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Diabetes Genetic Epidemiology and Associated Comorbidities: A Comprehensive Review

[1]Dr. Priya Kaushik; [2]Dr. Rashmi Nain; [3]Dr. Rupali Bains; [4*]Dr. Prashant Kumar
All India Institute of Medical Sciences Rishikesh.249201 Uttarakhand

Corresponding Author:- [4*]Dr. Prashant Kumar

Abstract:- Diabetes is characterized by elevated blood glucose levels in humans, which are mostly brought on by poor insulin production and utilization. Numerous genetic factors are responsible for causing TIDM such as PTPN22 and CTLA. People with diabetes mellitus are more likely to acquire a variety of linked conditions and conditions known as comorbidities because of a number of hereditary factors, environmental factors, certain medications, and other causes. Some of the common comorbidities that are prevalent in the T2DM patient population include congestive kidney disease, retinopathy, neuropathy, cardiovascular disease, urinary disorders, hyperlipidemia, and obesity. Diabetes has a high rate of hypertension, obesity, hyperlipidemia, and cardiovascular disease frequently coexist in patients as comorbid conditions. Knowing how genes function differs and how particular genetic factors raise the likelihood of comorbidities during diabetes can help develop effective medication for the management of diabetes Insight into how different genes operate and how specific genetic factors increase the risk of comorbidities during diabetes can aid in the development of effective diabetic medications to curb the epidemic of diabetes and its associated complications. A multifaceted approach is required, including early detection of diabetes, checking for its consequences, providing the best possible care at all levels of treatment for those who currently have the disease, and preventing diabetes in those with prediabetes. Diabetes prevalence is expected to increase, which will increase the need for rehabilitation therapy to decrease any problems the condition can cause. Exercise has been reported to improve insulin sensitivity to elevated blood sugar levels, enhance glucose absorption, decrease intra-abdominal fat a known risk factor for insulin resistance—and prevent cardiovascular issues.

Keywords:- *Diabetes, Epidemiology, Comorbidities, Polymorphism, Covid-19 Diabetes.*

I. INTRODUCTION

Globalization and changes in lifestyle have had a significant impact on politics, the environment, society, and human behavior over the last fifty years. Both in industrialized and emerging nations, there are significantly more persons with diabetes and obesity [1–3]. Diabetes refers to the increased blood glucose level in the human body which is basically due to impaired production and insulin utilization. The hormone insulin, which is secreted by beta cells in the pancreas, controls a person's blood sugar levels. The development of diabetes mellitus depends on the processes that control the mass of beta cells in the pancreas and the release of insulin. Diabetes maturity of the young is a group of single-gene disorders that affect pancreatic-cell function. Because the consequences of gene mutations in these illnesses are so severe, diabetes usually appears in childhood or adolescence [4]. It also causes a number of the body's systems to malfunction. Additionally, it demonstrates the harmful effects on the body's many systems, including the blood circulation and central nervous systems. Diabetes is divided into three main categories because of its many causes and manifestations. These are: (T1DM) Insulin insufficiency is the etiology of type 1 diabetes mellitus, whereas (T2DM) Insulin resistance, which stops the body from producing insulin, is the cause of type 2 diabetes mellitus. Gestational diabetes, which develops during pregnancy, is the cause of type 3 diabetes [5]. Out of them, T2DM is the most fatal which leads to numerous mortality death.

The second most common kind of diabetes mellitus worldwide, type 1 diabetes is characterized by an autoimmune cause, an absolute requirement for insulin, and a typically earlier start[4,6]. In type 1 diabetes, the condition is more critical and mostly brought on by auto-reactive T lymphocytes on islet beta cells and called an autoimmune attack. When clinical symptoms appear, they are usually severe and preceded by rapid metabolic decompensation. It is believed that 70–90% of the beta cell mass has been destroyed[7,8]. The progressive decrease of beta cell mass and function in diabetics is caused by a variety of reasons. The progressive loss of beta cell mass and function during the course of the disease exacerbates the continued deterioration of metabolic control, regardless of the underlying reasons and pathogenetic pathways. Network theory applied methodically to the metabolic and regulatory mechanisms beneath[9] . Because the genes linked to monogenic kinds of diabetes fit neatly into the current models of how biological networks may be predicted to function, faking glucose homeostasis may offer a useful way to prioritize genes for future research[10–13]. The goal of a relatively new field of research called "genetic epidemiology" is to elucidate the ways in which genetic and environmental factors combine to produce disease in populations. Studies have also been conducted on the genetic epidemiology of diabetes. Some of the genes that cause type 2 diabetes and its related comorbidities are HLA and INS, CTLA4, PTPN22, POSTN, and TCFL2[13,14]. The

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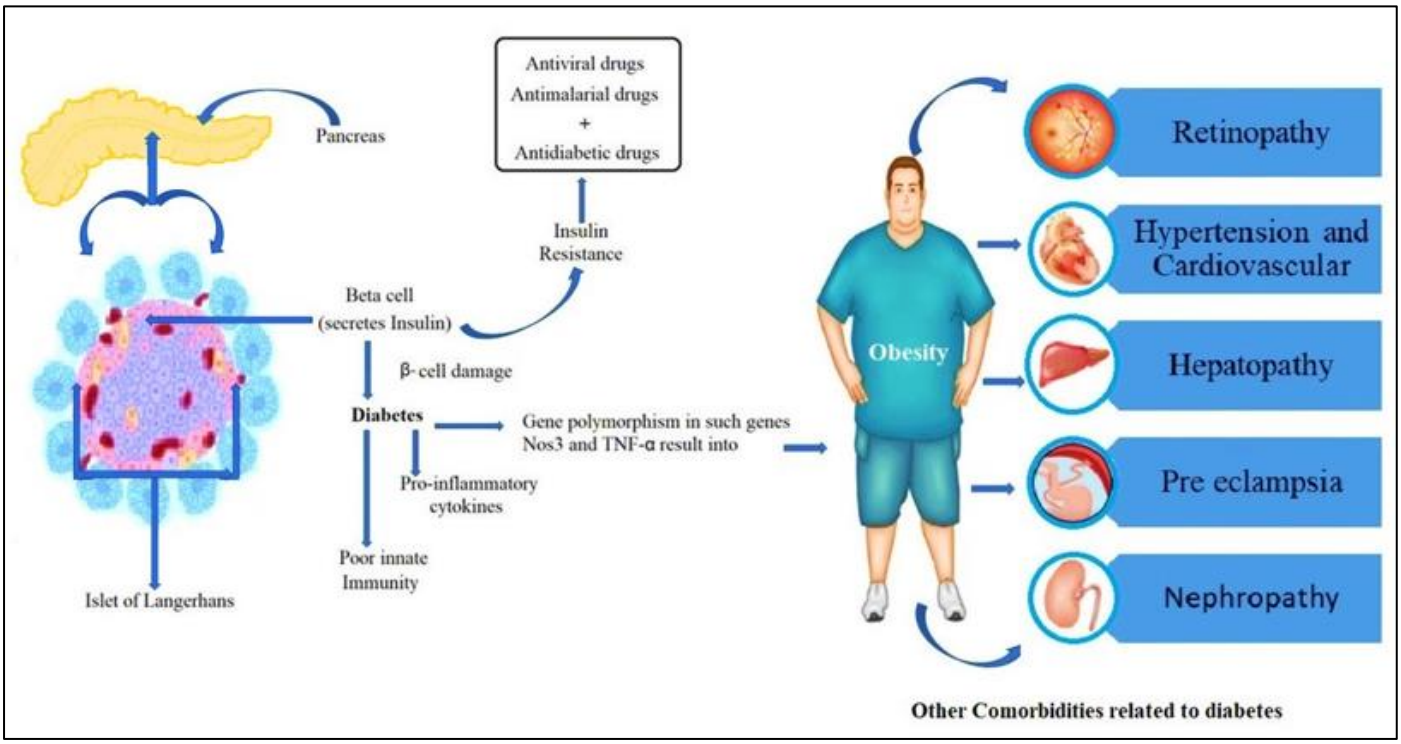
complications of both diabetes and hypertension share a lot of similarities. There are macrovascular and microvascular diseases among these problems such as heart failure, myocardial infection, coronary artery disease, stroke, peripheral vascular disease and retinopathy, nephropathy, and neuropathy [1,2].



II. GRAPHICAL ABSTRACT

➢ *Activation of the Beta Cell*

Beta cells present in the pancreas help in regulating glucose concentration in blood. Dysfunction and degradation in beta cells culminate in diabetes (Figure 1). The functioning of beta cells is influenced by different ways such as Hyperglycemia, lipotoxicity, autoimmunity, inflammation, adipokines, islet amyloid, and incretins. Changes in pancreatic beta cells' homeostasis affect the population dynamics and function of these cells because they are so sensitive to blood glucose levels [15]. Changes in lipoprotein profiles are frequently linked to diabetes [16].

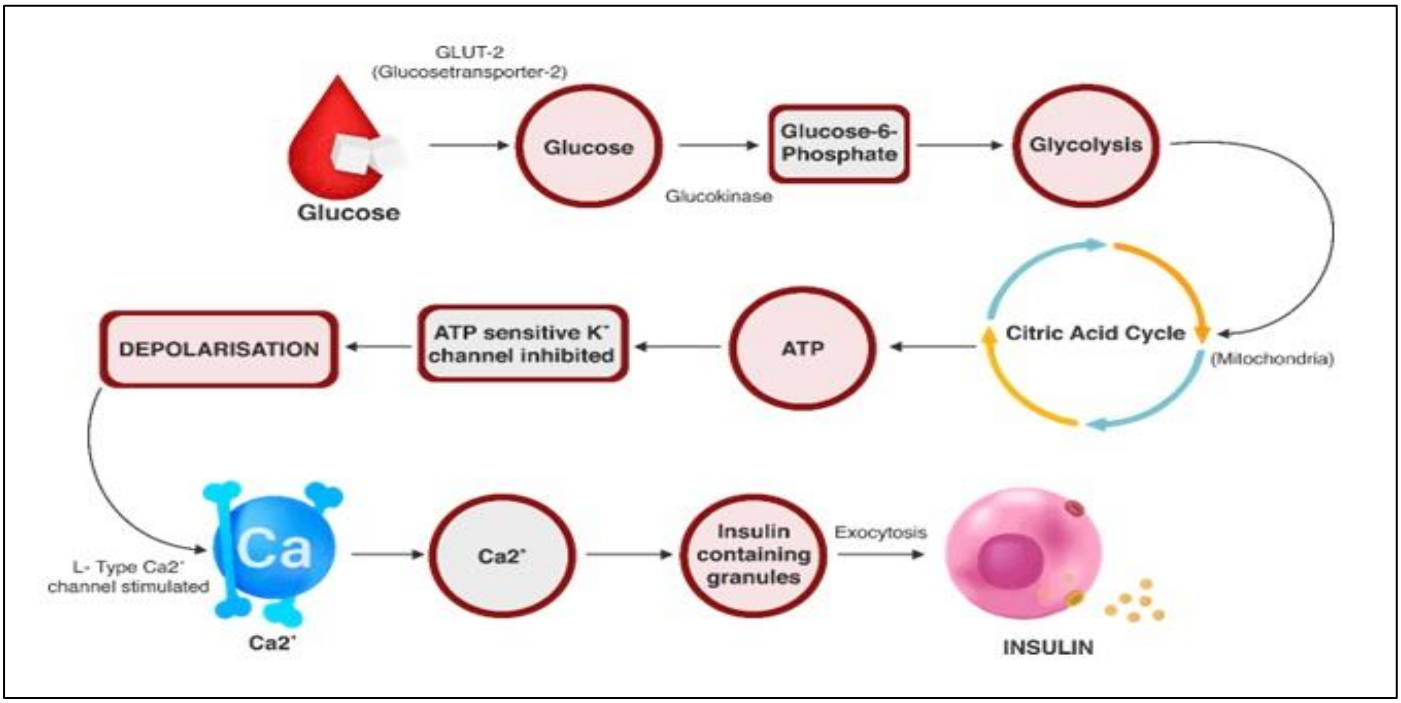


Fig 1 Process of Activation of the Beta Cell.

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In T1DM, autoimmune responses are involved. Insulin secretion and beta cell mass persistently decline as a result of autoimmune-mediated death of beta cells during the illness[17]. Many scholarly investigations have highlighted the way in which insulin resistance causes beta cells to proliferate in an attempt to compensate for insulin insufficiency, ultimately leading to beta cell malfunction and failure [18]. It is well established that incretin hormones enhance beta cell production and function [19,20]. Hypersecretion of islet amyloid in pancreatic islets has long been known to be a pathological feature of T2DM, and their connection to beta cell death has been extensively studied [21,22]. The "adipose-insular" axis is regulated by hormone-like peptides and proteins called adipokines. Certain adipokines, such as leptin, function as proinflammatory cytokines and impair beta cells [23,24].

➢ *Prevalence and Global Impact*

Diabetes and its related comorbidities are a foremost healthcare problem global and the major challenges faced by patients, healthcare systems, and national economies. The WHO projects that between 2000 and 2030, there will be a 37% increase in the world's population and a 114% increase in the number of diabetics. According to Asian predictions, China and India would have the highest rates of diabetes (49.4 and 42.3 million, respectively) by 2030. Estimates from 2003 showed that 314 million people worldwide had impaired glucose tolerance and 194 million adults had diabetes [25]. By 2007, this prevalence had risen to 60% and 75%, and by 2025, they are expected to reach 73% and 80%, respectively. It is estimated that 380 million people worldwide will suffer from diabetes in 2025. 85–95% of cases of type 2 diabetes occur in wealthier countries; in developing countries, this number is much higher [26, 27]. The results of the Diabetes Epidemiology Collaborative Analysis of Diagnosis Criteria in Asia (DECODA) study showed that the age-specific prevalence varied widely among Asian populations. Between the ages of 60 and 69, diabetes prevalence peaked in Indian populations, while between the ages of 70 and 89, it peaked in Chinese ones. In comparison to Chinese people, Indians have a higher age-specific prevalence and earlier onset of poor glucose control [28]. In India, it has been noted that young people have a significant prevalence of diabetes with mature onset [29,30]. Statistics from southern India demonstration that between 2000 and 2006, the occurrence of diabetes among people under the age of 44 increased from 25% to 35% [31,32]. The prevalent of obesity and young-onset diabetes has been exacerbated by quick changes in eating habits, decreased physical activity, changing leisure activity patterns, longer workdays, and shorter sleep lengths [33–35].

According to the latest edition of Atlas published in 2021 by IDF (International Diabetes Federation) 537 million worldwide population is diabetic and it is hypothetically increased to 643 million and 783 million in 2030 and 2045 (approx. 46%), previously in 2019, the projection was made to 700 million for 2045. The projection was made for the African continent where in the same timeline the projection is set to 134%.

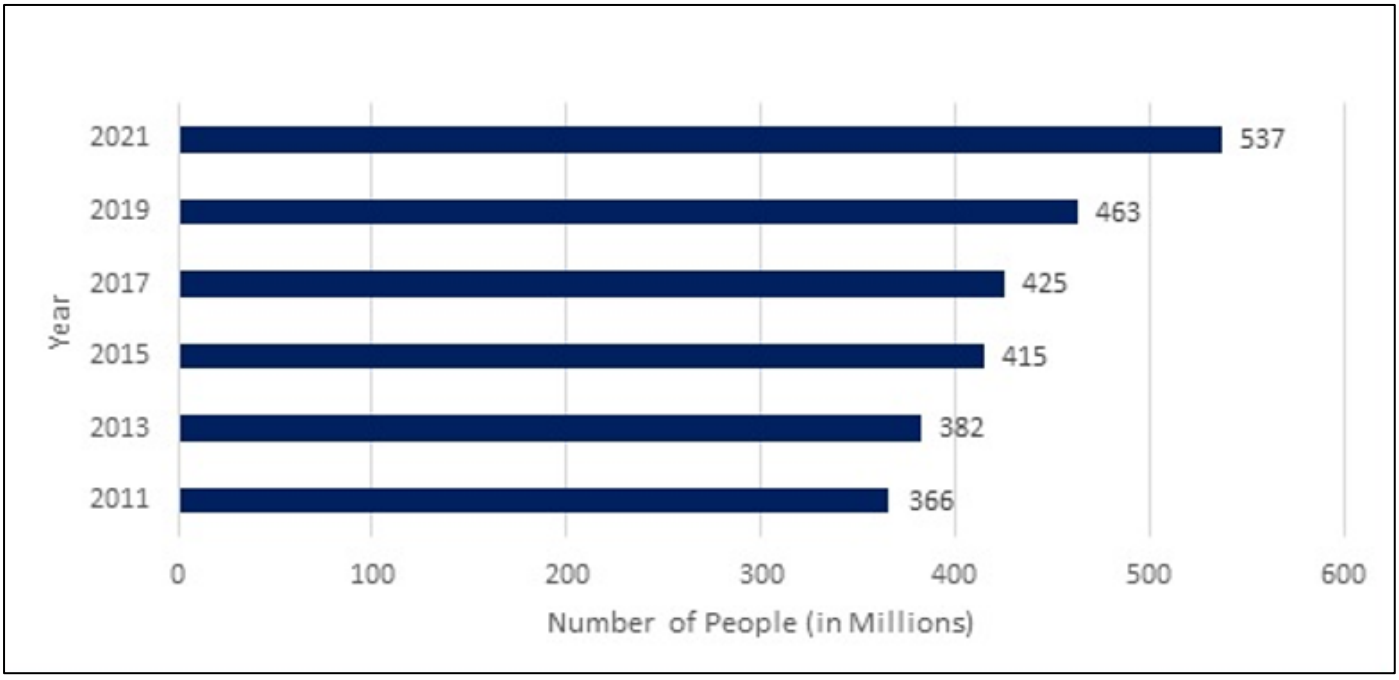

Fig 2 Number of People with Diabetes in Different years (2011-2021).

➢ *Prevalence of HIP (Hyperglycemia in Pregnancy)*

There have been 58 research overall on hyperglycemia in pregnancy (HIP), according to the IDF Atlas 2021. Estimates indicate that 16.7% of live births to women in 2021 entailed hyperglycemia in one form or another. The frequency of HIP as a percentage of all partum women increases dramatically with age, with the highest prevalence (42.3%) in women aged 45 to 49, despite the fact that few pregnancies occur in this age group. Figure 3 shows the age-wise prevalence of HIP. In addition, diabetes is more common in non-pregnant women in this age group. Because younger women had higher rates of reproduction, women under 30 accounted for less than half (46.3%) of all HIP cases (9.8 million).

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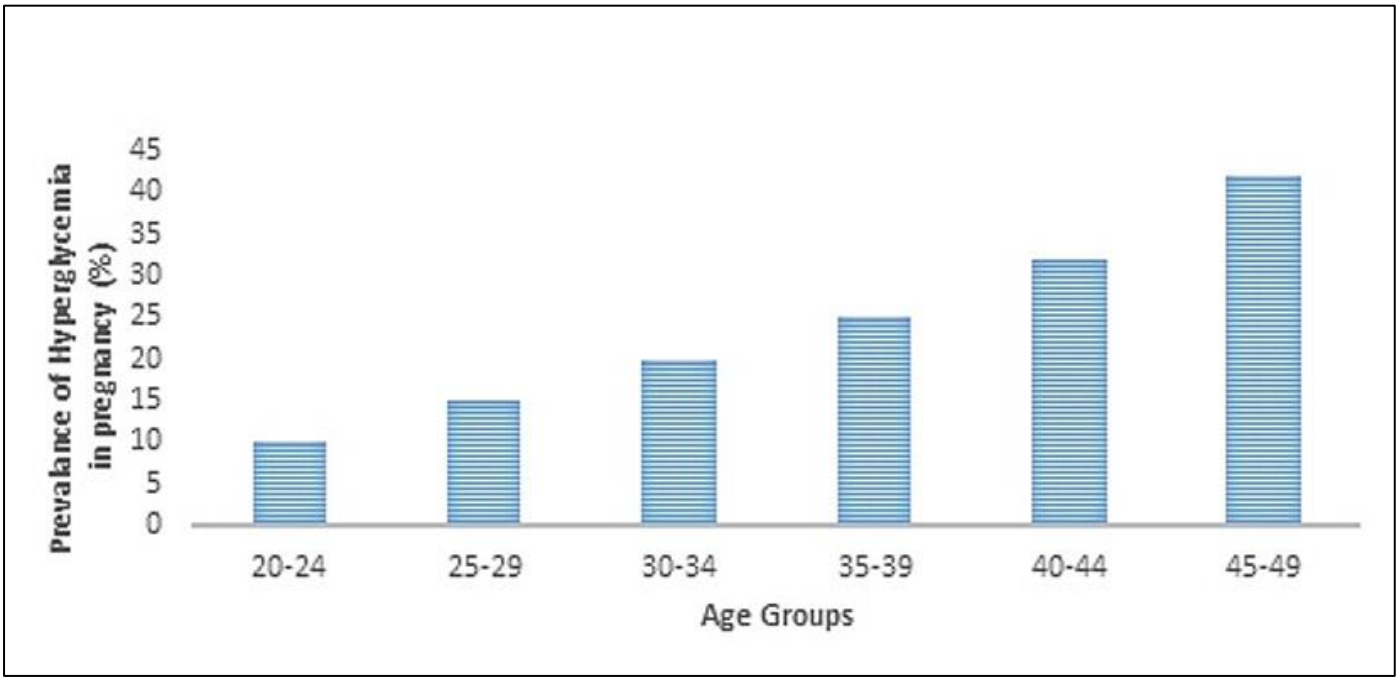

Fig 3 Prevalence of HIP in Different Ages.

➢ *Diabetes-Related Mortality (Excluding Pandemic)*

Globally, diabetes is the leading cause of death. Without the mortality risks associated with the COVID-19 pandemic, (6.7) million adults between the ages of 20 and 79 are expected to pass away in 2021 from diabetes or its consequences, according to the data in IDF Atlas 2021. This is the equivalent to 12.2% of all deaths in this age group worldwide due to all causes. As seen in Figure 4, persons under 60 who are employed account for more than a third (32.6%) of all diabetes-related deaths. This is the equivalent of 11.8% of all deaths globally among those under the age of sixty.

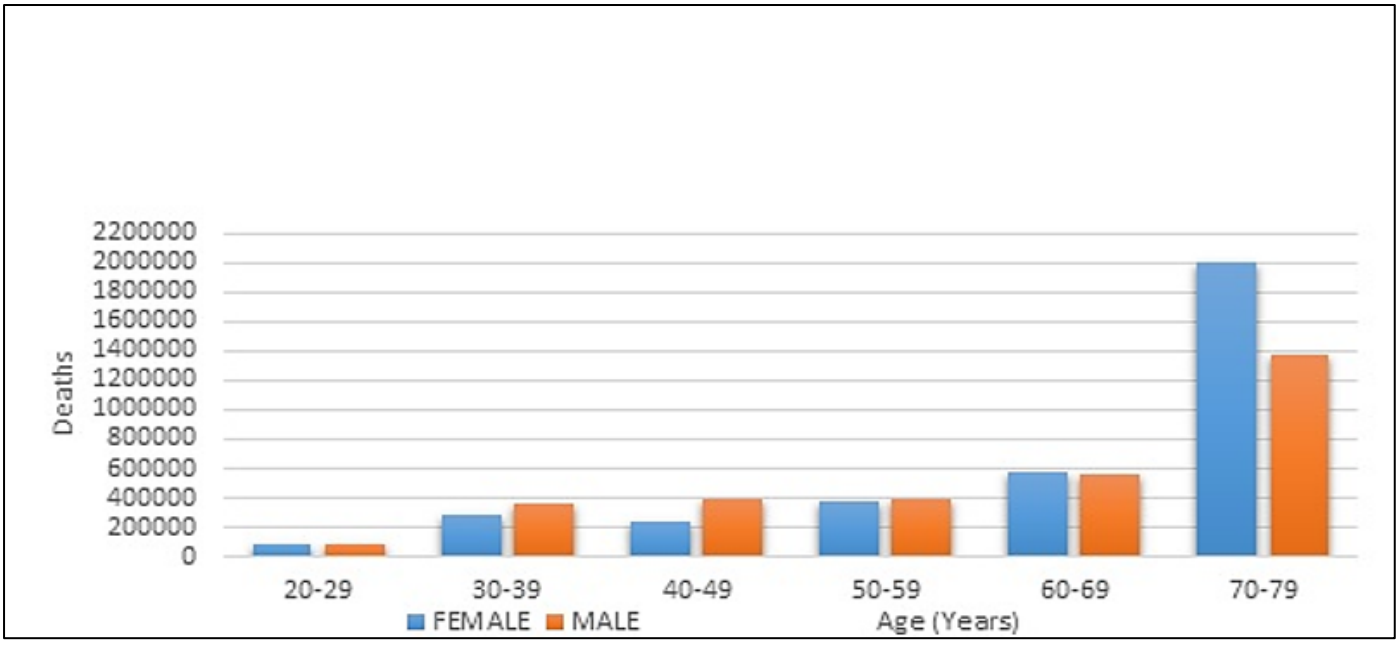

Fig 4 Diabetes-Related Mortality.

➢ *Economic Impact of Diabetic*

Diabetes significantly increases the cost of healthcare for entire countries, as well as for those who have the disease and their families. The term "Direct Cost" refers to all medical expenses related to diabetes, whether they are paid for out of pocket to people who suffer from diabetes or by private, public, or governmental payers. According to the International Diabetes Federation Diabetes Atlas, since its third edition in 2006, the health costs associated with diabetes have climbed from USD 232 billion (2007) to 966 billion (2021) for a person aged 20 to 79. Over the past 15 years, this has increased by 316%. The estimates of health expenditure related to diabetes up to 2045 as per the analysis done by IDF are given in Figure 5.

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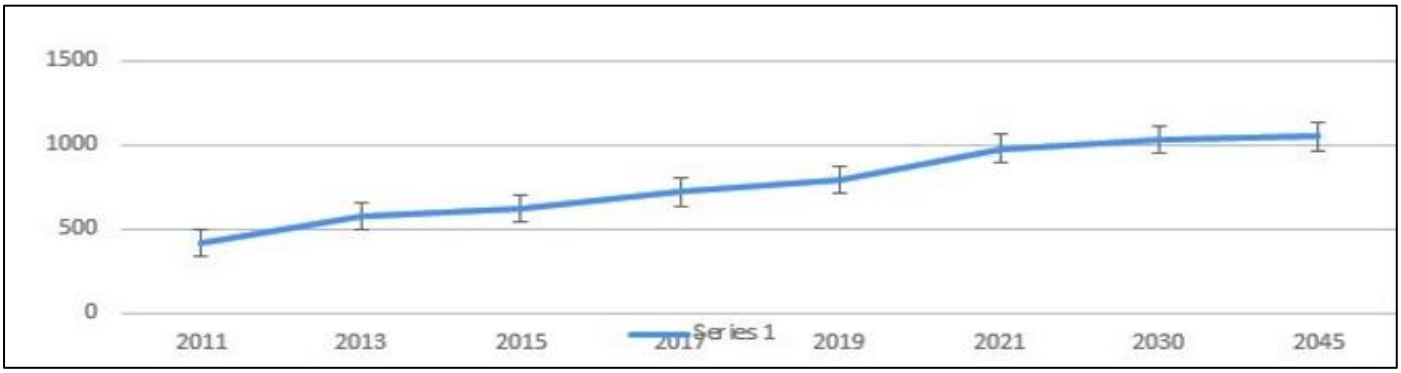

Fig 5 Total Diabetes-Related Health Expenditure for Adults (20–79 years) with Diabetes from 2011 to 2045.

➢ *Genetic Epidemiology and Polymorphism*

Positional cloning, linkage mapping, and candidate gene studies have advanced most rapidly in the types of diabetes with the simplest genetic models. Early research describing diabetes caused by mutations in the mitochondrial genome (World Health Organization, 2021), insulin (INS), and insulin receptor [36], genes offered crucial insights into glucose homeostasis. The balance between insulin action and production, which is controlled by cell mass and/or function, is known as glucose homeostasis. The most susceptible genes/proteins to deteriorating the system are those found at hubs that are most densely interconnected. Therefore, it may be more likely that genetic diversity at hub genes will result in observable changes in glucose homeostasis [37]. T1D stands out in comparison to other complex illnesses because of the extent of ancestral threat connected to a sole locus, the HLA (Human Leukocyte antigen). Even though there is compelling evidence linking some other autoimmune illnesses to the HLA region [38].HLA was first identified as a potential gene through association studies, and the evidence for a linkage at HLA in T1D is stronger than that reported for a linkage in any other complex disorder [38]. ..A region known as PTPN22 (Protein Tyrosine Phosphate Non-Receptor Type 22) has recently been connected to a putative T1D gene 39, 40. Additionally, T1 diabetes mellitus and cytotoxic T-lymphocyte associated protein-4 (CTLA-4) may be connected[41]. Some genes are affected and result in T2DM such as ABCC8 (ATP-binding cassette, subfamily C; sulfonylurea receptor), which is responsible for the regulation of potassium channels and insulin release), Calpain 10 is a protease and glucagon receptor that regulates hepatic glucose production and insulin secretion, Glucokinase aids in the metabolism of glucose, KCNJ11 (Potassium inwardly-rectifying channel, subfamily J, member 11), which regulates the secretion of insulin, PPARG (Peroxisome proliferator-activated receptor γ) and HN4FA (Hepatocyte nuclear factor 4 α) are transcription factors, SLC2A1 (Glut 1) which a glucose transporter [13]. POSTN and TCFL2 genes are responsible for T2DM and its associated comorbidities like obesity, heart diseases, asthma, cancer, and hypertension. OSF-2 (Osteoblst-specific factor) is a protein that facilitates the adhesion and migration of epithelial cells with the help of alpha-V/beta-3 and 5 integrins ligands [14]. TCFL2 (Transcription factor 7 like 2) is a protein acting as a transcription factor encoded by the TCFL2 gene located on chromosome 10q25.2-q25.3, which comprises 19 exons. TCF7L2 is an associate of the TCF family and has an impact on several biological pathways, including the Wnt signaling pathway, by forming a bipartite transcription factor [42]. The genes and gene functions related to diabetes are shown in Table 1.

Table 1 Diabetes Gene and its Functions.

Gene	Gene name	Gene Function	Type of Diabetes
HLA	Human leukocyte Antigen	Immune System Regulation	T1D
INS	Insulin	Involved in numerous aspects of metabolism	T1D
CTLA44	Cytotoxic- T-lymphocyte associated protein 4	Immune System Regulation	T1D
PTPN22	Protein Tyrosine Phosphate, non-receptor Type 22	Immune System Regulation	T1D
ABCC8	ATP Binding Cassette subfamily C, sulfonylurea receptor	Regulation of potassium channels and insulin release	T2D
CAPN10	Calpain 10	Protease	T2D
GCGR	Glucagon Receptor	Control hepatic glucose production and insulin secretion	T2D
GCK	Glucokinase	Glucose metabolism	T2D
KCNJ11	Potassium inwardly rectifying channel subfamily J, member 11	Regulation of insulin secretion	T2D
PPARG	Peroxisome proliferator-activated receptor- γ	Transcription Factor	T2D
HNF4FA	Hepatocyte Nuclear Factor 4α	Transcription Factor	T2D
SLC2A1	Glut 1	Glucose transporter	T2D

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➢ *Comorbidities Associated with Diabetes Mellitus*

Individuals diagnosed with diabetes mellitus are at a significant risk for a number of related problems and comorbidities, which can be brought on by particular drugs, environmental conditions, or hereditary factors. Hypoglycemia, pancreatitis, liver disease, cardiovascular disease, congestive heart failure, chronic kidney disease, genital mycotic infections, neuropathy, retinopathy, urinary tract infections, hyperlipidemia, and overweight/obesity are among the common comorbidities that are common in the T2DM patient population[43]. Cardio-vascular diseases and diabetes generally act as comorbidities in some patients. Certain macrovascular and microvascular complications result from T1DM. Genes are also altered or affected to cause various comorbidities along with diabetes such as POSTN and TCF7L2 [13,42].

The most prevalent co-occurring diseases, according to Merck and Co. researchers, were hypertension, obesity or overweight, hyperlipidemia, chronic renal disease, and cardiovascular disease. Researchers found that hypertension and hyperlipidemia were the most common comorbid co-conditions. These were followed by overweight or obesity and hypertension, overweight or obesity and hyperlipidemia, hypertension and chronic kidney disease (CKD), hyperlipidemia and cardiovascular disease (CVD), and overweight or obesity and CVD.. The data from the research is shown in Figure 6.

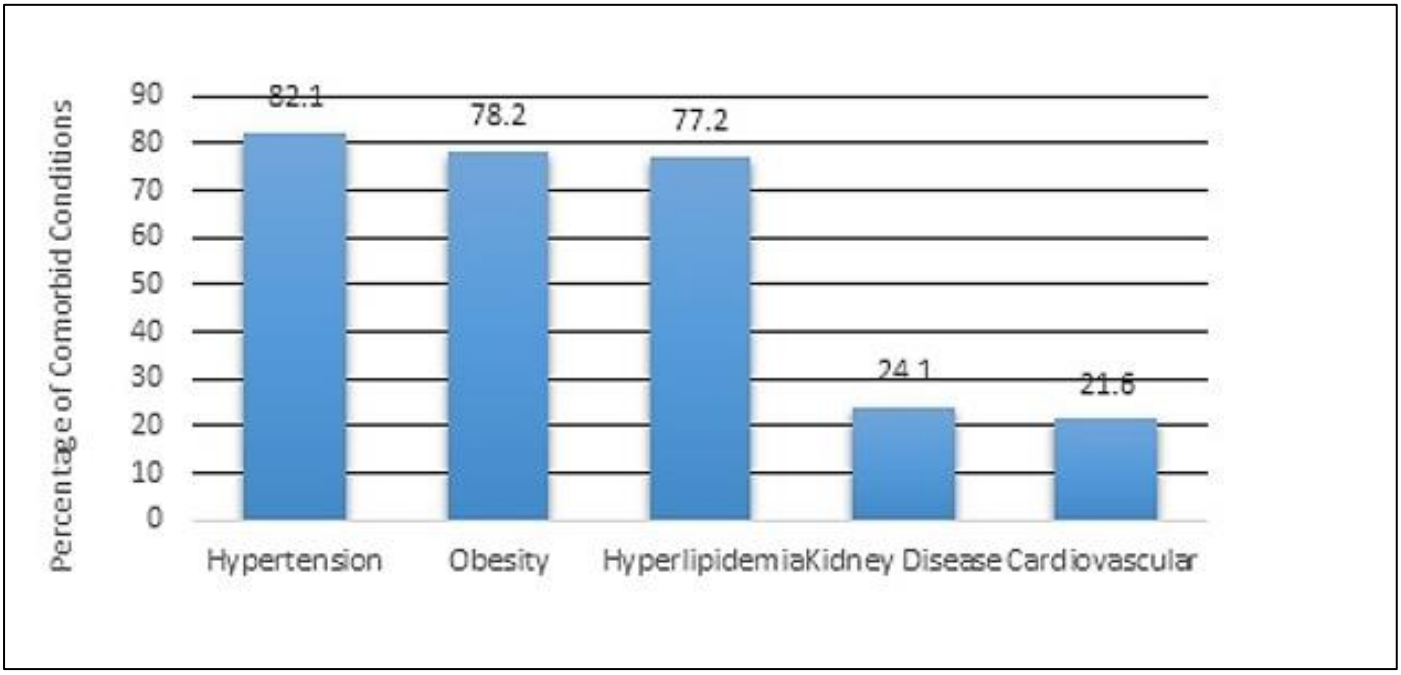

Fig 6 Comorbid Conditions in Diabetic Patients.

➢ *Microvascular Complications*

Microvascular complications are nephropathy, retinopathy, and neuropathy are shown in Figure 7. Each year, around (12,000 - 24,000) new cases of eye-related problems follow like loss of vision caused by diabetic retinopathy [44]. Within five years of diagnosis, diabetic retinopathy had manifested in 14% of type 1 and 33% of type 2 diabetes patients in the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) [45]. Diabetes-related tissue damage has been linked to anomalies in the hexosamine, polyol, and protein kinase C pathways that are brought on by hyperglycemia [46–48]. Up to 40% of diabetic patients develop diabetic nephropathy, and hypertension increases the risk of this microvascular disease [49,50]. On a histopathologic level, diabetic nephropathy is distinct from other causes of renal disease. The mesangial matrix first rises, then the glomerular basement membrane, which in some cases may proceed to more severe diffuse or nodular glomerulosclerosis [50]. Foot amputation is mostly caused by diabetic peripheral neuropathy, which affects about 70% of people with diabetes[44]. Peripheral neuropathy's pathogenesis is unknown, however it is believed to be related to inflammation, decreased blood flow, and nerve demyelination. It is also recognized that oxidative stress, lipid abnormalities, elevated polyol flux, and advanced glycosylation end products are metabolic abnormalities caused by chronic hyperglycemia that might result in peripheral neuropathy. Since exposure to hyperglycemia appears to be the most significant risk covariate, strict glycemic management is recommended to stabilize and occasionally improve symptoms[48]. Some of the findings suggested that several genetic factors/ candidate genes are responsible for enhancing the risk of diabetes nephropathy complications - Adiponectin, IGF-1, IGF-binding protein 1, TGF-β receptor, Collagen type, Laminin, Tissue inhibitor of metalloproteinase, Carnosinase, Neuropilin 1, Aquaporin 1.61.

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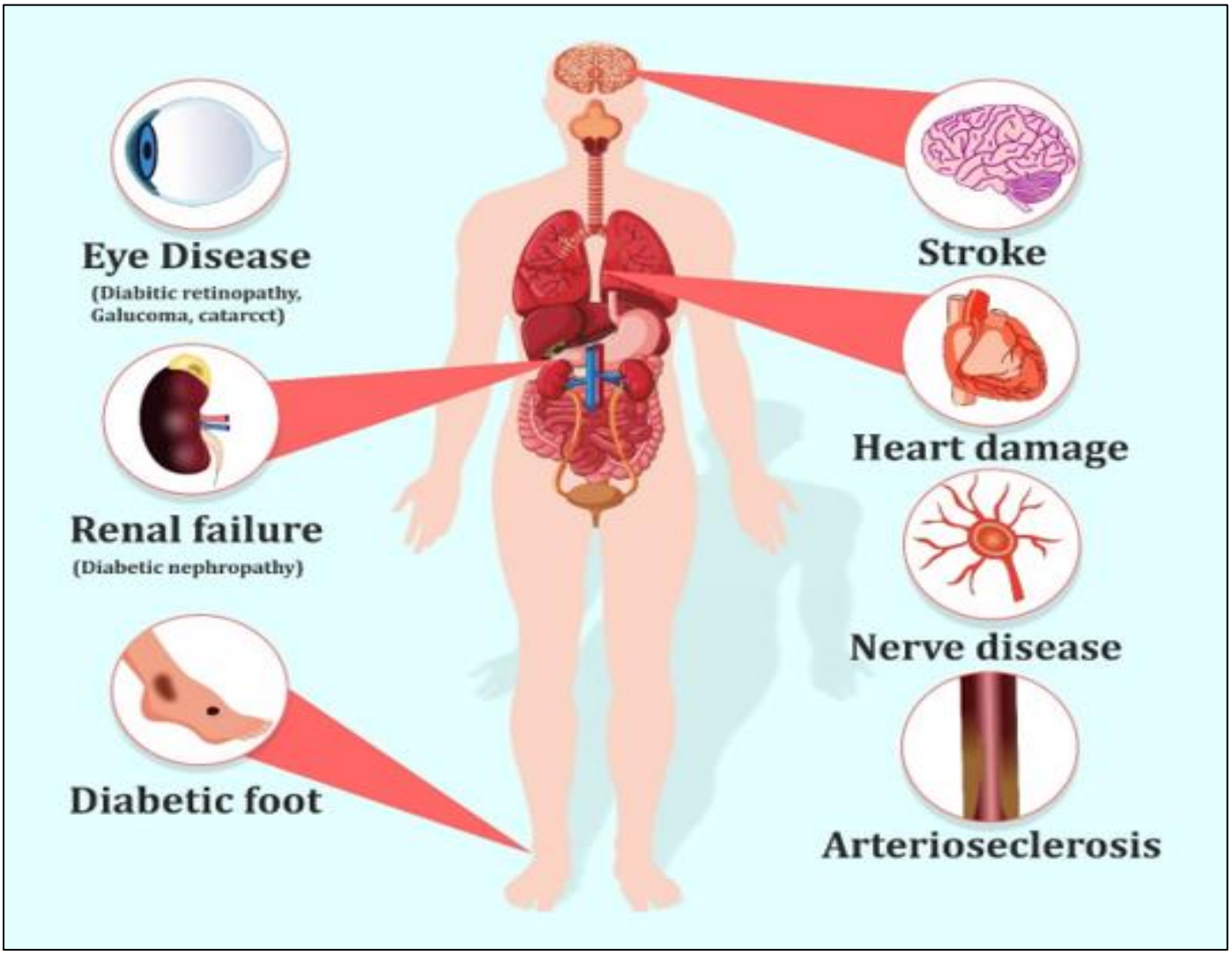

Fig 7 Complications of Diabetes.

➢ *Macrovascular Complications*

Diabetes raises a person's risk of CVD and stroke by two to four times [44] as compared to non-diabetics. The Multiple Risk Factor Intervention Trial (MRFIT) found that even after accounting for age and other CVD risk factors like smoking, hypertension, and hypercholesterolemia, patients with diabetes still had a higher likelihood of having a CVD. Cardiovascular disease (CVD) is much more common in people with type 1 and type 2 diabetes, and the risk is increased when additional risk factors are present[49].

➢ *Covid 19, Rehabilitation and Diabetes*

The World Health Organization (WHO) declared the (COVID-19) pandemic SARS-CoV-2 a global health emergency in March 2020. The pandemic has had a severe detrimental influence on healthcare systems, the global economy, and our way of life. Acute respiratory distress syndrome (ARDS), COVID-19 pneumonia, and respiratory failure are among the catastrophic consequences of COVID-19 infection that preliminary research suggested were more likely in people with diabetes. These exploratory investigations demonstrated that, as compared to individuals without diabetes, those with diabetes required more mechanical ventilation, hospitalization, and other life-sustaining procedures. Furthermore, likened to nations with a inferior incidence of diabetes, those with a high pervasiveness of diabetes recounted higher numbers of COVID-19 infections and fatalities. During the pandemic, hospitalization rates for COVID-19-positive diabetic patients were 1.7 times higher than for non-diabetic patients. According to IDF Atlas 2021, the risk of death for diabetics hospitalized with COVID-19 is estimated to be 2.3 times higher than for non-diabetics admitted to the same hospital or healthcare system. It is expected that if diabetes becomes more common, there will be a greater need for rehabilitation treatments to mitigate any negative effects the illness may have [3]. A thorough, lifelong treatment plan is necessary for diabetes management in order to meet predetermined objectives. Achieving glycemic control, enhancing quality of life, averting or delaying complications, and educating patients about their illness are the primary objectives of diabetes rehabilitation. It is well recognized that physical activity lowers intra-abdominal fat, a known risk factor for insulin resistance, improves insulin sensitivity to high blood glucose, and prevents cardiovascular problems. This is because more blood flowing to the muscles causes the muscles' cells to absorb more glucose [1,2].

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III. CONCLUSION

Diabetes has become a critical disease entirely with no known treatment or permanent cure. Numerous investigations and research projects are being conducted to combat this terrible disease. Most of the scientists' research on this topic is encouraged. It's important to comprehend the main causes of diabetes, which include hereditary and environmental factors. Understanding how genes differ and how particular genetic factors raise the likelihood of comorbidities during diabetes can help develop effective treatments for the management of the disease. A multimodal approach that includes early diabetes diagnosis, screening for complications, optimal psychiatric treatment at all levels of care for individuals with diabetes, primary diabetes prevention in those with prediabetes, and increased need for rehabilitation therapy to reduce any issues the condition may cause is needed to combat the diabetes epidemic and its associated complications.

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➢ *Conflict of Interest*

The authors declare that they have no conflict of interest in the publication.

REFERENCES

[1]. Chen L, Magliano DJ, Zimmet PZ. The worldwide epidemiology of type 2 diabetes mellitus--present and future perspectives. Nat Rev Endocrinol [Internet]. 2011;8:228–36. Available from: http://dx.doi.org/10.1038/nrendo.2011.183

[2]. Sun H, Saeedi P, Karuranga S, Pinkepank M, Ogurtsova K, Duncan BB, et al. IDF DIABETES ATLAS : Global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045. Epub. Diabetes Res Clin Pract. ; 2022.

[3]. Zimmet PZ, Magliano DJ, Herman WH, Shaw JE. Diabetes : a 21st century challenge. Lancet Diabetes Endocrinol [Internet]. 2014;2:56–64. Available from: http://dx.doi.org/10.1016/S2213-8587(13)70112-8

[4]. Bell GI, Polonsky KS. Diabetes mellitus and genetically programmed defects in beta-cell function. Nature. 2001;414:788–91.

[5]. Desisto CL, Kim SY, Sharma AJ. Prevalence Estimates o Gestational Diabetes Mellitus in the United States, Pregnancy Risk Assessment Monitoring System (PRAMS), 2007-2010. Prev Chronic Dis. 2014;11:1–9.

[6]. Hirschhorn JN. Genetic epidemiology of type 1 diabetes. Pediatr Diabetes. 2003;4:87–100.

[7]. Cernea S, Dobreanu M. Diabetes and beta cell function: from mechanisms to evaluation and clinical implications. Biochemia Medica (Zagreb). 2013;23:266–81.

[8]. Weir GC, Laybutt DR, Kaneto H, Bonner-Weir S, Sharma A. Beta-cell adaptation and decompensation during the progression of diabetes. Diabetes. 2001;50:S154-159.

[9]. Gepts W. Pathologic anatomy of the pancreas in juvenile diabetes mellitus. Diabetes. 1965;14:619–33.

[10]. Almaas E, Kovács B, Vicsek T, Oltvai ZN, Barabasi AL. Global organization of metabolic fluxes in the bacterium Escherichia coli. Barabasi, A L. 2004;427:839–43.

[11]. Barabási A lászló, Oltvai ZN. Network biology: understanding the cell's functional organization. Nat Rev Genet. 2004;5:101–13.

[12]. Jeong H, Tombor B, Albert R, Oltvai ZN, Barabási AL. The large-scale organization of metabolic networks. Nature. 2000;407:651–4.

[13]. Permutt MA. Genetic epidemiology of diabetes. Journal of Clinical Investigation. 2005;115:1431–9.

[14]. Gillan L, Matei D, Fishman DA, Gerbin CS, Karlan BY, Chang DD. Periostin secreted by epithelial ovarian carcinoma is a ligand for alpha(V)beta(3) and alpha(V)beta(5) integrins and promotes cell motility. Cancer Res. 2002;62:5358–64.

[15]. Robertson RP, Harmon J, Tran PO, Poitout V. Beta-cell glucose toxicity, lipotoxicity, and chronic oxidative stress in type 2 diabetes. Diabetes. 2004;53:S119-124.

[16]. Wajchenberg BL. beta-cell failure in diabetes and preservation by clinical treatment. Endocr Rev. 2007;28:187–218.

[17]. Sherry NA, Tsai EB, Herold KC. Natural history of beta-cell function in type 1 diabetes. Diabetes. 2005;54:S32-39.

[18]. Defronzo RA. From the triumvirate to the ominous octet: a new paradigm for the treatment of type 2 diabetes mellitus. Diabetes (Banting Lecture). 2009;58:773–95.

[19]. Cernea S, Raz I. Therapy in the early stage: incretins. Diabetes Care. 2011;34:S264-271.

[20]. Vilsbøll T. The effects of glucagon-like peptide-1 on the beta cell. Diabetes Obes Metab. 2009;3:11–8.

[21]. Hull RL, Westermark GT, Westermark PER, Kahn SE. Islet Amyloid : A Critical Entity in the Pathogenesis of Type 2 Diabetes. Journal of Clinical Endocrinol and Metabolism. 2004;89:3629–43.

[22]. Westermark P, Andersson A, Westermark GT. Islet amyloid polypeptide, islet amyloid, and diabetes mellitus. Physiol Rev. 2011;91:795–826.

[23]. Dunmore SJ, Brown JEP. The role of adipokines in β-cell failure of type 2 diabetes. Journal of Endocrinology. 2013;216:T37-45.

[24]. Kahn SE. The relative contributions of insulin resistance and beta-cell dysfunction to the pathophysiology of Type 2 diabetes. Diabetologia. 2003;46:3–19.

[25]. World Health Organization. GLOBAL REPORT ON DIABETES. 2021.

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/IJISRT24SEP726

[26]. Sicree R, Shaw J, Zimmet P. Prevalence and projections. In: Diabetes Atlas. In: International Diabetes Federation (3rd Edition). 3rd ed. Brussels, Belgium.: International Diabetes Federation; 2006. p. 16–104.
[27]. 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.
[28]. Qiao Q, Hu G, Tuomilehto J, Nakagami T, Balkau B, Borch-Johnsen K, et al. Age- and sex-specific prevalence of diabetes and impaired glucose regulation in 11 Asian cohorts. Diabetes Care . 2003;26:1770–80.
[29]. Mohan V, Ramachandran A, Snehalatha C, Mohan R, Bharani WG, Viswanathan M. High prevalence of maturity-onset diabetes of the young (MODY) among Indians. Diabetes Care. 1985;8:371–4.
[30]. Popkin BM. Global nutrition dynamics : the world is shifting rapidly toward a diet linked with noncommunicable diseases. American Journal of Clinical Nutrition. 2006;84:289–98.
[31]. 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.
[32]. Ramachandran A, Ching R, Ma W, Snehalatha C. Diabetes in Asia. The Lancet [Internet]. 2012;375:408–18. Available from: http://dx.doi.org/10.1016/S0140-6736(09)60937-5
[33]. Cockram CS. The epidemiology of diabetes mellitus in the Asia-Pacific region. Hong Kong Medical Journal. 2000;6:43–52.
[34]. Yoon K ho, Lee J hee, Kim J won, Cho JH, Choi Y hee, Ko S hyun, et al. Epidemic obesity and type 2 diabetes in Asia. Lancet. 2006;368:1681–8.
[35]. Zhai F, Wang H, Wang Z, Popkin BM, Chen C. Closing the energy gap to prevent weight gain in China. Obesity Reviews. 2008;9:107–12.
[36]. Ota A, Ulrih NP. An Overview of Herbal Products and Secondary Metabolites Used for Management of Type Two Diabetes. Front Pharmacol. 2017;8:1–14.
[37]. AMERICAN DIABETES ASSOCIATION. Diagnosis and Classification of Diabetes Mellitus. Diabetes Care [Internet]. 2010 [cited 2022 Dec 22];33:S62-69. Available from: care.diabetesjournals. org
[38]. Pereira Rolim LCDS, Sá JR de, Chacra AR, Dib SA. Clinical Update Diabetic Cardiovascular Autonomic Neuropathy : Risk Factors , Clinical Impact and Early Diagnosis. 2007;23–31.
[39]. Mogensen CE. Microalbuminuria predicts clinical proteinuria and early mortality in maturity-onset diabetes. N Engl J Med. 1984;310:356–60.
[40]. Vinik AI, Ziegler D. Diabetic cardiovascular autonomic neuropathy. Circulation. 2007;115:387–97.
[41]. Prince CT, Secrest AM, Mackey RH, Arena VC, Kingsley LA, Orchard TJ. Cardiovascular autonomic neuropathy, HDL cholesterol, and smoking correlate with arterial stiffness markers determined 18 years later in type 1 diabetes. Diabetes Care. 2010;33:652–7.
[42]. Viberti GC, Hill RD, Jarrett RJ, Argyropoulos A, Mahmud U, Keen H. Microalbuminuria as a predictor of clinical nephropathy in insulin-dependent diabetes mellitus. Lancet. 1982;1:1430–2.
[43]. Mogensen CE, Christensen CK. Predicting diabetic nephropathy in insulin-dependent patients. N Engl J Med. 1984;311:89–93.
[44]. Chaturvedi N, Bandinelli S, Mangili R, Penno G, Rottiers RE, Fuller JH. Microalbuminuria in type 1 diabetes: rates, risk factors and glycemic threshold. Kidney Int. 2001;60:219–27.
[45]. Hovind P, Tarnow L, Rossing P, Jensen BR, Graae M, Torp I, et al. Predictors for the development of microalbuminuria and macroalbuminuria in patients with type 1 diabetes: inception cohort study. British Medical Journal (BMJ). 2004;328:1105.
[46]. Craig KJ, Donovan K, Munnery M, Owens DR, Williams JD, Phillips AO. Identification and management of diabetic nephropathy in the diabetes clinic. Diabetes Care. 2003;26:1806–11.
[47]. Dejong RN. The nervous system complications of diabetes mellitus, with special reference to cerebrovascular changes. J Nerv Ment Dis. 1950;111:181–206.
[48]. Young BA, Maynard C, Boyko EJ. Racial differences in diabetic nephropathy, cardiovascular disease, and mortality in a national population of veterans. Diabetes Care. 2003;26:2392–9.
[49]. Adler AI, Stevens RJ, Manley SE, Bilous RW, Cull CA, Holman RR, et al. Development and progression of nephropathy in type 2 diabetes: the United Kingdom Prospective Diabetes Study (UKPDS 64). Kidney Int. 2003;63:225–32.
[50]. Andersen AR, Sandahl Christiansen J, Andersen JK, Kreiner S, Deckert T. Diabetic Nephropathy in Type 1 (Insulin-Dependent) Diabetes: An Epidemiological Study. Diabetologia. 1983;25:496–501.
[51]. Wong TY, Shankar A, Klein R, Klein BEK. Retinal vessel diameters and the incidence of gross proteinuria and renal insufficiency in people with type 1 diabetes. Diabetes. 2004;53:179–84.
[52]. Ewing F, Deary IJ, Strachan MW, Frier BM. Seeing beyond retinopathy in diabetes: electrophysiological and psychophysical abnormalities and alterations in vision. Endocr Rev. 1998;19:462–76.