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Review Article

Updates of Diabetes Mellitus: A Concern for Public Health - ②

Alok Raghav^{1*}, Jamal Ahmad¹, Saba Noor¹, Maaz Ozair¹, Khursheed Alam², Brijesh Kumar Mishra³, Zeeshan Ahmad Khan⁴ and Sumit Kumar Singh⁵

¹Rajiv Gandhi Centre for Diabetes & Endocrinology, J.N Medical College, Aligarh Muslim University, Aligarh-202002, U.P, India

²Department of Biochemistry, Faculty of Medicine, J.N Medical College, Aligarh Muslim University, Aligarh-202002, U.P, India

³Department of Endocrinology, Guru Teg Bahadur Hospital, University of Delhi, Dilshad Garden, Delhi, 110095

⁴Biological Rythm Laboratory, Institute of Bioresources and Sustainable Development, Imphal-795004

⁵Department of Biotechnology, National Dairy Research Institute, Karnal-132001, Haryana

***Address for Correspondence:** Alok Raghav, Rajiv Gandhi Centre for Diabetes & Endocrinology, J.N Medical College, Aligarh Muslim University, Aligarh-202002, U.P, India, Tel: +91-9412672185; E-mail: alokalig@gmail.com

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ABSTRACT

Diabetes mellitus is increasingly becoming a prime chronic threat and burden around the globe. This requires a transformation in healthcare priorities in epidemiology and impact of this disease in all regions to aware populations about the reactions of hyperglycemia and induced complications to decrease prevalence rate. A systematic literature review of prestigious papers on diabetes mellitus and its associated complications around the globe based on the data published. The recent classification of diabetes and its associated complications are reported. Current diabetes prevalence rate around the globe is 8.3% that further increases in the year 2030. The classification criteria of various international bodies efforts to improve the definition and diagnosis of diabetes mellitus. Diabetes mellitus is an important and chronic public health problem around the globe. Variations are observed around the world contributing to rising in prevalence rate. The current and past scenario of classification and diagnosis was shown to improve public concern.

Keywords: Diabetes mellitus; Hyperglycemia; Noncommunicable disease; Global health

INTRODUCTION

Noncommunicable Diseases (NCDs) are of greatest public health concern in developing world. Statistical data clearly signifies that 63% global death (36 million) were caused in 2008 by four major NCDs; diabetes, cancer, cardiovascular diseases and chronic respiratory diseases (WHO 2011 report). NCDs mortality is higher than that of maternal, neonatal, prenatal, communicable and nutritional related mortality. It is also estimated that by 2020 NCDs mortality increased globally by 15%, with 20% in low to middle-income countries (WHO 2010 report). Alcohol consumption, tobacco smoking, unhealthy diet, and inactiveness contribute majorly to NCDs. These may lead to four common metabolic conditions; high blood pressure, obesity, hyperglycemia along with raised cholesterol level. Statistical data from European Investigation in cancer and Nutrition (EPIC) clearly define consumption ≥ 5 portions of fruits and vegetables in the diet per day were associated with nearly 10 % lower risk of diabetes development [1]. Diabetes is a chronic metabolic disorder with insufficient insulin generation from the pancreas or insufficiency of the body to perceive insulin characterized by raised hyperglycemia causes damage to the body if prolonged.

Diabetes was detected in Egyptian populations characterized by weight loss and polyuria later on Greek physician Aertaeus coined the term Diabetes Mellitus (DM) that mean. In Greek, diabetes refers “to pass through” and Mellitus derived from Latin word means honey (referring sweetness). The canon of medicine literature, in medieval Persia, Avicenna describes the symptoms of abnormal appetite and sexual dysfunction along with the sweet taste of the urine. Chinese physicians state sweet urine in people with diabetes followed by the nomenclature of sugar urine disease. Frederick Banting and Charles Best in 1921 and 1922 developed insulin, an efficient treatment. They further elaborate the work of Von Mering and Minkowski, and further give the concept of revert diabetes in dogs by supplementation of pancreatic beta cells of healthy dogs.

German pathologist named Paul Langerhans discovered islets of Langerhans in 1869 stating their role in regulating blood glucose level. Eli Lilly company in collaboration with the university of toronto began the massive production of human insulin by the end of 1923 being proved a positive therapy for 25,000 patients in Canada and United States [2]. For this grand work Banting and John MacLeod jointly received the Noble prize in Physiology or Medicine in 1923.

American Diabetes Association (ADA) describes diabetes as a group of metabolic disorders characterized by hyperglycemia resulting from impairment in insulin secretion, insulin action or both [3]. It reduces the ability of individual to regulate and control glucose level in the blood that results in micro and macro-vascular complications

with classical symptoms of thirst, polyuria (increased urination), polydypsia (increased thirst), polyphagia (increased hunger) along with blurred vision and weight loss. Long-term effects include the progressive growth of retinopathy (blindness/blurred vision), potential nephropathy (renal failure) and peripheral neuropathy (foot ulcers, amputations, sexual dysfunction & Charcot’s joints) [4] and increased risk of cardiovascular [5] and cerebrovascular diseases. Recent studies showed that diabetes doubles the risk of cardiovascular diseases and proves to cause 75% deaths due to coronary artery diseases [6].

Regulation of blood glucose operates in a negative feedback loop system via the release of insulin and glucagon. When the blood glucose level is high, β -cells are triggered to release insulin via ATP-dependent voltage ions and calcium channels making changes in potential difference from -70 mV to more positive. Insulin is a 51 amino acid polypeptide composed of two chains (A and B) linked up by disulfide bridges that release as proinsulin and becomes functional by enzymatic cleavage with the simultaneous release of C-peptide. At high extracellular facilitated diffusion of glucose occurs, down its concentration gradient through GLUT 2 transporter [7]. Glucose generates ATP, thereby increasing the ratio of ATP to ADP, making a block of ATP-sensitive potassium ion channels [8]. As a result of this blockage membrane potential become more positive enable calcium ion channels to open up releasing calcium inside the cell. When the calcium ions enter the cells, they cause insulin release by exocytosis.

Prevalence around the Globe

The changes in lifestyle, life expectancy and lack of information in healthcare are in part accountable for the astounding increase in the diabetes mellitus incidences. As a result, there is an upward trend of incidence, especially in industrialized urban areas. The global prevalence of diabetes mellitus in the adult population in 2013 estimates that almost 382 million people suffer from diabetes mellitus with owning a prevalence rate of 8.3 %. North America and Caribbean region with a higher prevalence rate of 11% (37 million people). Western Pacific has 138 million diabetes populations with the rate of 8.6%. American diabetes Association (ADA) represents and launches National Diabetes Statistics Report, 2014 on June 10, 2014, revealing the facts as mentioned [9-10] (Figure 1).

- 29.1 million Americans with a prevalence rate of 9.3% have diabetes in 2012.
- 1.25 million (approx) American children and adults have diagnosed type 1 diabetes.
- Undiagnosed: 8.1 million populations are not diagnosed with diabetes mellitus.

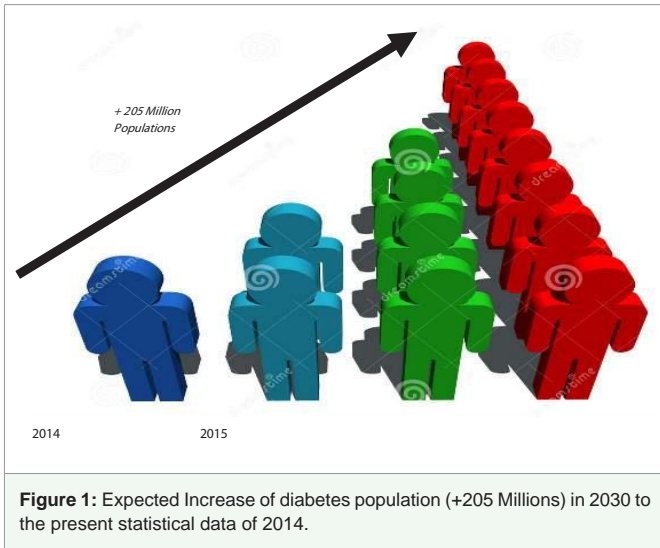


Figure 1: Expected Increase of diabetes population (+205 Millions) in 2030 to the present statistical data of 2014.

- Americans (≥ 65 Years) are having diabetes prevalence rate of 25.9%.
- 1.7 million new cases were registered for the incidence of diabetes mellitus.
- In the United States, diabetes is the 7th leading cause of deaths with 69,071 death certificates in 2010.
- About 208,000 youth within the age of 20 Years were diagnosed with diabetes mellitus.
- Diabetes mellitus prevalence rate on the basis of race and ethnicity were clearly demonstrated as below and table 1.

Prevalence rate of diagnosed diabetes mellitus by race/ethnicity background

- ❖ 7.6% of non-Hispanic whites
- ❖ 9.0% of Asian Americans
- ❖ 12.8% of Hispanics
- ❖ 13.2% of non-Hispanic blacks
- ❖ 15.9% of American Indians/Alaskan Natives.

Further breakdown of Asian Americans shows prevalence rate as

- ❖ 4.4% for Chinese
- ❖ 11.3% of Filipinos
- ❖ 13.0 for Asian Indians
- ❖ 8.8% of other Asian Americans.

Breakdown among Hispanic adults diabetes mellitus population is as

- ❖ 8.5% of Central and South Americans
- ❖ 9.3% for Cubans
- ❖ 13.9% of Mexican Americans
- ❖ 14.8% for Puerto Ricans.

Statistical results of diabetes mellitus in India shows the scary value of > 62 million diabetic individuals [11,12]. In the year 2000, India topped the outmost position with 31.7 million people with diabetes mellitus among other countries around the globe followed by China (20.8 million) and the United States (17.7 million) on second and third position respectively. Wild, et al. [13] clearly state the prevalence of diabetes mellitus to be double globally from 171 million in 20 to 366 million in 2030 with a maximum number of incidence in India. The predicted figure for individual in 2030 includes India (79.4 million), China (42.3 million) and the United States (30.3 million) [13,14]. Preliminary results obtained from a large population-based study conducted by Indian Council of Medical Research (ICMR), New Delhi revealed that lower mass of population is affected by diabetes in states of Northern India (Chandigarh 0.12 million, Jharkhand 0.96 million) as compared to Maharashtra (9.2 million) and Tamil Nadu (4.8 Million) [15]. National urban Survey of metropolitan cities in India revealed the statistical figure of 11.7% in Kolkata (Eastern India), 6.1% in Kashmir Valley (Northern India) [16], 11.6% in New Delhi (Northern India), 9.3% in Mumbai (West India), 13.5% in Chennai (South India), 16.6% in Hyderabad (South India), 12.4 % in Bangalore (South India) [17]. Undiagnosed diabetes is also the hidden danger for India. Although studies for prevalence has been clearly reflected the rate of diabetes among the Indian population but also have reported the very high prevalence of undiagnosed diabetes. Chennai Urban Rural Epidemiology Study (CURES) establish the undiagnosed-prevalence rate of 9.1% [16]. Similarly, Diabetes and Endocrine Population Survey (ADEPS) showed a prevalence rate of diagnosed and undiagnosed as 9.0% and 10.5% respectively [17-19]. Kashmir Valley has undiagnosed diabetes prevalence rate of 4.25% [20]. The individuals who are undiagnosed for diabetes mellitus and left untreated are more prone to micro -vascular and macro -vascular complications, thus it is strictly necessary to diagnose the precise and accurate prevalence rate of diabetes mellitus in Indian population. The difference in urban and rural prevalence rate of diabetes was found out by the study of ICMR as 2.1% and 1.5% respectively [21]. A later study showed a prevalence rate of urban (8.2%) and rural (2.4%) [21]. A study by The prevalence of diabetes in India study (PODIS) also establishes prevalence rate of diabetes in urban and rural population as 4.7% and 2.0 % respectively according to ADA criteria [22] and 5.6% and 2.7% respectively according to WHO criteria [23,24] (Figure 2).

Table 1: Demonstrating the statistical data of diabetes mellitus in continent population around the world. Source: Diabetes Atlas 2014 (International Diabetes Federation).

Regions/Parameters	North America & Caribbean	Europe	South & Central America	Middle East & North Africa	South East Asia	Africa	Western Pacific
Diabetes Population (Millions)	39	52	25	37	5	22	138
Prevalence rate (%)	11.4	7.9	8.1	9.7	8.3	5.1	8.5
Undiagnosed (%)	27.1	33.1	27.4	48.6	2.8	62.5	53.6



Figure 2: Recent trends of prevalence of type 2 diabetes mellitus in Indian population [26].

Criteria for diagnosis of diabetes mellitus

The current diagnostic criteria for diabetes mellitus and intermediate hyperglycemia have globally accepted widely for almost a period of decades. However, American Diabetes Association (ADA) tailored recommendations of World Health Organization (WHO) resulting in discrepancies. Stepping towards the diabetes diagnosis and its criteria information about the parameters is needed and to be defined as below:

Normal fasting Plasma Glucose: Each of the ADA publications updates the diagnostic criteria for diabetes mellitus. The 2003 ADA

statement [25] gives a definition of normal fasting plasma glucose as < 5.6 mmol/l (modifies from 6.1 mmol/l in 1997) and normal 2-h plasma glucose as < 7.8 mmol/l. Although 1999 WHO report establish normal fasting plasma glucose as < 6.1 mmol/l and normal 2-h plasma glucose as < 7.8 mmol/l [26].

Impaired glucose tolerance: It is a pre-diabetic state of persistence hyperglycemia that is strictly associated with insulin resistance. WHO criteria for fasting Impaired Glucose Tolerance (IGT) is < 7.0mmol/l and 2-h plasma glucose in the range of ≥ 7.8 and < 11.1mmol/l [27].

Impaired fasting glucose: It is a more common form of pre-

diabetes refers to a physiological condition in which fasting blood plasma glucose level is continuously increased above normal level for initiating of prognosis of diabetes mellitus. WHO defines the criteria for fasting plasma glucose level ranging from 6.1 mmol/l to 6.9 mmol/l [28]. Whilst ADA gives the value of IFG between 5.6 mmol/l to 6.9 mmol/l [29].

Oral glucose tolerance test (OGTT): An oral glucose tolerance test (OGTT) was performed after administration of WHO recommended a dose of 75 gms oral glucose in adults [30]. Measurement of plasma glucose level after 2-h gives the exact tolerance of glucose in diabetes patients except for gestational diabetes where 50 gms were administered orally followed by 1-h examination of plasma glucose level. A value of below 7.8 mmol/l indicates normal-glycemia where as higher value indicates hyperglycemia. Blood plasma glucose level ranging between 7.8 mmol/l and 11.1 mmol/l indicates the impaired glucose tolerance while above 11.1 mmol/l indicates a diagnosis of diabetes mellitus. For 75 gms OGTT, the fasting blood plasma glucose value should be below 6.1 mmol/l; for 1 hour it should be below 10.0 mmol/l and for 2-hour it should be below 8.5 mmol/l. The classification according to WHO and American Diabetes Association (ADA) was given in table 2, 3 and 4.

Complications & co-morbidities conditions in diabetes mellitus

Hypoglycemia: In the year 2011, about 282,000 persons visit causality clinics within age 18 years and above due to hypoglycemia [31].

Hypertension: In 2009-2012 adults within age 18 and above were diagnosed diabetes, 71% has blood pressure greater than 140/90 [31].

Dyslipidemia: In 2009-2012, adults persons with age 18 and older diagnosed with diabetes, 65% had LDL cholesterol greater than 100 mg/dl [31].

Cardiovascular Diseases death rates: in 2003-2006, CVDs death

rates were about 1.7% higher among adults aged 18 years or older diagnosed with diabetes [31].

Heart Attack rates: In 2010, rates of heart attacks were 1.8 times higher among adults aged between 20 years or older diagnosed with diabetes [31].

Strokes: In 201 strokes rate among diabetes population between the age group of 20 years or older were 1.5 times [31].

Blindness and Eye complications: 4.2 million (28.5%) adults with diabetes aged from 40 years and above in 2005-2008 had an incident of diabetic retinopathy [31].

Kidney disorders: Diabetes is the prime cause of kidney damage in 44% of all diabetes patient newly diagnosed in 2011 [31].

Amputations: in the year 2010, approximately 73,000 non-traumatic lower-limb amputations were performed in adults [31].

CLASSIFICATION OF DIABETES MELLITUS

The first globally accepted classification of diabetes mellitus was published by World Health Organization in 1980 [32] modified in 1985 [33]. Presenting a certain class of diabetes to an individual often depends on the conditions present at the time of investigations and diagnosis, and many people with diabetes do not readily place into a single class. For instance, if an individual with Gestational Diabetes (GDM) may continue with persistence hyperglycemia may be placed into the category of type 2 diabetes mellitus. Alternatively, a person with increased hyperglycemia due to an excessive dose of exogenous steroids may become normoglycemic once the intake is inhibited. Another classical example of this event id that if a person with prolonged treatment of thiazides drugs may develop type 2 diabetes symptoms but may discontinue if treatment was finished. Thus for clinicians and patients, it is important to place individual in proper class with the well-defined label of diabetes for the effective treatment. The American Diabetes Association (ADA) categorized diabetes

Table 2: Summary of World Health Organization (WHO) diagnostic criteria for diabetes mellitus and intermediate hyperglycemia [29].

	1965	1980	1985	1999
Normal Fasting glucose 2-h glucose	Not specified <6.1 mmol/ l	Not defined	Not defined	<6.1 mmol/ l Not specified but <7.8 mmol/ l implied
Diabetes Fasting glucose 2-h glucose	Not specified ≥7.2 mmol/ l	≥8.0 mmol/ l and/or ≥11.0 mmol/l	≥7.8 mmol/ l Or ≥11.0 mmol/ l	≥7.0 mmol/ l or ≥11.0 mmol/ l
IGT Fasting glucose 2-h glucose	Referred to as borderline state 6.1-7.1 mmol/l	<8.0 mmol/l and ≥8.0 mmol/l and <11.0 mmol/l	<7.8 mmol/l and ≥7.8 mmol/l and <11.0 mmol/l	<7.0 mmol/l and ≥7.8 and <11.1 mmol/l
IFG Fasting glucose 2-h glucose	Not defined	Not defined	Not defined	≥6.1 mmol/l and <7.0 mmol/l and <7.8 mmol/l (if measured)

Table 3: Criteria* for diagnosis of diabetes mellitus as per recommendations of American Diabetes Association (ADA) [31].

Criteria for diagnosis of diabetes mellitus
1. Symptoms of diabetes plus casual plasma glucose concentration ≥200 mg/ dl (11.1 mmol/ l). Casual is defined as any time of day without regard to time since last meal. The classic symptoms of diabetes include polyuria, polydipsia, and unexplained weight loss.
or
2. FPG ≥126 mg/ dl (7.0 mmol/ l). Fasting is defined as no caloric intake for at least 8 h.
or
3. 2-h post load glucose ≥200 mg/dl (11.1 mmol/ l) during an OGTT. The test should be performed as described by WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.
*Note: In the absence of unequivocal hyperglycaemia, these criteria should be confirmed by repeat testing on a different day. The third measure (OGTT) is not recommended for routine clinical use

Table 4: Diagnosis of GDM* with a 100-g or 75-g glucose load as per recommendations of American Diabetes Association (ADA) [31].

	mg/dl	mmol/l
100-g Glucose load		
Fasting	95	5.3
1-h	180	10.0
2-h	155	8.6
3-h	140	7.8
75-g Glucose load		
Fasting	95	5.3
1-h	180	10.0
2-h	155	8.6

*Note: Two or more of the venous plasma concentrations must be met or exceeded for a positive diagnosis. The test should be done in the morning after an overnight fast of between 8 and 14 h and after at least 3 days of unrestricted diet (≥150 g carbohydrate per day) and unlimited physical activity. The subject should remain seated and should not smoke throughout the test.

in varied classical forms to differentiate individuals with diabetes mellitus [34].

Type 1 diabetes mellitus/immune mediated diabetes mellitus

An expert peer review committee of the American Diabetes Association (ADA), with its etiological diagnostic criteria, has decided and recommended dividing Type 1 diabetes (T1DM) into two subclass type 1A (immune cells mediated) and type 1B (other forms of diabetes with severe insulin deficiency). This severe form of diabetes accounts for only 5-10% of diabetic people. Previously this form of diabetes was popularly known as insulin dependent diabetes, juvenile onset diabetes that results from destruction of pancreatic beta cells via the cellular mediated autoimmune mechanism. The prime participants for this destruction include autoantibodies to insulin, GAD65 and tyrosine phosphatases IA-2. Either one or usually more antibodies are present in 85%-90% individuals during hyperglycemia in fasting state was detected. Also, the disease has a strong link up with the HLA associations in connection with DQA and DQB genes regulated by DRB genes. Islets of type1A diabetic patients' over express class I HLA antigens, rarely class II HLA molecules. The up-regulation of IFN-α are being reported to initiate the expression of Fas molecules on all islets cells [35-38]. The HLA alleles i.e., HLA-DR/DQ may be either predispose or protective. The rate of destruction of islets cells varies from children (high) to adults (slow). Ketoacidosis is the first symptoms that appear in diabetes patients with this class. Other classical symptoms include mild or severe hyperglycemia followed by infection and other stress. At the chronic stage of this diabetes class, no or little insulin secretion along with low C-peptide levels was observed. Autoimmune destruction of insulin producing β-cells has multiple genetic predispositions along with environmental factors that are poorly diagnosed. Patients with this class of diabetes are rarely obese and may prone to various autoimmune disorders such as Graves' disease, Hashimoto's thyroiditis, Addison's disease, vitiligo, celiac sprue, autoimmune hepatitis, myasthenia gravis and pernicious anemia [39].

Idiopathic diabetes

Some patients with no known etiologies are identified under type 1 class known as idiopathic diabetes. These patients have a permanent sign of insulinopenia and prone to ketoacidosis [40] but

no autoimmune response was observed [41]. Although few people fall under this criterion belonging to African and Asian ancestry. Classical symptoms of this form of diabetes with varying degree of insulin deficiency between episodes. This form of diabetes mellitus is inherited and not linked up with HLA interaction.

Type 2 diabetes mellitus (predominant insulin resistance with relative insulin deficiency)

This form of diabetes mellitus accounts for 90-95% populations referred to as non-insulin dependent diabetes mellitus/type 2 or adult onset diabetes. This form encompasses to those who have insulin resistance and usually have a relative (rather than absolute) deficiency of insulin. People with this diabetes form are insulin resistant [42,43]. Type 2 diabetes is frequently undiagnosed for a long time because of the insincerity of hyperglycemia in the body that shows the symptoms [44,45]. Nevertheless, such patients with this form of diabetes are at high risk of development of macro-vascular and micro-vascular complications [44,45]. The majority of patients with this form of diabetes mellitus are obese thereby causing insulin resistance [46,47]. Those patients who are not obese may represent fat deposition in abdominal region changing into central obesity [48]. Ketoacidosis in association with infections is frequently associated with this form of diabetes [49,50]. Whereas patients in this class may have normal or elevated insulin and persistence hyperglycemia. Thus, insulin secretion is impaired and insufficient to compensate the insulin resistance. Some patients in this form may have normal insulin action but marked insulin secretion. The risk of developing type 2 diabetes mellitus increases with age, obesity and physical inactiveness [51,52]. Women prior to GDM are more prone to this form of diabetes mellitus with appeared symptoms of hypertension and dyslipidemia. Its rate of occurrence and frequency varies with different racial/ethnic subgroups [53-56]. It is associated with strong familial, likely genetic and predisposition [55-57]. However, the genetic form this diabetes is complex and undefined.

Other specific types of diabetes mellitus /genetic defects of cells

Several forms of diabetes mellitus may be linked up with monogenic defects in beta cells function, characterized by the onset of mild hyperglycemia at a nearly stage (>25 Years). They have usually inherited autosomal dominant pattern. This form of diabetes referred to as Maturity Onset Diabetes of Young (MODY) and is associated with impaired insulin secretion and insulin action [58,59]. Abnormalities at chromosome 12 genetic loci have now been characterized and are closely associated with hepatic nuclear transcription factor HNF1 alpha [60]. Another form is linked with mutations in the glucokinase gene at chromosome 7p that in turn impairs insulin secretion and glucose-6-phosphate metabolism [61,62]. Another form is dealt with the mutations in HNF4-α gene on chromosome 20q that involved in the regulation of HNF4-α transcription factor involved in the expression of HNF1-α [60]. A recent variant in IPF-1 mutations has been contributing to pancreatic agenesis [63]. Diabetes mellitus is also associated with point mutations in mitochondria [64]. Genetic inability to convert proinsulin into functional insulin have identified in several patients due to inherited autosomal dominance [65,66]. Similarly, mutations were found in insulin molecules along with impaired insulin receptors [67,68].

Gestational Diabetes (GDM)

Gestational diabetes is glucose intolerance resulting in hyperglycemia with onset or first recognition during pregnancy.

Although most of the cases of this form of diabetes are resolved with delivery. The definition of GDM implies irrespective of whether or not insulin application for treatment or condition persists after pregnancy. After deliberations in 2008-2009, the International Association of Diabetes and Pregnancy Study Groups (IADPSG) including American Diabetes Association (ADA) recommended that high-risk women found to have diabetes mellitus at their prenatal visit with standard diagnostic criteria, receive a diagnosis of overt, not gestational diabetes. Nearly 7% pregnancies are complicated with GDM. The precise mechanism underlying the causes of gestational diabetes is unknown. Insulin resistance may be the probable cause for GDM, as pregnancy hormones (placental) along with other unknown (fat depositions) factors binds with insulin receptors causing insulin resistance [69]. The statistical figure reflects that about 1.5-2.5 times more insulin is secreted than in normal pregnancy [69]. Glucose travels freely through facilitated diffusion by GLUT1 located in the syncytiotrophoblast on basal membranes. If the GDM is untreated fetus is exposed to hyperglycemia that leads to fetal insulin level at a high level leading to excessive growth and macrosomia.

OTHER FACTORS ASSOCIATED WITH HYPERGLYCEMIAS

Genetic defect in insulin secretion

There are several unusual causes of diabetes mellitus that are resultant of genetically derived abnormalities of insulin action. The metabolic anomalies related to mutations of insulin receptors may be the cause of hyperinsulinemia and modest hyperglycemia leading to diabetes complications [70,71]. *Acanthosis nigricans* in some individuals may be due to these related mutations. Women may develop virilisation and have enlarged cystic ovaries. In past, this syndrome was classified as Type A insulin resistance [70]. Occasionally occurring pediatric syndromes include Leprechaunism and Rabson-Mendenhall associated with mutations in insulin receptor genes along with impaired insulin receptor function and extreme insulin resistance [71].

Diseases of the exocrine pancreas

The injury may be the causative factor for diabetes mellitus. Acquired phenomenon includes pancreatitis, trauma, infection, pancreatic carcinoma and pancreatectomy [72,73]. However, adenocarcinoma that involves pancreas with the slight role may also involve in hyperglycemia. This clearly implies a mechanism other than a simple decrease in beta cell mass [74]. Cystic fibrosis and hemochromatosis will also damage beta cells and impairs insulin

secretion [75,76]. A serious disorder fibrocalculous pancreatopathy may be accompanied by abdominal pain and ductal dilations [77].

Endocrinopathies

Numerous hormones (e.g cortisol, glucagon, epinephrine, growth hormone) antagonize insulin action. Excessive secretion of these hormones causes diabetes (e.g Acromegaly, Cushing’s syndrome, Glucagonoma and Pheochromocytoma) [78]. Aldosteronoma-induced hypokalaemia and somatostatinoma is the probable cause of diabetes [79,80].

Drug or chemical induced diabetes

Several drugs impair insulin secretion. These drugs may solely or with a combination of other factors may induce diabetes and hyperglycemia that in turn may cause insulin resistance [80,81]. Certain toxins (Vacor) and pentamidine can permanently damage and destroy the pancreatic beta cells [82-86]. Glucocorticoids and nicotinic acid are also the probable causes of diabetes [76,77] and detailed are given in table 5.

CONCLUSION

Diabetes mellitus is a major health concern to global population and is widely associated with several micro-and macro-vascular complications. The prevalence rate of diabetes is increasing dramatically proving a serious threat to upcoming generations. This review focused on the major issues of diabetes and its associated complications. The direct and indirect benefit of this work is to provide a gentle message to the welfare of mankind.

REFERENCES

- Andrew J Cooper, Forouhi NG, Ye Z, Buijsse B, Arriola L, Balkau B, et al. Fruit and vegetable intake and type 2 diabetes: EPIC-InterAct prospective study and meta-analysis. *Eur J Clin Nutr.* 2012; 66: 1082-1092.
- Anatomy and Physiology: The Unity of Form and Function. Saladin Sixth Edition. New York: NY. McGraw- Hill Companies; 2012.
- American Diabetes Association. Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care.* 2004; 27: s5-s10.
- Diabetes Programme. World Health Organization. Retrieved 22 April 2014: <http://www.who.int/diabetes/en/>
- Sarwar N, Gao P, Seshasai SR, Gobin R, Kaptoge S, Di Angelantonio E, et al. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: A collaborative meta-analysis of 102 prospective studies. *The Lancet.* 2010; 375: 2215-22.
- O’Gara PT, Kushner FG, Ascheim DD, Casey DE, Chung MK, de Lemos JA, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/ American Heart Association Task Force on Practice Guidelines. *Circulation.* 2013; 127: e362-425.
- De Vos A, Heimberg H, Quartier E, Huypens P, Bouwens L, Pipeleers D, et al. Human and rat beta cells differ in glucose transporter but not in glucokinase gene expression. *Journal of Clinical Investigation.* 1995; 96: 2489-2495.
- Keizer J, Magnus G. ATP-sensitive potassium channel and bursting in the pancreatic beta cell. A theoretical study. *Biophysical Journal.* 1989; 56: 229-242.
- Insulin and Glucagon: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1471421/>
- American Diabetes Association. Statistics about Diabetes: <http://www.diabetes.org/diabetes-basics/statistics/#sthash.9avix8dx.dpuf>.
- Joshi SR, Parikh RM. India - diabetes capital of the world: now heading towards hypertension. *J Assoc Physicians India.* 2007; 55: 323-4.

Table 5: List of drugs responsible for induction of diabetes mellitus.

S. No	Name of Drugs
1	Nicotinic acid
2	Glucocorticoids
3	Thyroid hormone
4	Alpha-adrenergic agonists
5	Beta-adrenergic agonists
6	Thiazides
7	Dilantin
8	Pentamidine
9	Vacor
10	Interferon-alpha therapy

12. Kumar A, Goel MK, Jain RB, Khanna P, Chaudhary V. India towards diabetes control: Key issues. *Australas Med J.* 2013; 6: 524-31.
13. Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes-estimates for the year 2000 and projections for 2030. *Diabetes Care.* 2004; 27: 1047-53.
14. Whiting Dr, Guariguata L, Weil C, Shawj. IDF Diabetes atlas: Global estimates of the prevalence of diabetes for 2011 and 2030. *Diabetes Res Clin Pract.* 2011; 94: 311-21.
15. Anjana RM, Ali MK, Pradeepa R, Deepa M, Datta M, Unnikrishnan R, Rema M, Mohan V. The need for obtaining accurate nationwide estimates of diabetes prevalence in India - rationale for a national study on diabetes. *Indian J Med Res.* 2011; 133: 369-80.
16. Zargar AH, Khan AK, Masoodi SR, Laway BA, Wani AI, Bashir MI, et al. Prevalence of type 2 diabetes mellitus and impaired glucose tolerance in the Kashmir Valley of the Indian subcontinent. *Diabetes Res Clin Pract.* 2000; 47: 135-46.
17. Ramachandran A, Snehalatha C, Kapur A, Vijay V, Mohan V, Das AK, et al. High prevalence of diabetes and impaired glucose tolerance in India. National Urban Diabetes Survey. *Diabetologia.* 2001; 44: 1094-101.
18. Gupta A, Gupta R, Sarna M, Rastogi S, Gupta VP, Kothari K. Prevalence of diabetes, impaired fasting glucose and insulin resistance syndrome in an urban Indian population. *Diabetes Res Clin Pract* 2003; 61: 69-76.
19. Menon VU, Kumar KV, Gilchrist A, Sugathan TN, Sundaram KR, Nair V, et al. Prevalence of known and undetected diabetes and associated risk factors in central Kerala - ADEPS. *Diabetes Res Clin Pract.* 2006; 74 : 289-94.
20. Raman Kutty V, Joseph A, Soman CR. High prevalence of type 2 diabetes in an urban settlement in Kerala, India. *Ethn Health.* 1999; 4: 231-9.
21. Shah SK, Saikia M, Burman NN, Snehalatha C, Ramachandran A. High prevalence of type 2 diabetes in urban population in north eastern India. *Int J Diabetes Dev Countries* 1999; 19: 144-7.
22. Mohan V, Deepa M, Deepa R, Shantirani CS, Farooq S, Ganesan A, et al. Secular trends in the prevalence of diabetes and glucose tolerance in urban South India - the Chennai Urban Rural Epidemiology Study (CURES-17). *Diabetologia.* 2006; 49: 1175-8.
23. Ahuja MMS. Epidemiological studies on diabetes mellitus in India. In: Ahuja MMS, editor. *Epidemiology of diabetes in developing countries.* New Delhi: Interprint; 1979. p. 29-38.
24. Ramachandran A, Snehalatha C, Dharmaraj D, Viswanathan M. Prevalence of glucose intolerance in Asian Indians. Urban-rural difference and significance of upper body adiposity. *Diabetes Care.* 1992; 15: 1348-55.
25. Sadikot SM, Nigam A, Das S, Bajaj S, Zargar AH, Prasannakumar KM, et al. Diabetes India. The burden of diabetes and impaired fasting glucose in India using the ADA 1997 criteria: prevalence of diabetes in India study (PODIS). *Diabetes Res Clin Pract.* 2004; 66: 293-300.
26. Mohan V, Sandeep S, Deepa R, Shah B, Varghese C. Epidemiology of type 2 diabetes: Indian scenario. *Indian J Med Res.* 2007; 125: 217-230.
27. Genuth S, Alberti KG, Bennett P, Buse J, DeFronzo R, Kahn R. Follow-up Report on the Diagnosis of Diabetes Mellitus. *Diabetes Care.* 2003; 26: 3160-3167.
28. World Health Organization: Definition, Diagnosis and Classification of Diabetes Mellitus and its Complications: Report of a WHO Consultation. Part 1: Diagnosis and Classification of Diabetes Mellitus. Geneva, World Health Org, 1999.
29. World Health Organization. Definition, diagnosis and classification of diabetes mellitus and its complications: Report of a WHO Consultation. Part 1. Diagnosis and classification of diabetes mellitus. Retrieved 2007-05-29.
30. American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care.* 2005; S37-42.
31. Diagnosis and Classification of Diabetes Mellitus. American Diabetes Association. *Diabetes Care.* Volume 27, Supplement 1, January 2004: <http://www.diabetes.org/diabetes-basics/statistics/#sthash.9avix8dx.dpuf>.
32. World Health Organ Tech Rep Ser. WHO Expert Committee on Diabetes Mellitus. Second Report. 1980; 646:1-80.
33. World Health Organization. Diabetes Mellitus: Report of a WHO Study Group. 1985; 727: 1-113.
34. American Diabetes Association. Clinical practice recommendations. 2002. *Diabetes care.* 2002; 25(Suppl 1) : S1-S147.
35. Foulis AK, Clark A. Pathology of the pancreas in diabetes mellitus. In Kahn CR, Weir GC, eds. *Joslin's Diabetes mellitus.* 13th ed. Philadelphia: PA: Lea & Febiger; 1994. p. 265-281.
36. Foulis AK, Liddle CN, Farquharson MA, et al. The histopathology of the pancreas in type 1 diabetes (insulin dependent) mellitus. a 25 year review of deaths in patients under 20 years of age in the United Kingdom. *Diabetologia.* 1986; 29: 267-274.
37. Foulis AK, Farquharson MA, hardman R. Aberrant expression of class II major histocompatibility complex molecules by beta cells and hyper expression of class I major histocompatibility complex molecules by insulin containing islets in type 1 (insulin dependent) diabetes mellitus. *Diabetologia.* 1986; 30: 333-343.
38. Huang X, Yuan J, Goddard A, Foulis A, James RF, Lernmark A, et al. Interferon expression in the pancreas of patients with type 1 diabetes. *Diabetes.* 1995; 44: 658-664.
39. Betterle C, Zanette F, Pedini B, Presotto F, Rapp LB, Monsciotti CM, et al. Clinical and subclinical organ-specific autoimmune manifestations in type 1 (insulin-dependent) diabetic patients and their first-degree relatives. *Diabetologia.* 1984; 26: 431-36.
40. McLarty DG, Athaide I, Bottazzo GF, Swai ABM, Alberti KGMM. Islet cell antibodies are not specifically associated with insulin-dependent diabetes in rural Tanzanian Africans. *Diabetes Res Clin Pract.* 1990; 9: 219-24.
41. Ahrén B, Corrigán CB. Intermittent need for insulin in a subgroup of diabetic patients in Tanzania. *Diabet Med.* 1985; 2: 262-64.
42. DeFronzo RA, Bonadonna RC, Ferrannini E. Pathogenesis of NIDDM. In: Alberti KGMM, Zimmet P, DeFronzo RA, eds. *International Textbook of Diabetes Mellitus.* 2nd edn. Chichester: John Wiley. 1997: p. 635-712.
43. Lillioja S, Mott DM, Spraul M, Ferraro R, Foley JE, Ravussin E, et al. Insulin resistance and insulin secretory dysfunction as precursors of non-insulin-dependent diabetes. Prospective Study of Pima Indians. *N Engl J Med.* 1993; 329: 1988-92.
44. Mooy JM, Grootenhuys PA, de Vries H, Valkenburg HA, Bouter LM, Kostense PJ et al. Prevalence and determinants of glucose intolerance in a Dutch population. The Hoorn Study. *Diabetes Care.* 1995; 18: 1270-73.
45. Harris MI. Undiagnosed NIDDM; clinical and public health issues. *Diabetes Care.* 1993; 16: 642-52.
46. Campbell PJ, Carlson MG. Impact of obesity on insulin action in NIDDM. *Diabetes.* 1993; 42: 405-10.
47. Bogardus C, Lillioja S, Mott DM, Hollenbeck C, Reaven G. Relationship between degree of obesity and in vivo insulin action in man. *Am J Physiol.* 1985; 248: E286-E291.
48. Kissebah AH, Vydellingum N, Murray R, Evans DF, Hartz AJ, Kalkhoff RK, et al. Relationship of body fat distribution to metabolic complications of obesity. *J Clin Endocrinol Metab.* 1982; 54: 254-60.
49. Banerji MA, Chaiken RI, Huey H, Tuomi T, Norin AJ, MacKay IR, et al. GAD antibody negative NIDDM in adult black subjects with diabetic ketoacidosis and increased frequency of human leukocyte antigen DR3 and DR4: flatbush diabetes. *Diabetes.* 1994; 43: 741-45.
50. Umpierrez GE, Casals MMC, Gebhardt SSP, Mixon PS, Clark WS, Phillips LS. Diabetic ketoacidosis in obese African-Americans. *Diabetes.* 1995; 44: 790-95.
51. Zimmet PZ. Kelly West Lecture 1991. challenges in diabetes epidemiology: from West to the rest. *Diabetes Care* 1992; 15: 232-52.
52. Harris MI, Cowie CC, Stern MP, Boyko ES, Reiber GE, Bennett PH, eds. *Diabetes in America.* 2nd edn. Washington DC: US Government Printing Office; 1995. (NIH publ. No. 95-1468).
53. Zimmet PZ. Kelly West Lecture 1991: challenges in diabetes epidemiology: from West to the rest. *Diabetes Care* 1992; 15: 232-52.
54. Harris MI, Cowie CC, Stern MP, Boyko ES, Reiber GE, Bennett PH, eds. *Diabetes in America.* 2nd edn. Washington DC: US Government Printing Office, 1995 (NIH publ. No. 95-1468).

55. Valle T, Tuomilehto J, Eriksson J. Epidemiology of NIDDM in Europids. In: Alberti KGMM, Zimmet P, DeFronzo RA, eds. *International Textbook of Diabetes Mellitus*. 2nd edn. Chichester: John Wiley; 1997. p. 125-42.
56. de Courten M, Bennett PH, Tuomilehto J, Zimmet P. Epidemiology of NIDDM in Non-Europids. In: Alberti KGMM, Zimmet P, DeFronzo RA, eds. *International Textbook of Diabetes Mellitus*. 2nd edn. Chichester: John Wiley; 1997. p. 143-70.
57. Knowler WC, Nelson RG, Saad M, Bennett PH, Pettitt DJ. Determinants of diabetes mellitus in the Pima Indians. *Diabetes Care*. 1993; 16: 216-27.
58. Byrne MM, Sturis J, Menzel S, Yamagata K, Fajans SS, Dronsfield MJ, et al. Altered insulin secretory response to glucose in diabetic and nondiabetic subjects with mutations in the diabetes susceptibility gene MODY 3 on chromosome 12. *Diabetes*. 1996; 45: 1503-10.
59. Clement K, Pueyo ME, Vaxillaire M, Rakotoambinina B, Thuillier F, Passa P, et al. Assessment of insulin sensitivity in glucokinase-deficient subjects. *Diabetologia*. 1996; 39: 82-90.
60. Yamagata K, Oda N, Kaisaki PJ, Menzel S, Furuta H, Vaxillaire M, et al. Mutations in the hepatocyte nuclear factor-1alpha gene in maturity-onset diabetes of the young (MODY 3). *Nature*. 1996; 384: 455-58.
61. Froguel P, Vaxillaire M, Sun F, Velho G, Zouali H, Butel MO, et al. Close linkage of glucokinase locus on chromosome 7p to early-onset non-insulin-dependent diabetes. *Nature*. 1992; 356: 162-64.
62. Vionnet N, Stoffel M, Takeda J, Yasuda K, Bell GI, Zouali H, et al. Nonsense mutation in the glucokinase gene causes early-onset non-insulin-dependent diabetes. *Nature*. 1992; 356: 721-22.
63. Stoffers DA, Ferrer J, Clarke WL, Habener JF. Early-onset type-II diabetes mellitus (MODY4) linked to IPF1. *Nature Genetics*. 1997; 117: 138-39.
64. Walker M, Turnbull DM. Mitochondrial related diabetes: a clinical perspective. *Diabet Med*. 1997; 14: 1007-09.
65. Gruppuso PA, Gorden P, Kahn CR, Cornblath M, Zeller WP, Schwartz R. Familial hyperproinsulinemia due to a proposed defect in conversion of proinsulin to insulin. *N Engl J Med* 1984; 311: 629-34.
66. Robbins DC, Shoelson SE, Rubenstein AH, Tager HS. Familial hyperproinsulinemia: two cohorts secreting indistinguishable type II intermediates of proinsulin conversion. *J Clin Invest*. 1984; 73: 714-19.
67. Haneda M, Polonsky KS, Bergenstal RM, Jaspan JB, Shoelson SE, Blix PM, et al. Familial hyperinsulinemia due to a structurally abnormal insulin. Definition of an emerging new clinical syndrome. *N Engl J Med*. 1984; 310: 1288-94.
68. Sanz N, Karam JH, Horita S, Bell GI. Prevalence of insulin-gene mutations in non-insulin-dependent diabetes mellitus. *N Engl J Med* 1986; 314: 1322-23.
69. Carr DB, Gabbe S. Gestational Diabetes: Detection, Management, and Implications. *Clin Diabetes*. 1998; 16: 4.
70. Kahn CR, Flier JS, Bar RS, Archer JA, Gorden P, Martin MM, et al. The syndromes of insulin resistance and acanthosis nigricans. *N Engl J Med*. 1976; 294: 739-45.
71. Taylor SI. Lilly Lecture: molecular mechanisms of insulin resistance: lessons from patients with mutations in the insulin-receptor gene. *Diabetes*. 1992; 41: 1473-90.
72. Gullo L, Pezzilli R, Morselli-Labate AM. Diabetes and the risk of pancreatic cancer. *N Engl J Med*. 1994; 331: 81-84.
73. Larsen S, Hilsted J, Tronier B, Worning H. Metabolic control and B cell function in patients with insulin-dependent diabetes mellitus secondary to chronic pancreatitis. *Metabolism*. 1987; 36: 964-67.
74. Permert J, Larsson J, Westermark GT, Herrington MK, Christmansson L, Pour PM et al. Islet amyloid polypeptide in patients with pancreatic cancer and diabetes. *N Engl J Med*. 1994; 330: 313-18.
75. Moran A, Pyzdrowski KL, Weinreb J, Kahn BB, Smith SA, Adams KS et al. Insulin sensitivity in cystic fibrosis. *Diabetes*. 1994; 43: 1020-26.
76. Phelps G, Chapman I, Hall P, Braund W, Mackinnon M. Prevalence of genetic haemochromatosis among diabetic patients. *Lancet*. 1989; ii: 233-34.
77. Yajnik CS, Shelgikar KM, Naik SS, Kanitkar SV, Orskov H, Alberti KGMM, et al. The ketoacidosis-resistance in fibro-calculeous-pancreatic-diabetes. *Diabetes Res Clin Pract*. 1992; 15: 149-56.
78. MacFarlane IA. Endocrine diseases and diabetes mellitus. In: Pickup JC, Williams G, eds. *Textbook of Diabetes*. 2nd edn. Oxford: Blackwell; 1997: p 64.1-64.20.
79. Krejs GJ, Orci L, Conlon JM, Ravazzola M, Davis GR, Raskin P, et al. Somatostatinoma syndrome. *N Engl J Med*. 1979; 301: 285-92.
80. Conn JW. Hypertension, the potassium ion and impaired carbohydrate tolerance. *N Engl J Med*. 1965; 273: 1135-43.
81. Pandit MK, Burke J, Gustafson AB, Minocha A, Peiris AN. Drug-induced disorders of glucose tolerance. *Ann Intern Med*. 1993; 118: 529-40.
82. Gallanosa AG, Spyker DA, Curnow RT. Diabetes mellitus associated with autonomic and peripheral neuropathy after Vacor poisoning: a review. *Clin Toxicol*. 1981; 18: 441-49.
83. Esposti MD, Ngo A, Myers MA. Inhibition of mitochondrial complex I may account for IDDM induced by intoxication with rodenticide Vacor. *Diabetes*. 1996; 45: 1531-34.
84. Assan R, Perronne C, Assan D, Chotard L, Mayaud C, Matheron S, et al. Pentamidine-induced derangements of glucose homeostasis. *Diabetes Care*. 1995; 18: 47-55.
85. Amadori M. Condensation products of glucose with p-toulidine. *Atti. R. Accad. Naz. Lincei. Mem Cl. Sci. Fis. Mat Nat*. 1931; 13: 72-78.
86. Abrams A, Lowry PH, Borsook H. Preparation of 1-amino-1-deoxy-2-ketohexoses from aldohexoses and α -amino acids. *J. Am. Chem. Soc*. 1955; 77: 4794-4796.