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ASSOCIATION OF DIABETES MELLITUS WITH REACTION TIME, COGNITIVE FUNCTION AND PHYSICAL FITNESS

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ABSTRACT

Background: Diabetes mellitus is a chronic metabolic disorder with systemic complications that may impair cognitive and motor functions. Simple reaction time (SRT) is a measure of sensory-motor performance and an important indicator of central nervous system processing speed.
Objective: This study aimed to investigate the effect of diabetes mellitus on simple reaction time and cognitive abilities decline comparing results between individuals with diabetes and healthy controls.
Methods: A review paper based on studies found on PubMed and Google Scholar. The majority of metanalyses and studies involve two groups: a diabetic group (patients diagnosed with type 1 or type 2 diabetes) and a non-diabetic control group. Participants performed a standardized computer-based simple reaction time test. Reaction times were measured and statistically analyzed to assess differences between the groups.
Results: The results indicated that individuals with diabetes had significantly longer simple reaction times compared to the control group. The findings suggest that diabetes mellitus negatively affects sensory-motor integration and neural processing speed.
Conclusion: The study concludes that diabetes mellitus can impair cognitive-motor function as reflected in prolonged simple reaction times. This highlights the need for cognitive assessment and monitoring in diabetic patients as part of their routine clinical care.

KEYWORDS

Diabetes Mellitus, T1d, T2d, Reaction Time, Simple Reaction Time, Cognitive Function, Motor Function, Dementia, Alzheimer's Disease

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Introduction

Diabetes mellitus is a chronic metabolic disease affecting 5–8% of society and affecting the quality of their life. [1] Despite common awareness, prevention measures and improved health care access throughout the years, a significant increase in the prevalence of the disease has been noticed since 1990 when diabetes affected 200milion patients worldwide, reaching 830 million in 2022 [2].

The aim of this research paper is to analyze clinical and observational studies published on PubMed, all concerning diabetes mellitus, the course of disease, its complication and effect on cognitive functions and simple reaction time. It is crucial to focus on risk factors and pathophysiology to study possible preventive measures and improve cognitive functions and decrease cental nervous system degeneration.

Methods

This study analyzed articles and studies found in PubMed and GoogleScholar using keywords such as “diabetes” “diabetes mellitus,” “reaction time,” “neuropathy diabetes,” “cognitive function in diabetes,” “hypoglycemia effect on brain.” “hyperglycemia”, ‘’, ‘reaction time improvement’, ‘’, ‘visual stimuli dettection’. The bibliography consists of meta-analyses, randomised trials and systematic reviews, and online articles published by the public health organisations. All the papers date from 1978 to the present with special emphasis on papers published after 2000.

Diabetes Mellitus

Diabetes mellitus is a group of medical conditions associated with hyperglycemia, impaired insulin production, glucose transport and the regulation of glucose level in the blood. [3] The most common types of diabetes are the autoimmune condition – type 1 diabetes (T1D)), and the type 2 diabetes (T2D) caused by the insulin resistance linked to overweight, poor diet and lack of exercise. Gestational Diabetes Mellitus (GDM) is another type characteristic to pregnancy. Other Specific Types include monogenic diabetes syndromes, diseases of the exocrine pancreas (e.g., cystic fibrosis), and drug- or chemical-induced diabetes (e.g., due to glucocorticoid therapy)[2, 3, 4]. T2D contributes to more than 95% cases of diabetes, with 9 million people diagnosed with T1D in 2017 [2].

Type 1 diabetes pathogenesis

Type 1 diabetes (T1D) is an autoimmune disease caused by the progressive destruction of insulin-producing β-cells in the pancreas. [4] The β-cells are responsible for sensing glucose and – in effect - releasing insulin to maintain blood glucose levels within its physiological narrow range. The destruction of pancreatic cells results in lack of glucose level control in T1D patients, which may lead to direct threat of life in case of acute conditions, such as ketoacidosis or severe hypoglycemia [5]. Although current insulin therapies improve glucose control and increase quality of life, chronic diabetes leads to secondary complications affecting major organs exposed to hyperglycemia most commonly causing heart disease, retinopathy, neuropathy, nephropathy [6],[7]. The pathogenesis of this complex condition involves immune system dysregulation, genetic susceptibility and environmental factors, resulting in β-cell dysfunction.

Genetic factors

Genetic factors are crucial in T1D development. The increased risk of the prevalence of T1D is connected to the specific human leukocyte antigen (HLA) genotypes, especially class II genes: HLA-DR3 and HLA-DR4 [8]. HLA complex, located on chromosome 6p21 is significant in the proper immune system function, the ability to recognize and distinguish the self and non-self by presenting peptides to the T-cells[9][10]. The autoimmune reaction may potentially result in β-cells damage and impair its function.[8][11] Understanding the full spectrum of genetic factors contributing to T1D is important for risk assessments improvement and obtaining potential therapeutic strategies, considering both class II and non-class II genes within the HLA complex [11].

Enviromental factors

It is believed that autoimmune response resulting in β-cell destruction may be affected by environmental factors in individuals predisposed to T1D [12]. Islet autoimmunity may be triggered by diet, infections and toxins exposure during childhood and in prenatal conditions [13,14]. Viral infections may cause immune response, especially enteroviruses leading to cross-reactions with β-cell antigens, therefore destroying pancreatic cells and impairing its function [12]. Ather biological environmental factors that has been studied include HCV infection, the gut microbiome and prion-like protein aggregates [13].

Immune mechanisms

The autoimmune processes involved in T1D include activation of autoreactive T-cells targeting pancreatic β-cells. Both genetic predisposition and environmental factors act as triggers[10,14]. In diabetes mellitus the production of IL1β by peripheral blood mononuclear cells is impaired. As IL1β is a mediator in inflammatory reactions, innate cell activation is reduced in diabetes [14,15,16]. T1D is related to elevated IL15 serum levels and its soluble receptor: sIL15R α. The dysregulated expression of IL15 signaling is characteristic for many other autoimmune disorders, hence indicates immune pathogenesis [17]. NK cells and CD8 T-effector memory cells are activated in response to this membrane-associated molecule, especially in viral infections when IL15/IL15Ra is expressed [18]. The reduced number of free NK cells and impaired cytokine signaling has been observed not only in T1D, but also in gestational diabetes mellitus – a condition associated with pregnancy [18,19].

Type 2 diabetes pathogenesis

Glucose homeostasis aims to maintain blood glucose levels in a narrow physiological range: proximately 5 mM, which is controlled mainly by the liver, fat, and skeletal muscle [20]. In the pancrease, the langerhans islets contain beta cells responsible for insulin production regulation by monitoring glucose levels, keto acids, amino acids and fatty acids within the blood plasma. Insulin function is to optimaize energy conservation and use during fasting and food intake [21]. Glucoregulatory hormones include not only insulin and glucagon, but also amylin,glucose-dependent insulinotropic peptide (GIP), GLP-1, epinephrine, cortisol, growth hormon [22]. Insulin resistance and β-cell deterioration are the hallmark of T2D, contributing to elevated blood glucose levels [20].

Insulin Resistance

Insulin inhibits the decomposition of liver glycogen, stimulates glycogen synthesis, converts glucose into fatty acids and triglycerides, and facilitates glucose uptake by peripheral tissues, muscle and fat tissues by intensified glucose transporter 4 translocation to the cell surface [20]. Insulin resistance results in insufficient glucose uptake and utilization in peripheral tissues, (e.g. adipose tissue, muscles, liver), initially increasing insulin production to compensate. In later stages 4rolonged insulin production causes progressive β-cell failure leading to chronic hyperglycemia [23]. This process is aggravated by inflammatory cytokines like TNF-α and IL-6 from visceral adipose tissue, which activate signaling pathways interfering with insulin receptor function [24].

Adipose disfunction and lipotoxicity

Insulin resistance leads to hepatic glucose overproduction and increased lipolysis, as the adipose tissue releases free fatty acids (FFAs). It leads to lipid-induced oxidative stress and inflammatory cytokine release [25]. These excessive FFAs together with their metabolites cumulate in non-adipose tissues (e.g. muscle, liver) compromising insulin action, signaling and promoting β-cell apoptosis [25,26].

The majority of T2D patients (aproximatelly 80%) are obese [24]. The anormal glucose and lipid metabolism leads to central obesity, defined by the WHO as a waist circumference exceeding 80 cm for females and 94 cm for males [28]. Excessive adipose tissue, especially visceral fat accumulation leads to adipocyte dysfunction.

Chronic inflammation

The adipose tissue secretes pro-inflammatory cytokines: TNF-α and IL-6 which inńcline insulin signaling dysfunction, increase hepatic glucose production and contribute to β-cell impairment [26,27]. T2D is characterized by the impaired IL-1β production due to improper NLRP3 inflasomme activation, its effect on circulating monocytes and excessive anti-inflamatory production. The proper treatment and sufficient glycemic control may significantly improve interleukin balance [16]

Oxidative Stress is one of factors leading to T2D**.** Increased glucose levels amplify reactive oxygen species (ROS) production, therefore activating inflammatory pathways; NF-κB and MAPK molecules.[24]

Moreover, altered gut microbiota may contribute to T2D by metabolites like lipopolysaccharides and short-chain fatty acids, which influence systemic inflammation and insulin sensitivity. [23,24]

Genetic Predisposition

Unlike T1D, HLA genes do not contribute to T2D occurence. However, the risk genes (e.g., **TCF7L2**, **PPARG**, **KCNJ11**, **FTO**) responsible for impaired insulin secretion and function have been discovered [29]. Over 240 loci is associated with T2D. Genetic studies have identified specific genes like glucokinase (GCK) and studied its importance in glucose metabolism. Gene regulation affecting glucose and insuline homeostasis may be influenced by some epigenetic modifications, e.g. DNA methylation and microRNA expression [30].

Diagnosis and treatment

Early diagnosis can be acomplished by recognizing common syptoms, including frequent urination, excessive thirst, unexplained weight loss, fatigue or blurred vission [3].

Diabetes diagnosis is based on either specific blood glucose criteria or glycated hemoglobin (HbA_{1c}) levels. The American Diabetes Association (ADA) and the WHO have standardized diagnostic criteria to ensure diagnostic consistency and accuracy worldwide [2,31,32].

1. Fasting Plasma Glucose (FPG)

≥ 126 mg/dL (7.0 mmol/L) after an overnight fast of at least 8 hours, twicely assessed is an easily accesible method to diagnose diabetes.

FPG levels: 100–125 mg/dL (5.6–6.9 mmol/L) implies impaired fasting glucose (IFG) which may evolve into diabetes [31, 32].

2. Oral Glucose Tolerance Test (OGTT)

This test is based on plasma glucose masurement after an overnight fast and 2h later, after administering a 75 g oral glucose load.

≥ 200 mg/dL (11.1 mmol/L) after 2hours indicates diabetes.

Plasma glucose levels: 140–199 mg/dL (7.8–11.0 mmol/L) indicates impaired glucose tolerance (IGT) [31,32].

3. Glycated Hemoglobin (HbA_1c)

≥ 6.5% (48 mmol/mol) corresponds to increased glucose levels during the last 2-3months, thus is one of the diabetic diagnostic criteria.

HbA_1c levels: 5.7–6.4% (39–46 mmol/mol) indicate increased risk for diabetes [31,32].

4. Random Plasma Glucose (RPG)

≥ 200 mg/dL (11.1 mmol/L) accompanied by classic hyperglycemia symptoms (e.g., polyuria, polydipsia, weight loss) is a circumstance that supports diagnosis without another episode FPG assessment [32].

T1D can be diagnosed with additional help of the β-cell- destruction immunological markers, such as islet cell autoantibodies, autoantibodies to insulin, autoantibodies to glutamic acid decarboxylase (GAD_{65}), and autoantibodies to the tyrosine phosphatases IA-2 and IA-2β. However, these autoantibodies are present in 85–90% individuals while diagnosing hyperglycemia on early onset [4].

Insulin injections are the main treatment in T1D, while T2D is focused on keeping a healthy lifestyle, minimizing insulin resistance and - in some cases - requires oral medication.

Metformin, sulfonylureas or sodium-glucose co-transporters type 2 (SGLT-2) inhibitors are most commonly used [2].

It is important to screen for diabetes complications: kindey failure, nerve demage, retinopathy, digestive issues [6,7].

Neuropathy

Diabetic neuropathy is a prevelent complication of diabetes leading to nerve damage. It encompasses various forms, including peripheral, autonomic, and focal neuropathies, each affecting different nerve types and presenting distinct clinical manifestations [1,2,33]. The underlying mechanisms of diabetic neuropathy involve hyperglycemia-induced oxidative stress and other factors. Microvascular dysfunction is caused by Impaired blood supply to nerves due to blood vessels damage, causing ischemia and subsequent nerve injury. Chronic inflammation also contributes to nerve degeneration and dysfunction [33,34,35].

Progressive nerve damage, resulting from chronic hyperglycemia can slow the transmission of impulses between the synapsis withing the brain, central and the peripheral nervous system, causing the delay in auditory and visual reaction times, correlating with poor glycemic control [35]. A study involving 44 high-risk od diabetes and 28 healthy controls concluded that those at increased risk for diabetes had almost 6 times higher odds of experiencing parasympathetic neuropathy [36].

Peripheral neuropathy can be experienced as a tingling sensation or numbness, often starting in the toes, feet and potentially spreading proximately to lower and upper extermities. The common occurrence of neuropathic pain can manifest as sharp, burning, or throbbing sensations, usually worsening during the nighttime. With the progression of nerve damage the characteristic and duration of symptoms may change from intermittent to constant and significantly lower the quality of patients' life [33, 36]. The treatment of neuropathic pain in diabetes is limited to pregabalin and duloxetin at present, approved by the FDA, Health Canada and European Medicine Agency. In the U.S. and Canada tapentadol, an opioid, has been regulatory approved [37].

Studies on diabetic mice have indicated its increased expression of IL-6 binding to and inducing the dimerization of multiple can bind to and induce the dimerization of multiple receptor complexes, leading to JAK activation in the cell membrane [24]. This process induces the transcription of related neuroprotective genes. Diabetic neuropathy ethiology includes oxidative stress, while the anti-oxidative stress effect of the JAK-STAT signaling pathway provides a new approach for the treatment of neuropathy [24].

Reaction time

Reaction time refers to the interval between the presentation of a stimulus and the initiation of a motor response. This process involves a complex sequence of neural events, beginning with sensory detection, activation of visual and then motor cortex responsible for response initiation. It culminates in muscle activation as the spinal cord receives the message from the motor cortex and finally sends a message to the muscles causing the movement. The reaction time and movement time are referred to as the total response time [38,39].

Of the sensory systems, visual stimuli requires the most time with an average reaction time proximately 0.180 s - 0.200s,. depending on the task conditions, while the auditory reaction time has mean values between 0.140 and 0.160s. Kinaesthetic reaction time is the fastest (0.120-0.140s) [40,41].

Reaction time vary across different age groups, influenced by various physiological and cognitive factors. In the early childhood, the central nervous system develops rapidly. Children's reaction times improve significantly from ages 5 to 15 as they develop better motor skills and cognitive functions [42]. Their reaction times can be relatively fast due to high levels of physical activity and cognitive processing abilities. 15-18 years old youths have reaction time comparable to adults. A simulator study found that children aged 6–9 years showed significant reductions in RTs, reaching adult-like levels by age 10. [43,44]

Individuals with diabetes mellitus, particularly T2D, often experience impaired reaction times including visual, auditory, and whole-body responses [48,49]. Delayed reactions are due to severe diabetic complication, such as peripheral neuropathy, fluctuations in blood glucose levels, chronic hyperglycemia or cardiovascular diseases impairing blood flow and oxygen transport to the brain and muscles [1,2,48,49,50,51].

Visual and auditory reaction time in chronic diabetes

A study comparing visual reaction times between individuals with and without diabetes concluded that those with insuficient treatment and high plasma glucose levels exhibited longer reaction times. This delay was significantly noticed in the 40–59 age group, suggesting that elevated HbA1c levels are linked to delayed neural processing and slower speeds [51,52]

Visual reaction times are more delayed than auditory ones, possibly due to the involvement of multiple neural pathways in visual processing. Investigation into auditory and visual reaction times in patients with chronic type 2 diabetes indicates that both reaction times were delayed compared to controls [48,50,53]. Diabetic adults had significantly longer reaction times to plantar touch and whole-body lateral movement stimuli than control subject nom-diabetics in a study. Auditory reaction times were not significantly different between these groups [49]. A study measuring whole-body reaction times (WBCRT) in diabetic patients found that these were more delayed than visual reaction times, suggesting that WBCRT could be a potential screening tool for cognitive dysfunction detection in diabetes [49,52].

Impact of disease duration and glycemic control

Glucose homeostasis is the maintenance of blood glucose concentration in a physiological range. Diabetes is characterized by impaired glucose and insulin balance [1,2]. Higher glycemic levels are associated with cognitive function decline, including executive function and memory [51,52,57]. Chronic hyperglycemia as well as severe hypoglycemia can negatively affect cognitive abilities. Sudden plasma glucose levels changes affect cognitive function and physical responses. Hyperglycemia is charactarized by fatigue, reduced alertness while hypoglycemia may cause confusion, dizziness, impaired coordination impairing reaction time and responses [5]. A systematic review and meta-analyses implied the significance of the glycemic control in cognitive decline prevention in conditions involving hyperglycemia, insulin resistance and diabetes [57,58]. High HbA1c values corresponding to chronic hyperglycemia, as well as disease duration were associated with attention deficits, executive function decline and increased visual reaction times in type 2 diabetes patients [48,50,53,54,55,56]. High average glucose levels were related to an increase in risk of dementia among individuals without diabetes as well [59].

Reaction time as cognitive function decline indicator

Diabetes mellitus, particularly type 2 diabetes, has been reportedly associated with an increased risk of acquiring conditions characterized by declined cognitive functions [1.3] Mechanisms contributing to impaired cognitive function include all diabetic complications' pathogenic factors: chronic hyperglycemia and insulin resistance, vascular damage inflammation, oxidative stress and impaired glucose metabolism in the brain. A comprehensive meta-analysis with 28 prospective observational studies concluded that diabetic patients have a 73% increased risk of developing all types of dementia (ATD), a 56% increased risk for Alzheimer's disease (AD), and a 127% increased risk for vascular dementia (VaD) when compared to healthy population [46]. These affect attention, processing speed, and decision-making skills.

Increased risk of dementia in diabetes

T2D patients often experience cognitive deficits, impairments in both short-term and long-term memory. Executive functions are distrupted, especially problem-solving, decision-making and planning. T1D is characterized by 50% increased risk of developing dementia compared to healthy population, due to factors such as chronic hyperglycemia and severe hypoglycemic episodes [77]. Higher average glucose levels were linked to an increased risk of dementia, even among healthy individuals without diabetes. A glucose level of 190 mg/dL (10.5 mmol/L) compared to 160 mg/dL (8.9 mmol/L) was correlated with a 40% increased risk of dementia (hazard ratio 1.40; 95% CI, 1.12 to 1.76) [59]. Severe hypoglycemic episodes may increase the risk of dementia due to neural injuries. A study concluded that these episodes doubled the probability of developing dementia [78]. A study from the Sydney Memory and Ageing Study estabolished that mean reaction time and intraindividual variability in reaction time were predictive of incident dementia over a four-year period. Subjects with delayed and more variable reaction times were more prone to develop dementia, despite other risk factors [68,69].

Some antidiabetic medications, such as metformin and sodium-glucose cotransporter-2 inhibitors (SGLT2i) have been associated with reducing risk of dementia [74][75]. A systematic review and meta-analysis concluded that pioglitazone, a thiazolidinedione, was associated with a 47% reduced risk of dementia among diabetic patients [76].

Insulin resistance and Alzheimer's disease

Diabetes nearly doubles the risk of Alzheimer's disease [46] Imaging studies show that diabetics may have reduced brain volume, especially in a region crucial for memory – the hippocampus [79]. Insulin resistance is associated with brain cells degradation, affecting memory and learning. Due to overlapping mechanism Alzheimer's has been referred to as **"type 3 diabetes"**[60]. Tau phosphorylation is a crucial pathological feature of AD and is promoted by reduced insulin signaling which also impairs amyloid beta clearance. Insulin resistance leads to impaired glucose metabolism, oxidative stress, neuroinflammation, accumulation of amyloid-beta and tau proteins. Insulin plays a role in synaptic maintenance, neuroplasticity, and cognitive function [61].

The Rotterdam Study has found a strong connection between T2D and heightened AD risk. It was established that diabetes is associated with a 1.9-fold increased risk of dementia and AD in elderly. The most prominent risk has related to Insulin-treated diabetes, with a relative risk of 4.3 (95% CI, 1.7 to 10.5) [59,62,63]. Delayed reaction times can be indicative of cognitive decline and may serve in early dementia detection. Individuals with mild cognitive impairment (MCI) exhibited significantly longer simple reaction times in comparison to healthy controls, and it's been studied in meta-analysis published in 2019. Reaction time progressive delay could be an early sign of Alzheimer's disease [64,67,68]

However, a large-scale study analyzed data from over 500,000 participants and concluded no significant causal link between genetically predisposed T2D and AD. Despite T2D association with increased dementia risk, the correlation may be strongly supported by modifiable clinical or environmental factors rather than direct causality [77].

Physical fitness, coordination and balance

Individuals with diabetes may experience reduced physical activity due to complications, which can lead to decreased overall fitness and slower reflexes. Neuropathy, retinopathy, and musculoskeletal issues can cause pain, balance problems, and reduced vision, making exercise more challenging and less safe [80]. Impaired sensation can affect coordination and balance, increasing the risk of falls. Muscle weakness, particularly in the feet and hands is common also affecting balance and coordination [81]. Regular exercise improves insulin sensitivity and has been shown to enhance cognitive function. A study of elderly subjects with prediabetes estabilished that moderate to high-intensity exercise increased levels of brain-derived extracellular vesicles carrying insulin-related proteins, essential for neuron communication and brain health [72,73,81].

Another study systematically reviewed existing literature to evaluate the effects of physical activity on glycemic variability in T2D patients. It utilized continuous glucose monitoring (CGM) data to assess these fluctuations over time. The findings suggest that engaging in regular physical activity can significantly reduce glycemic variability, thereby potentially mitigating the associated risks of complications such as cognitive impairment and dementia [73].

Potential for future research

The studies strongly implied that the reaction time and intraindividual variability in reaction time were predictive of incident dementia over a four-year period [68,69]. These findings underscore the potential of reaction time measures as simple and cost-effective tools for early detection of cognitive decline and dementia risk. However, it's important to highlight that while reaction time can be an accessible indicator, it should be used alongside other cognitive assessment methods and clinical evaluations for a comprehensive understanding of an individual's cognitive abilities [70].

Furthermore, given the established link between glycemic variability and increased risk of dementia, incorporating regular physical activity as a part of T2D treatment could be a beneficial strategy to alliviated this risk of dementia and reduce insulin resistance [71]. Further research is required to explore the optimal types and durations of physical activity to optimize glycemic variability reduction and associated complications [73].

Conclusion and clinical implications

Diabetic patients often experience slower reaction times, primarily due to complications such as neuropathy, reduced physical activity, and impaired cognitive function. These factors collectively affect neural processing speed and motor responses, highlighting the importance of managing blood glucose levels and encouraging regular physical activity to preserve neurological and physical function. Managing strategies include controlling blood glucose, blood pressure, and cholesterol. Peripheral neuropathy results in sensory and motor nerves signal transmission impairment. Diabetes may affect central processing pathways, further contributing to delayed reaction times. These impairments not only affect reaction times but also increase the risk of falls and injuries due to compromised balance and coordination. Regular exercise is crucial for maintaining proper reaction times. Regular assessment of reaction times, alongside glycemic control measures, is crucial for the early detection and management of diabetic neuropathy as well as highlighting the need for comprehensive management strategies that address both sensory and cognitive aspects of diabetes-related complications.

Author's contribution

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