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EFFECT OF DIABETES MELLITUS ON NEURODEGENERATIVE CHANGES IN THE CENTRAL NERVOUS SYSTEM

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The central nervous system (CNS) is highly susceptible to both aging and metabolic disturbances, particularly those associated with diabetes mellitus. Neurodegenerative disorders—including cognitive decline, dementia, Parkinson's disease, Alzheimer's disease, Huntington's disease, and amyotrophic lateral sclerosis—often involve neuronal loss alongside abnormalities in glucose metabolism [7]. Cellular insulin signaling defects, compounded by elevated glucose and insulin levels, contribute to mitochondrial damage, increased oxidative burden, and chronic inflammation. These pathological mechanisms collectively alter CNS architecture and function, facilitating neurodegenerative progression is vital for unraveling disease mechanisms and identifying potential interventions.

Keywords: neurodegeneration, diabetes, Alzheimer's disease, insulin, metabolism

INTRODUCTION

Diabetes mellitus and neurodegenerative disorders constitute critical health problems worldwide. In the population aged 60 years and older, type 2 diabetes mellitus (T2DM) along with cognitive impairments emerge as the leading chronic illnesses. The concept of "neurodegeneration" encompasses the progressive and selective loss of neurons, their structures, and functional capacity within the CNS [2,8]. This process underlies the gradual impairment observed in neurodegenerative disorders. For example, Alzheimer's disease features the degeneration of pyramidal neurons in the hippocampal Ammon's horn, resulting in memory loss and cognitive decline **[6].** Parkinson's disease is characterized by the progressive degeneration of dopaminergic neurons in the substantia nigra and the associated striatal connections, leading to motor and cognitive deficits [4,11]. Dementia is distinguished by declining competence in everyday activities, with impairments in memory, decision-making, judgment, and social behavior. Cognitive deterioration typically begins with subtle deficits and progresses to pronounced dementia over time[10]. High blood glucose, or hyperglycemia, is a hallmark of type 2 diabetes mellitus (T2DM) and commonly affects patients with the disease. Often resulting from insulin resistance, hyperglycemia can exert neurotoxic effects, leading to elevated glucose within neurons, neuronal injury, and the development of neuropathy [9].

The aim of this study is to analyze the effects of age-related factors and diabetes mellitus on metabolic processes in the CNS and neurodegenerative changes.

MATERIALS AND METHODS.

The simulated results include the following groups: age healthy (20-30 years, n=20), middle-aged healthy (40-55 years old, n=20), young diabetic (20-30 years old, n=20), diabetic of middle age (40-55 years, n=20).

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Analysis encompassed glucose concentration (mmol/L), ATP content (µmol/g), oxidative stress quantified via malondialdehyde (MDA, AU) and key neurodegenerative biomarkers, namely beta-amyloid and tau proteins (pg/ml). Data are expressed as the mean ± standard deviation (SD). Differences between groups were checked using ANOVA. Correlations were evaluated using Pearson's r. $P < 0.05$ was considered statistically significant.

RESULTS

Table-1

Parameter	Young healthy	Middle-aged healthy	Young diabetic	Diabetic middle age
Glukoza (mmol/L)	5.1 ± 0.3	5.5 ± 0.4	7.9 ± 0.6	8.4 ± 0.7
ATP darajasi (µmol/g)	2.6 ± 0.2	2.2 ± 0.3	1.9 ± 0.3	1.6 ± 0.2
Oksidlovchi stress (MDA, AU)	1.0 ± 0.1	1.3 ± 0.2	2.1 ± 0.3	2.7 ± 0.4

Glucose levels were significantly higher in diabetic groups, while ATP levels were reduced and MDA levels were increased. This indicates metabolic imbalance and increased oxidative stress in the CNS. In young diabetic individuals, the decrease in ATP was less pronounced, whereas in middle-aged diabetic individuals, energy deficiency was much more significant. This suggests an age-related decline in CNS metabolism.

An inverse association was detected between glucose and ATP levels ($r = –0.68$, $p < 0.01$), suggesting that elevated glucose impairs ATP synthesis. Additionally, MDA levels exhibited a positive correlation with neurodegenerative biomarkers ($r = +0.74$, $p < 0.001$), with higher oxidative stress linked to increased beta-amyloid and tau protein expression, implying that oxidative damage accelerates neurodegenerative processes.

Neurodegenerative Markers

Table-2

Markers	Yosh sog‘lom	O‘rta yosh sog‘lom	Yosh diabetik	O‘rta yosh diabetik
Beta amiloid (pg/mL)	17 ± 3	21 ± 4	29 ± 5	35 ± 6
Tau protein (pg/mL)	30 ± 5	34 ± 6	45 ± 7	51 ± 8

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The results show that diabetes mellitus accelerates neurodegenerative processes in the CNS. In diabetes, brain proteinopathy is characterized by two main forms of misfolded proteins. One type comprises neurofibrillary tangles (NFTs) formed by hyperphosphorylated tau, while the other consists of extracellular plaques composed of aggregated amyloid-β (Aβ) peptides.Neurodegenerative markers, particularly beta-amyloid and tau proteins, were highest in middle-aged diabetic individuals.

Evidence indicates that impaired insulin signaling underlies the pathological accumulation of amyloid-β (Aβ). Normally, neuronal Aβ is regulated and removed by local proteases [1]. Aberrant processing or mislocalization increases levels of the neurotoxic Aβ42 isoform, promoting neuronal damage.

Tau, a microtubule-associated protein (MAP) located in axons, exists in six isoforms due to alternative splicing. It is essential for microtubule assembly and stabilization, impacting morphogenesis, intracellular transport, and cell division. Insulin regulates both tau expression and phosphorylation by inhibiting GSK-3β [3]. Impaired insulin signaling reduces AKT activity, enhancing GSK-3β activity, resulting in tau hyperphosphorylation and fibril formation. In Alzheimer's disease, tau phosphorylation is approximately three times higher than in healthy brains, and reduced insulin signaling worsens tau dysregulation[5].

Discusión

The results of this study indicate that age-related factors and diabetes mellitus influence metabolic processes in the CNS and CXneurodegenerative changes through complex and multifactorial mechanisms. In diabetic individuals, increased oxidative stress and elevated glucose levels significantly alter neuronal metabolism. These changes, particularly when combined with diabetes, significantly impair synaptic plasticity and memory processes.These results emphasize that diabetes affects not only peripheral metabolic processes but also has a significant impact on the CNS.

Conclusion

Diabetes mellitus disrupts CNS metabolism: glucose levels increase, ATP levels decreas and oxidative stress rises. Neurodegenerative markers (beta-amyloid and tau) are significantly elevated in diabetic groups. The results confirm the relationship between CNS metabolism, oxidative stress, and neurodegeneration. This indicates that controlling diabetes is essential for maintaining healthy CNS function. Therefore, monitoring metabolic parameters and reducing oxidative stress in diabetic patients are crucial for protecting the CNS from neurodegeneration and for optimizing treatment and prevention strategies.

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