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Review

A concise review of the technical and medical implications of type 2 diabetes mellitus

Jayakrishnan Balakrishnapillai [1, 2] *

[1] Educare Institute of Dental Science, Malappuram, Kerala, India
[2] SafeCare Clinics, Tirur, Kerala, India

* Correspondence to: Jayakrishnan Balakrishnapillai, Educare Institute of Dental Science, Road Kiliyamannil Campus, Chattiparamba-Kootlangadi Rd, Malappuram, Kerala 676504, India. E-mail: jaykdr@gmail.com

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Abstract

Diabetes mellitus (DM) is considered a burdensome global disease, and decades of constant research demonstrate that the severity of this disease continues to affect people disproportionately. This review investigated the information about this disease characterization that increases blood glucose levels, leading to high mortality and morbidity. This review is motivated by the above-described factors. It presents various technical information such as animal models, digital diabetes, treatment methods, and diabetes management during the COVID-19 pandemic from recent research on DM. This article also emphasizes that more research should be considered in the retardation of disease progression by appropriate detection of targeted medications. Furthermore, most recently, the coronavirus pandemic emphasized unequal vulnerabilities among certain diabetic groups, making the intractable nature of the disease more severe. Hence, fortified research has to be adopted urgently to effectively prevent, monitor, and treat diabetes and its complications. Chronic disease increases medical expenses and disease-related deaths and reduces the quality of life. In particular, type 2 diabetes mellitus needs an in-depth understanding of optimized diagnosis and treatment methods, thereby reducing the burden on medical experts and patients.

Keywords: type 2 diabetes, COVID-19, biomarker, diagnosis, diabetes treatment.

Introduction

Diabetes mellitus is broadly recognized as a chronic disease that cumulatively impacts almost all countries, every age group, and the world economy. The disease is characterized by a heterogeneous group of metabolic disorders with severe complications associated with significant mortality and morbidity. The International Diabetes Federation approximately stated that the count of diabetes patients is expected to reach more than 640 million by 2040 [1]. Furthermore, it has also been estimated that most diabetes patients were observed to be unaware of their disease, which leads to the rapid development of diabetic complications. Diabetes management during the final stage is highly complex in terms of time and cost affordability [2]. However, without proper management, a large loss of life exists that necessitates experts in medicine, digital science, nutrition etc., to rule out the increasing chronic condition [3]. The present review article has been motivated by this urgent requirement and attempted to collect possible information regarding the trending diabetes research worldwide.

Figure 1 states that beta-cell dysfunction associated with insulin resistance may occur due to various environmental and genetic factors. At first, the beta cell compensates by raising the level of insulin release, but consequently, this process does not work effectively, followed by a decrease in the beta-cell mass. This reduction leads to an increase in glucose levels.

Hyperglycaemia is a condition associated with diabetes and is caused due to the absolute lack of insulin. Type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM) are the two major types of diabetes in which T1DM is caused because of the autoimmune destruction of the pancreatic β cells that produce insulin,

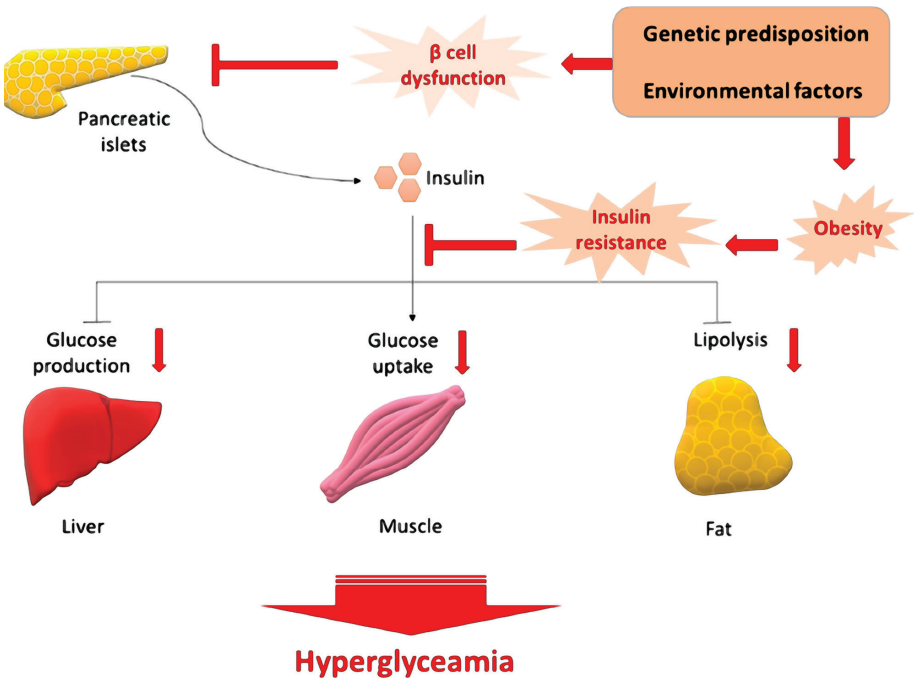

Figure 1: Pathophysiology of T2DM.

and T2DM develops when there is insulin resistance associated with less production of insulin by pancreatic beta cells. T2DM has been modeled in both obese and non-obese animal models with varied conditions of beta-cell failure and insulin resistance [4]. The complications of diabetes are observed to be common among both types, but researchers found significant mortality and morbidity differences between the types. Accordingly, the chronic complications of T2DM disease are broadly classified as macrovascular and microvascular, in which the latter complications are more prevalent.

Retinopathy, neuropathy, and nephropathy were the complications associated with microvascular complications, and consequently, PAD, stroke, and cardiovascular disease were correlated with macrovascular complications. Following this, diabetic foot syndrome and dental disease are also associated with the prevalence of T2DM.

Need for the study

Gaining technical information related to clinical research on diabetes will certainly help to change the future negative impacts of the disease. Generally, clinical trials enable researchers to perform a careful evaluation of the medications before acquiring FDA approval and releasing the drugs to the public. These trials can be utilized for monitoring blood glucose levels, tracking the body's metabolism, and supervising the subsequent functionality of the organ in accordance with the incorporated medications.

These collected data were employed to organize their unique drug formulas, thereby improving the effectiveness of diabetic treatment. Hence, the presented review article poured more effort into collecting and summarizing the recent trends in diabetes research. Furthermore, the study also determined the absorption, breakdown, and removal of the drug from the body in T2DM patients. It is known that working toward an organized and comprehensive diabetes treatment would certainly enable medical experts to improve the lifestyles of diabetic patients. Hence, the study focused on conducting a brief survey of the existing diabetes research.

Research on animal model for type 2 diabetes mellitus

The development of T2DM has been highly influenced by several environmental factors, and hence, a relevant animal model for replicating disease development may be considered to pertain to immense value in assessing treatment methods. In general, the animal models were generated by several gene manipulations for the production of transgenic animals. Similarly, the animals have also been prepared by providing

modified diets to the desired normal animals. The prevailing complications due to T2D, like nephropathy, cardiovascular diseases, neuropathy, and retinopathy, are significant examples that animal models would considerably help to understand the therapeutic opportunities. However, the maintenance and production cost of the transgenic animals, their life span, and restrictions regarding their distribution from one country to another make the limited utilization of the models in developing countries. In contrast, the nongenetic models are easy to produce and are also economical. This section provides an overview of the understanding of the initiation and progression phase of T2DM. Hence, this article demonstrates the appropriate selection and utilization of various animal models in the preclinical testing for treating T2DM.

The animal models were previously produced by using a combination of streptozotocin injection and a high-fat diet. However, variations exist in food type, diet duration, and injection doses. Hence, this article, as per the recommendation of Fang *et al.*, suggested that an inexpensive animal model has to be investigated in various aspects, such as insulin resistance, with great interest [5]. Accordingly, Vatandoust *et al.* fed a high carbohydrate and high-fat diet to Winstar rats for 10 weeks associated with the incorporation of low-dose STZ for the development of diet-induced T2DM animals [6].

Spexin is a peptide that was discovered in 2007 and prohibits food intake, followed by the regulation of lipid and carbohydrate metabolism. Spexin's ability to improve liver function and metabolic control in T2DM animals and obese animals has been investigated by Kolodziejski *et al.* [7]. The 30-day treatment effects of the experimented model were characterized in terms of lipid levels, serum glucose, hormonal profile, and insulin sensitivity. This study concluded that Spexin could be effectively used to induce T2DM or obesity and to further evaluate potential drug targets. Similarly, Sakimura *et al.* investigated depression-related features in novel animal models of Spontaneous DiabeticTorii (SDT) [8]. This study evaluated the depression-like behaviour, neurotransmitter levels, and the hyperactivation of the hypothalamic-pituitary-adrenal axis in the brain region. Finally, the study revealed that the fatty rat is an appropriate model for diabetic research.

By using an automatic feeding system, fish food was overfed to zebrafish to create a DIO animal model. This study assessed the fasting glucose levels in both the overfed and normal groups for eight weeks. This research observed that there is a significant increase in fasting glucose levels in the DIO zebrafish when compared with the normal model. Furthermore, the glimepiride and metformin drugs ameliorated hyperglycaemia in the overfed group, suggesting the effectiveness of the zebrafish as an animal model. In addition, the article performed RNA sequencing methods and observed similar liver pancreatic profiling pathways with human T2DM, thereby emphasizing the therapeutic usage of diet-induced tolerance and insulin resistance with the zebrafish animal model [9].

Digital diabetes

The pervasiveness of the Internet of Things opened the gateway to various new opportunities and solutions in healthcare systems, including remote patient monitoring. The severe social impacts of diabetes-associated diseases render it to be the main priority in medical research. Moreover, there are some new software-assisted tools that can predict heart disease, blood pressure, and diabetes so that patients can be advised to possess regular physical and medical advice and use dietary plans or weight management programs. Considerable advances in the field of biotechnology constantly increase the production of large data that usher AI-based methods to manage inexpensive data. Numerous technologies like MRI, mass spectroscopy, and digital microscopy will generate a plethora of digital data, but they need to provide the most needed analysis followed by interpretation.

The effectiveness and power of AI methods could be effectively used for applications like prognosis and diagnosis of human-threatening or life-quality-reducing diseases like diabetes mellitus. Patients with diabetes will be given ID cards, which will be scanned and linked to the cloud that stores the EHRs (Electronic Health Records) and essential laboratory results, prescriptions, and records of medical history so that nurses and physicians can easily access these records on a desktop laptop or tablet. Hence, this section reviews the technical information on the existing AI-based methods in diabetes research. Kavakiotis *et al.* conducted a systematic review of various applications of data mining and machine learning methods in diabetes research, such as diagnosis and precise prediction, complications associated with diabetes, and health care management [10].

Likewise, the following section describes several other recent existing models of diabetes research. This study explored that relevant feature detection assists in eliminating all redundant and irrelevant attributes from the corresponding database. This affords a quick

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and good predictive outcome. In DM (Data Mining), feature selection and classification methods use training data to develop a model. Subsequently, this model has been applied to the testing data for obtaining better outcomes. Several classification methods have been utilized for the early prediction of DM.

As there exist no exact symptoms during the initial stage, patients are unable to notice these particular diseases. Early detection makes patients obtain treatment promptly to deteriorate their progress [11]. Training and annotation considerations have also been explored, particularly as they are associated with deep learning algorithms. A conclusion has been made that indicated a solid establishment towards inducing the Machine Learning (ML) classifier to help the efforts of tissue quantification on a large scale as well as machine and human interaction protocol implementation in pathology and clinical workflows. Moreover, a reliable and efficient clinical tool has been proposed that permits finding diabetes-associated kidney disease at its early stage and suggests preventive strategies accordingly Jayapandian *et al*. and Zhao *et al*. [12, 13].

Biomarker identification

Biomarkers are biological molecules that act as measurable indicators for certain types of health and disease states. These biomarkers are characteristically estimated in body fluids such as saliva, blood, or urine and are considered independent regarding their etiopathogenic mechanism. These biomarkers are used to monitor the subclinical and clinical features of the disease and to determine treatment methods. Furthermore, the biomarkers could be regarded as direct endpoints or indirect indexes of similar complications. For Diabetes mellitus, the biomarkers represent the existence and severity of hyperglycaemia and other complexities [14]. Contreras *et al*. analysed several kinds of applications in uncovering the issues of diabetes mellitus, ranging from disease diagnosis, interpretation, monitoring, treatment development plans, and drug design [15].

Imamura *et al*. investigated the association between circulating adipose tissue with odd-chain fatty acids and trans palmitoleic acid as vital biomarkers of T2DM [16]. The study stated that biomarkers could not be distinguished between various food sources, and further residual confounding also exists. Panahi *et al*. assessed the impact of curcuminoids and piperine administration on hepatic, glycaemic, and inflammatory biomarkers in T2DM [17]. The study observed no significant variations in the CR protein concentrations between the placebo and curcuminoid groups. The results revealed the investigated biomarkers on the hepatic and glycaemic parameters. However, the study did not reveal CRP levels as the biomarker.

Generally, prevailing studies depicted that the measurement of waist circumference to evaluate the fat distribution could enhance the prediction rate of chronic diseases like diabetes. However, a study stated that even though MRI can predict body fat distribution, they are easily available, and hence, health-relevant cut-offs need to be established [18]. Such measurable biomarkers may reflect the prevailing biological mechanisms in disease prediction. Similarly, a study examined the impacts of canagliflozin on cardiac biomarkers in old-aged T2DM patients [19]. When compared with the placebo effects, the treatment delayed the serum rise in the investigated groups.

Diabetes and COVID-19 pandemic

Coronavirus is enveloped with positive SS RNA virus and is distributed widely in animals and humans [20]. Despite there being no animal research on this aspect, robust human studies in COVID-19 associated with ant-diabetic medication still need to be developed. Chen *et al*. demonstrated that the diabetic patients infected with COVID-19 were observed to be in serious illness and required prompt treatment measures like ICU admission and mechanical ventilation when compared with normal COVID-19 patients [21]. They also revealed that the severity of COVID-19 among diabetes patients causes an inflammatory response. Being diabetic is considered a risk factor in COVID-19 patients, and it often requires cautious management. Pal *et al*. discussed the usage and effects of antidiabetic drugs like insulin, hydroxychloroquine, and other drugs in COVID-19 patients [22]. Moreover, the lack of solid evidence made them choose a specific drug. However, they provide a key point in choosing drugs for glycaemic control.

A study provided a meta-analysis of COVID-19 severity and deaths in hospitals [23]. The analysis includes four months of data of COVID 19 patients admitted to a hospital from January to May 2020 and used random-effects modelling. It is observed that 14.34% of admitted patients were diabetic, particularly among non-Asian countries above 60 years of age. The study stated that pre-existing diabetes had a higher mortality rate in-hospital death.

Shi *et al*. conducted a statistical analysis of hospital diabetics regarding mortality and aimed to point out the characteristics and outcomes of diabetic COVID-19 patients [24]. With the patient data from two hospitals in Wuhan and China from January to March 2020, the study performed Cox Regression analyses on the data to look for the factors affecting the mortality of the patients. The analysed study showed that hypertension, cardiovascular disease, and chronic pulmonary disease had a vital role in the death of COVID-19 patients with diabetic conditions, and diabetes as an independent condition is not associated with hospital death.

Gregory *et al*. conducted a quantified study at around 137 locations within the regional healthcare network and were able to observe the reason for the severity of COVID-19 patients [25]. They collected non-diabetic and diabetic patients from different locations. Among that, diabetic patients show illness severity irrespective of type 1 and type 2 diabetes conditions. These potentially modifiable factors have a significant effect on type 1 diabetes, and reducing severe acute respiratory syndrome requires immediate and continuous attention.

Applications

Automated retinal screening

Deep learning algorithms have been developed to perform automatic diagnosis of diabetic retinopathy (DR), in which AI-based screening is a feasible, well-accepted, and accurate method for the identification and monitoring of DR. These algorithms achieved high specificity and sensitivity of about 94% and 93%, respectively, in the retinal screening. Furthermore, the satisfaction of the patients was also found to be so high, up to 96%, with the employment of deep learning methods. Accordingly, convolutional neural networks were trained on particular datasets for generating lesion-based probability mapping for micro-aneurysms, haemorrhages, exudates, normal appearance, and neovascularization in the retina.

Clinical decision-supporting tools

Decision-making tools based on machine learning were developed for the prediction of short-term and long-term HbA1c responses after the initiation of insulin in T2DM. These tools could be effectively utilized to identify HbA1c response-influencing variables. The deep learning approach could be utilized effectively as an intuitive method for the customization of medical interventions and DM prediction

Risk stratification of the predictive population

Machine learning-based healthcare recommendation systems could help predict risks associated with diabetes by investigating lifestyle, physical and mental health factors, and social activities. The predictive models were constructed to deal with the large data of diabetic patients. Several such models were synthesized for the prediction of short-term and long-term complications of the disease, like hypoglycaemia and retinal, renal, and cardiovascular influences. Furthermore, some of the deep learning models were employed to follow up the patients with diabetic foot ulcers and to monitor the mechanism of gestational diabetes in pregnant women. Such discriminating power of AI-based models was observed to be nearly 85% in the training data set and 77% in the testing dataset, which proved the effectiveness of the computer-aided design models.

Genomic studies

Large diabetes data arising due to the chronic and heterogeneous nature of the disease provided a great emphasis on genomics, molecular phenotyping, epigenetic alterations, and the generation of novel biomarkers.

The optimized data could be effectively utilized to build a microbial marker repository that predicts the possibility of disease development, thereby guiding the treatment in an optimal way. Still, now, more than 400 signals that are genetically susceptible to diabetes have been identified.

Development of self-management tools

Various studies recommend that self-management acts as a predominant tool in the treatment of diabetes. AI-based empowered tools generate patients' data based on their parameters, thereby promoting healthcare awareness among them. Such digital platforms allow targeted education for diabetic patients. Knowledge and awareness about activity patterns and eating habits were recently available through several web-based programs, smartphones, and mobile phone applications. Particularly, these applications could be used in diabetes management for gestational diabetes [26, 27]. This allows attention to daily intake activity.

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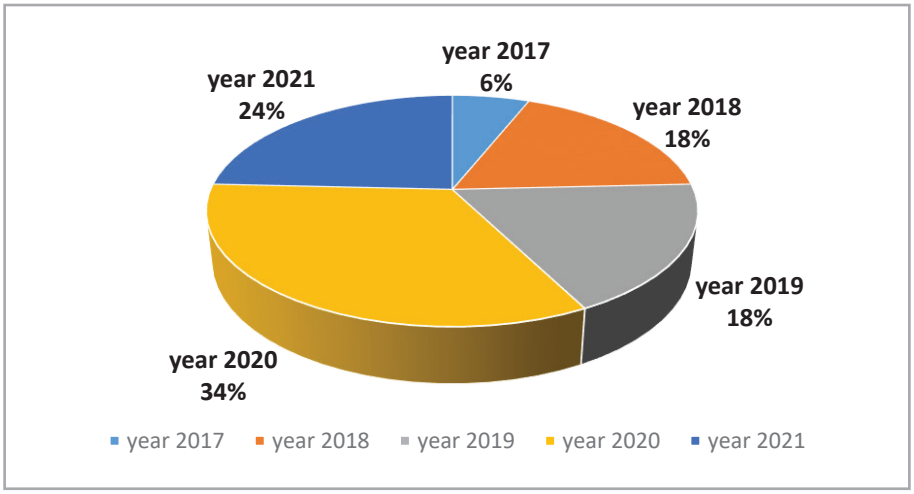

Figure 2: Year-wise distribution of the articles reported in the present study.

Challenges

The following are the factors associated with the limitations of artificial intelligence in diabetes research.

Human factors

Artificial intelligence could impose a risk of deskilling physicians due to dependence. Further, younger people were observed to attain more benefits due to their knowledge of handling the models. Therefore, inadequate accuracy prevails and needs periodic refinement by the experts.

Technological factors

This comprises the access, cost, and implementation of diabetes care devices. With growing applications, interoperability has been reported as a potential barrier

Paucity of data

Missing values or inadequate data is a common challenge in building logical and inadequate data. Hence, impactful solutions also depend on the seamless adoption of the security concerns [28].

Poor glycaemic control has a detrimental impact on the well-being, economy, and health of patients. Insulin therapy has been proven to decrease glycated haemoglobin levels considerably, but both physicians and patients could be reluctant to initiate insulin therapy. The research depicted that both factors and the patient were responsible for the delay in insulin therapy and its effectiveness [29]. Islet transplantation and whole organs are now the gold standard procedures in obtaining glucose control in T2DM patients; the lack of suitable donors adversely impacts the broader application of the prevailing therapies [30].

Critical analysis

Figure 2 provides the year-wise distribution of the selected articles. Most of the articles in this review belong to the year. The information presented in this review is summarized from recent and standardized publications.

Conclusion

Diabetes mellitus has been considered a major non-communicable disorder that seeks rapid attention from all fields, ranging from healthcare, stakeholders, education, and the economy. It is regarded as one of the top 10 reasons for death globally and ultimately kills nearly 1.6 million people worldwide. Furthermore, it is also regarded as the predominant risk factor for premature mortality. Despite several studies incorporating its vast efforts with rending tools and ideologies, the crucial prevalence and death rate of the disease have been observed to reach greater heights periodically. Hence, a clear understanding between hyperglycaemia, inflammation, and the progression of the disease has to be adopted to optimize the treatment and management process. Hence, the presented article compiles the possible information from various standardized sources related to diabetic research. This review will pour information to attain the restoration of the glycaemic index and management of the disease cost-effectively, so people from every standard could be able to fight and prevent this ever-alarming disease.

Conflict of interest

The author declares no conflict of interest.

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