Updates of Diabetes Mellitus: A Concern for Public Health -

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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 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, perinatal, 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 Aertzeus 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 Lily company in collaboration with the university of toronto began the massive production of human insulin by the end of 1923 and launches National Diabetes Statistics Report, 2014 on June 10, 2014 stating the rate of 8.6%. 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.
• 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% for 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).
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 < 7.0 mmol/l and 2-h plasma glucose in the range of ≥ 7.8 and < 11.1 mmol/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 and 11.1 mmol/l indicates normal-glycemia. Blood 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 2011 stroke 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 persistent 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>
<thead>
<tr>
<th>Table 2: Summary of World Health Organization (WHO) diagnostic criteria for diabetes mellitus and intermediate hyperglycemia [29].</th>
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<tbody>
<tr>
<td>Normal Fasting glucose 2-h glucose</td>
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<tr>
<td>Diabetes Fasting glucose 2-h glucose</td>
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<td>IGT Fasting glucose 2-h glucose</td>
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<td>IFG Fasting glucose 2-h glucose</td>
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<th>Table 3: Criteria* for diagnosis of diabetes mellitus as per recommendations of American Diabetes Association (ADA) [31].</th>
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<tbody>
<tr>
<td><strong>Criteria for diagnosis of diabetes mellitus</strong></td>
</tr>
<tr>
<td>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.</td>
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<td>or</td>
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<td>2. FPG ≥126 mg/dl (7.0 mmol/l). Fasting is defined as no caloric intake for at least 8 h.</td>
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<td>or</td>
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<tr>
<td>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.</td>
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*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

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permanent sign of insulinopenia and prone to ketoacidosis but type 1 class known as idiopathic diabetes. These patients have a pernicious anemia. vitiligo, celiac sprue, autoimmune hepatitis, myasthenia gravis and such as Graves' disease, Hashimoto's thyroiditis, Addison's disease, factors that are poorly diagnosed. Patients with this class of diabetes β-cells has multiple genetic predispositions along with environmental followed by infection and other stress. At the chronic stage of this diabetes class, no or little insulin secretion along with low C-peptide islets cells varies from children (high) to adults (slow). Ketonoadosis 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.

### 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 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]. Ketonoadosis 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 inactivity [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 [53-57]. 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-a gene on chromosome 20q that involved in the regulation of HNF4-a transcription factor involved in the expression of HNF1-a [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 resolve 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 Phaeochromocytoma) [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**


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

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<tr>
<th>S. No</th>
<th>Name of Drugs</th>
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<tbody>
<tr>
<td>1</td>
<td>Nicotinic acid</td>
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<tr>
<td>2</td>
<td>Glucocorticoids</td>
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<td>3</td>
<td>Thyroid hormone</td>
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<td>4</td>
<td>Alpha-adrenergic agonists</td>
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<td>5</td>
<td>Beta-adrenergic agonists</td>
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<td>6</td>
<td>Thiazides</td>
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<td>7</td>
<td>Dilantin</td>
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<td>8</td>
<td>Pentamidine</td>
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<tr>
<td>9</td>
<td>Vacor</td>
</tr>
<tr>
<td>10</td>
<td>Interferon-alpha therapy</td>
</tr>
</tbody>
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69. SRL Diabetes & Metabolism


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