactive or in dysfunctional attire. These stress induced misfolded proteins may cause pathological consequences. To avert such events, cells have developed elaborate surveillance mechanism for detecting misfolded proteins and taking appropriate adjustments to the intracellular signalling machinery responsible for protein synthesis and/or degradation. Molecular chaperones, which help peptide scaffolding to stabilize proteins from unfolding, and the ubiquitin proteasome system, which degrades terminally misfolded proteins are the important contributors to protein quality control device at cytosolic and organelle level. Both devices play important roles in cardiovascular biology [133].

Thus it is seen that diabetes, hypertension and cardiovascular anomalies are influenced by number of pathways, which may even cause a vicious cycle and they may develop one after another in the same individual. While hypertension is a close associate of Type-2 variety, onset of diabetic nephropathy is a common episode in Type-1 diabetes.

In most of the cases, diabetic hypertension is the predecessor of the risk of macrovascular and microvascular complications including stroke, coronary artery disease and peripheral vascular disease.

In the prevailing years, adequate competent result from well-designed randomised clinical trials have shown the effectiveness of invading treatment of hypertension in reduction of both types of diabetic complications.

Daily dietary management with moderate sodium restriction has been found effective in reducing blood pressure in individuals with hypertension. Weight reduction is the alternative guide to reduce blood pressure independent of sodium intake and can also improve blood glucose and lipid profile of the subjects suffering from metabolic syndrome like diabetes. Overall there is strong evidence that pharmacologic therapy of hypertension in subjects with diabetes is effective in producing substantial decrease in cardiovascular and microvascular disease [134].

Diabetes and Cancer

Our present knowledge provides evidence by virtue of which it can be stated that there is a mild increase in cancer risk and its associated mortality in diabetic patients. Now as expected on the basis of large majority of epidemiological data on the incidence of type 1 and type 2 diabetes, indicating approximately 10:1 ratio, and considering the fact that cancers generally occur in advancing age, much of the cancer mortality occurs in type 2 diabetes. A number of confounding factors associated with diabetes namely obesity, metabolic profile of the patient, diet and drugs employed in the treatment are employed in linking the two diseases.

Some known factors which increase the risk of cancer in diabetic people are as follows:

- Hyperglycemia, which occurs in diabetes is an independent risk factor for cancer as studies have been conducted which clearly suggest that high intake of sugars and refined carbohydrates are associated with increase in cancer risk [135].
- There occurs a common Fatty Acid Synthase (FASN) driven 'lipogenic state', which is common in obesity, type-2 diabetes and cancer cells and might be a possible link between diabetes and cancer [136].
- Diabetes is well known to be associated with oxidative stress. Since it is a chronic disease, the pro-inflammatory state persists for years may lead to continuous formation of reactive oxygen species (ROS) leading to cell membrane and DNA damage.
- Mitochondrial dysfunction is another well recognised abnormality in diabetes [137], which impairs DNA repair mechanisms and enhances cancer risk in type-1 diabetes.
- Also participation of TNFα , a pro-inflammatory cytokine which is produced by adipose tissue, mediates many pro-carcinogenic effects by strongly activating nuclear factor kappa B (NFkB) and is also co-related with insulin resistance[138].

However the overall increase in the incidence of various types of cancer in diabetic patients is well documented as mentioned below:

- Several studies indicate strongest association between diabetes mellitus with liver and pancreatic cancer risk [139-142], as it is understood that these are the key organs involved in metabolic derangements in diabetes.
- There has been 2-3 fold increase in hepatocellular carcinoma (HCC) in diabetic patients. The mechanisms might include steatosis and cirrhosis of liver which are more common in diabetic people and well known causes for HCC as well. Not only this, other factors like Non-alcoholic fatty liver disease (NAFLD), Infections like Hepatits B and Hepatitis C are more common in diabetic population are other known causes for HCC [141,142].
- Similarly, 'pre-diabetes' is also considered a strong risk factor for pancreatic cancer [143]. Hyperinsulinemia, associated with this state, might be involved in the possible mechanism of action [144].
- Kidney cancers, either due to generalised mechanisms like hyperinsulinemia or specific mechanisms like hypertension are associated with diabetes [145-147].

- There is also increase in the risk of cancers associated with female reproductive organs e.g. breast cancer and endometrial cancer. Possible mechanism might involve hyperinsulinemia which in this case may lead to increase in the levels of bioactive estrogens by decreasing the concentration of circulating sex hormone-binding globulin and might also stimulate androgen synthesis in the ovarian stroma [148].
- According to some studies, increase in the risk of colorectal adenoma and carcinoma has been reported in type-2 diabetic patients [149,150].
- Immune dysfunction due to abnormalities in cellular and humoral immunity in diabetes has also been incidence of non-Hodgkin's lymphoma in diabetic patients [151].
- In contrast to number of studies indicating increase in the risk of various cancers in diabetes, there are reports, indicating reduction in the risk of prostate cancer in men with diabetes [152].

Not only affecting the risk of various cancers but number of studies conducted during the last decade, clearly highlight the increase in the rate of cancer deaths in diabetes [153]. Possible mechanisms could be:

- Hyperglycemia and Hyperinsulinemia with their consequent growth promoting effect on cancer cells and insulin is well known mitogen.
- General co-morbid conditions associated with diabetes.
- Lower prescribed dozes of chemotherapeutic agents in diabetic patients due to their severe side effects.
- Generalised immune dysfunction in diabetic patients which makes them more vulnerable to cancer progression.

It is becoming increasingly clear from the research work reported till 2014 that lipids are also one of the major fuels in the development and progression of cancer tumour. Levels of cholesterol rich lipid rafts in cancer cells were correlated with apoptosis, cancer cell adhesion and migration as well as cell growth and signalling [154-156]. Especially, progressions of breast and prostate cancer cells have been correlated incisively with lipid metabolism [156-160]. BBC in London ran a news article in December 2006 reporting that soaring obesity levels would inevitably lead to an increase in "weight related" cancer [161]. Adipocytes and adipokines (majorly leptin and adiponectin) are the prime regulators of Body Mass Index (BMI) and incidentally in their failure become the axils for chances of developing carcinoma [162].

It is well known that prostate cancer metastases to subcutaneous fat deposits are rare but prostate cancer cells have been shown to migrate to adipocytes within red bone marrow [163], where metastases are very common. Since obesity, dyslipidemia and hypercholesterolemia are related developments with the progression and severity of type-2 diabetes mellitus; inductance of carcinogenesis may not be un-inevitable phenomena in long run diabetics.

Diabetes and Intervention

Treatment of Diabetes includes diagnosing the disease, its risk management and hyperglycemic control.

Diagnosis of Diabetes Mellitus

For asymptomatic patient

Diagnosis can be confirmed either from two abnormal values of the same test on different days or from different tests performed on same day/different days. If only one test shows abnormal, it should be repeated on a different day. Abnormal values of the repeated tests confirm the diagnosis positive for diabetes.

For symptomatic patient (i.e., polyuria, polydipsia, Polyphagia): Diagnosis can be confirmed from a single random test of plasma glucose at fasting or post prandial state as shown in Table 1.

Test	Results	Interpretation
HbA1c	6.5% or higher	Diabetes
	5.7-6.4%	Impaired glucose tolerance
	Lower than 5.7%	Normal
Random blood glucose or post-prandial blood glucose	200 mg/Dl or higher	Diabetes
	140-199 mg/dL	Impaired glucose tolerance
	Lower than 140 mg/dL	Normal
Fasting	126 mg/dL or higher	Diabetes
	100-125 mg/dL	Impaired glucose tolerance
	Lower than 100 mg/dL	Normal

Table 1: Single random test of plasma glucose at fasting or post prandial state.

Abrupt symptoms of patients with type-1 diabetes are mostly diabetic ketoacidosis as the initial presentation and these patients are generally not overweight. Tests like Islet cell antibody (ICA) and Glutamic acid decarboxylase antibody (GADA) can be considered as differential diagnosis in case of:

- Early onset of type 1 and type 2 diabetes in children and teenagers.
- Overweight adults and for those who are not responding well in diabetic management e.g. to oral hypoglycemic drugs and lifestyle (diet/exercise) modification.

Risk management

Coronary artery disease (CAD) is the most apparent risk in diabetic subjects. To reduce the chances of developing CAD in diabetic patients is the priority goal in risk management protocol as mentioned in Table 2.

Risk factor	Goal
Blood pressure	
Age 79 or younger	Lower than 140/90 mm Hg
Age 80 or older	Lower than 150/90 mm Hg
With microalbuminuria (at any age)	Lower than 130/80 mm Hg
LDL Cholesterol	Lower than 100 mg/dL
Haemoglobin A1c (HbA1c)	Lower than 7%
Fasting blood glucose	80-120 mg/dL

Table 2: Diabetic patients-risk management.

Lifestyle modification and non-pharmacologic approaches

- All patients of diabetes should make smart choice diet chart to meet their caloric needs avoiding the chances of raising the blood glucose level.
- Needed to perform a routine 30 min of moderate to intense physical exercise on daily basis.

Extra vigilant awareness of diabetic patients on blood glucose monitoring and control is an essential role during phases of acute illness.

Risk reduction with pharmacologic options

As atherosclerosis is the most important complication in diabetes mellitus, various pharmacologic approaches that can be adopted are depicted in the figure below.

Excess liberation of free fatty acids which results in the typical diabetic dyslipidemia can be treated by use of statins and fibric acid derivatives (Figure 9), which improve the lipid profile of the patients as well as atherogenic tendency.

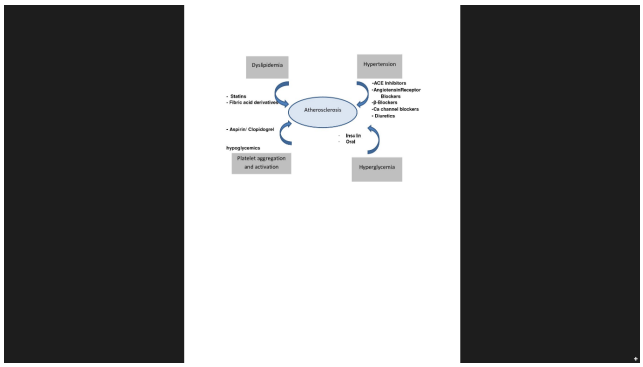

Figure 9: Pharmacological options for risk reduction in diabetes mellitus.

Treatment of hypertension especially in type 2 diabetic patients by agents modifying renin-angiotensin system like ACE inhibitors etc. significantly decreases the incidence of myocardial infarction and stroke. β-Blocker therapy in diabetic patients with cardiovascular disease decreases morbidity and mortality. Anti-platelet therapy may be considered in diabetic patients due to their increased thrombotic potential, which may again reduce the incidence of myocardial infarction and death in these patients.

Blood glucose control with pharmacologic options

In type-1 diabetes mellitus, insulin is the treatment of choice to bring back plasma glucose concentration to its maximally possible normal level to avoid secondary complications.

In type-2 diabetes mellitus oral-hypoglycemic agents are the treatment of choice. The various groups of oral-hypoglycemic drugs along with their mechanism of action is shown in the Table 3.

More recently in the last decade, transplantation therapies have been investigated which include whole pancreas transplantation, islet cell transplantation and stem cell transplantation [164]. However, out of all, stem cell transplantation has gained greater momentum than others.

Pharmacologic class	Pharmacologic compound	Mechanism of action
Biguanides	Metformin	Insulin sensitizers (mainly at hepatic level)
Thiazolidinediones	Roziglitazone	Insulin sensitizers(mainly at muscle and fat level)
(glitazones)	Pioglitazone	
Sulphonylureas	Glipizide	Secretagogues (stimulate insulin secretion)
	Gliclazide	
	Gliburide	
	Gliquidone	
	Glyclopyramide	
	Glimepiride	
Meglitinides	Repaglinide	Short-term secretagogues
	Nateglinide	
α-Glucosidase inhibitors	Acarbose	Reduce carbohydrate Absorption

Table 3: Various groups of oral-hypoglycemic drugs along with their mechanism of action.

WHO Guidelines

World Health Organization (WHO) fact sheet [Revised in January 2015]

Key facts:

- In 2014 the global prevalence of diabetes * was estimated to be 9% among adults aged 18+ years [165]. This shows about 422 million adults were living with diabetes in 2014, compared to 108 million in 1980.
- In 2012, an estimated 1.5 million deaths were directly caused by diabetes [166].
- More than 80% of diabetes deaths occur in low- and middle-income countries [166].
- WHO projects that diabetes will be the 7th leading cause of death in 2030 [167].
- Healthy diet, regular physical activity, maintaining a normal body weight and avoiding tobacco use can prevent or delay the onset of type 2 diabetes [168].
- **WHO Response:** WHO aims to stimulate and support the adoption of effective measures for the surveillance, prevention and control of diabetes and its complications, particularly in low and middle-income countries. To this end, WHO:
- provides scientific guidelines for diabetes prevention;
- develops norms and standards for diabetes diagnosis and care;
- builds awareness on the global epidemic of diabetes; celebration of World Diabetes Day (14 November);
- conducts surveillance of diabetes and its risk factors.

The WHO *Global strategy on diet, physical activity and health* complements WHO's diabetes work by focusing on population-wide approaches to promote healthy diet and regular physical activity, thereby reducing the growing global problem of overweight and obesity.

Prevalence of diabetes worldwide in the year 2000 is shown in Figure 10. A brief summary is as follows:

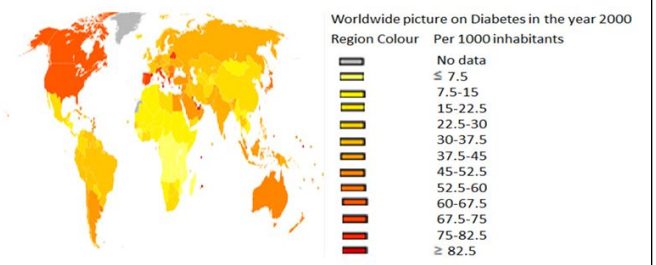

Figure 10: Rates of diabetes worldwide in 2000 (per 1,000 inhabitants).

Diabetes - Present and Future

Type-1 diabetes mellitus

It is a well-known fact that one of the reasons of type-1 diabetes mellitus is due to destruction of pancreatic β-cells by autoimmune attack and most of the times a major loss of β-cell mass is noted by the time type-1 diabetes is diagnosed. Moreover insulin is the only mode of treatment in type-1 diabetes and at present, efforts are made to design the improved technologies like insulin pumps or continuum glucose monitoring which leads to better control of blood glucose levels in type-1 diabetes mellitus.

The future goals in type-1 diabetic research aim at ensuring the survival of β-cells and replacing the cells that are already lost. While transplantation of whole pancreas or its islet cells is the current approach to aim replacing of the pancreatic β-cells, the major drawback comes from failure to implement this approach because of limited availability of human pancreas and need of extensive immunosuppression. On average, at least two donor pancreases are required to harvest enough islets for one allogeneic islet cell transplantation and many patients require more than one infusion to maintain insulin independence. Targeting stem cell replacement therapy may become an innovative successful approach for restoration of β-cells. Resource of stem cells could be from embryonic/adult tissue or from biotechnological reprogramming of α-cells/replication of existing β-cells [168]. Sequestration or encapsulation of immune system by other alternative ways may also resist rejection or recurrence of anti-islet cell autoantibody generation without complications of immunosuppressive therapy [169]. Last but not the least that many attempts are in progress to grow β-cells in bio-laboratories by cell culture technique as part of the programme of next generation regenerative medicine discovery [170,171] and to develop devices through which these cultured cells may get adopted in the body without provoking further immune response.

Type-2 diabetes mellitus

While the genetics of type-2 diabetes mellitus has advanced rapidly since the last decade by virtue of various advances in technology including analytical approaches like candidate gene approach which led to the discovery of PPAR gene, which was the first gene identified [172] and genome-wide association studies (GWAS) [173], which have largely helped to explain the genetic basis of this disease, but the pathogenic process in type-2 diabetes mellitus is heterogenous and involves a number of environmental factors as well. It is possible that these environmental factors and hyperglycemia contribute to epigenetic changes in DNA and histones leading to modification of genetic transformation that precipitates the pathogenesis of type-2 diabetes mellitus [174,175]. Therefore, the approaches involving metabolomics, lipidomics, proteomics, genomics and transcriptomics are being integrated for better understanding of the disease process in future and also to apprehend the heterogeneity of responses to different glucose lowering therapies which are employed in treating type-2 diabetes mellitus [176]. Therefore in the coming times, it might be possible that these new approaches may identify additional genes and metabolic markers which might be involved in the feedback loop that interconnects the β-cells with insulin sensitive tissues and thus help in unravelling the heterogeneity of the disease.

We can only hope that the next decade will provide us with the knowledge and approaches that will allow us to limit the global harm of diabetes by not only managing the condition more effectively with the combination of various pharmacological and non-pharmacological approaches but also by preventing the disease and identifying new strategies to directly target its complications.

Conflict of Interest

All the authors declare that they have no conflict of interest.

Ethical Approval

This is a review article and so ethical restriction does not apply here.

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