Research article

Role of glycemic status and insulin resistance indices on cognition

Ramya C.M.[1], Rajalakshmi R.[1], Uma Vijayashankar[1], Bhanukumar M.[2]

[1]Department of Physiology, JSS Medical College, JSS AHER, Mysuru, Karnataka, India
[2]Department of General Medicine, JSS Medical College and Hospital, JSS AHER, Mysuru, Karnataka, India

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Corresponding author: **Ramya C. M.** Email: ramyacm@jssuni.edu.in

ABSTRACT

Introduction and Aim: Type 2 Diabetes Mellitus (T2DM) is presently the commonest and most prevalent disorder of metabolism which, if unmanaged, can lead to macro and micro-vascular disorders as complications. The preventive and therapeutic options for the same have been drastically improved than before and the life expectancy of the affected population has risen, but with the emergence of few other new complications like cognitive impairment and dementia. Insulin Resistance (IR) is a preclinical stage during diabetes and can potentially affect cognition. Cognition is the capability of an individual to process the given information through perception. Cognition is a broad spectrum including different cognitive domains like learning, attention, memory, language, reasoning, decision making, visuospatial skills etc., which forms the basis of intellectual development. Our present aim is to study the relationship between the glycemic profile and cognition status in diabetics.

Materials and Methods: The study population included a total of 232 subjects with the age of 40-70 years of both genders. They were recruited after obtaining the informed written consent. Fasting blood glucose, Insulin levels, HbA_1C were analyzed. The insulin resistance indices such as The HOmeostasis Model of IR (HOMA-IR), QUantitative Insulin-sensitivity Check Index (QUICKI) and HOMA percent beta-cell function (HOMA-beta) were derived. Cognition status was assessed and scored using the Modified Mini Mental Status (3MS) test.

Results: HbA_1c score and the 3MS score showed an association where both were negatively correlated. Insulin resistance induces too were negatively correlated with cognitive function.

Conclusion: Thus, our study suggests that unmanaged diabetes mellitus type 2 may affect the cognition. Accordingly, early diagnosis of the condition and its management is crucial to bring down the incidence of cognitive impairment, further dementia, and other neurodegenerative diseases.

Keywords: Cognition; type 2 diabetes mellitus; insulin resistance.

INTRODUCTION

Type 2 Diabetes mellitus (T2DM) along with progressing insulin resistance has been perpetually associated with metabolic, cardio-vascular, and endocrine derangements, to name systemic hypertension, dyslipidemia and obesity constituting the Insulin Resistance (IR) syndrome. From the previous epidemiologic studies, it can be hypothesized now that hyperinsulinemia might lead to cognitive impairment, as IR is more frequently seen in patients suffering from dementia when compared to healthy individuals (1).

The exact pathological phenomenon of this association is still unclear, but few studies depict that this involves the modifications of amyloid beta peptide (Aβ) metabolism resulting in increased amyloid protein deposition and its reduced clearance. It has also been said that hyperinsulinemia alone can hike the possibility of cognitive decline via microvascular aberrations (2).

Indices of insulin resistance were developed to measure the severity of IR and they include fasting serum insulin level (FSI), IR index which can be estimated using the HOMA-IR and HOMA-S, insulin sensitivity index, derived with the QUICKI. These are the mathematical models which are computed depending on experimental facts and figures, both from humans and animal models, on the estimate of insulin production *de novo*, hepatic glucose amounts and insulin dependent efflux and uptake of glucose, and rate of insulin decay.

'Cognition' is a terminology used for a wide array of mental abilities that relate to knowledge, intellect, and information processing. thus, it is the set of all processes like attention, perception, recent memory, delayed memory, judgment, orientation, reasoning, problem solving, visuospatial skills, decision making, language etc.,

Cognitive performance was assessed and scored for 100 using the 3MS test. It evaluates cognitive function parameters like naming, spatial orientation, attention modality, immediate recall, long-term recall, language skills, and the ability to comprehend and follow the given simple verbal and written commands (3).

The modern view and appreciation of the symbiotic relationship between T2DM and neurocognitive dysfunction with or preceding dementia presents us an opening to combine the works and resources to address both complex and related complications combinedly. The pathological process of cerebral

amyloidosis can precede symptomatic clinical cognitive decline, and during this early phase may occur in limited and specific areas of the brain. Hence, it is likely that AD pathology may be already present in the hypothalamus very earlier to the onset of evident cognitive symptoms, and this pathology onset in hypothalamus could certainly disrupt homeostatic bodily functions like energy balance and metabolism prior to the outset of detectable cognitive dysfunction (4).

The presence of comorbid conditions along with diabetes, are hypertension, dyslipidemia, obesity, and cardiac complications such as myocardial infarction, might pave the way to cerebrovascular disease and degeneration of neurons in specific regions of brain leading to dementia, either solely or in conjunction with each other (5). Thus, this study was undertaken to assess the relationship within glycemic profile & cognition and to check the sensitivity of the several insulin resistance indices which are currently used as surrogate markers of IR.

MATERIALS AND METHODS

This is a cross-sectional study and was conducted on a total of 232 individuals belonging to the age bracket of 40-70 years of both genders. The study was approved by the ethical committee of the Institution. The subjects were selected for the study after obtaining written informed consent. Inclusion criteria consisted of those with established diabetes mellitus and Subjects with complications like retinopathy, nephropathy and coronary artery disease and existing dementia were excluded from the study.

Fasting serum glucose, insulin, HbA1c was measured. Insulin was analyzed by ELISA using automated ELISA reader and washer from Bio Rad Laboratories as per the manufacturers' instructions. Glucose levels were estimated using fully automated clinical chemistry analyser Toshiba 40 FR from Agappe diagnostics. HbA1c was estimated by HPLC method using Bio-Rad analyser.

Insulin resistance indices like HOMA-IR, HOMA-β and QUICKI were calculated using a validated formula.

HOMA-IR = Glucose × Insulin /405
HOMA-β = (360× Insulin) / (Glucose-63) %
QUICKI = 1 / [log (fasting insulin μU/mL) + log (fasting glucose mg/dL)] (6)

Cognition levels were assessed and scored using the 3MS test. This test includes a questionnaire which assesses the subjects' various cognitive modalities like attention, perception, short- and long-term memory, ability to follow the given verbal and written commands. The total score is for 100 and scores below 75 is considered as impaired cognition (7).

Statistical analysis

Descriptive statistics such as Mean and Standard deviation (SD) was used to describe continuous variables & numbers and percentages will be used for categorical variables. Independent t test was used to compare the parameters between study and control groups. The significance was tested at 5% level of significance. Pearson's correlation test was applied to study the relationship between the glycemic values with 3MS scores. The data was analyzed using SPSS for windows (Version 22).

Table 1: Comparison of study participant characteristics between diabetic and non-diabetic groups

Characteristics	**Diabetics (n=126) Mean ± SD**	**Non-diabetics (n=106) Mean ± SD**	**P value**
Age (years)	57.68 ± 5.24	58.47 ± 5.59	0.11
Gender	M: F (61:65)	M: F (56:50)	
3MS Score (76 – 100)	78.83 ± 6.21	86.74 ± 5.59	0.0001**

** Statistically highly significant

RESULTS

The characteristics between the study (diabetics) and control (non-diabetics) groups are shown in Table 1. There was not much difference in the age and gender distribution. But there was a statistically significant difference between the two groups in 3MS scoring which showed a decline in cognitive performance among diabetics when compared to that of non-diabetics.

The glycemic profile and insulin resistance indices are presented in Table 2. There was a statistically significant difference in these parameters among both the groups. The diabetic group exhibited a higher FBS, HbA1C and FSI values and a higher HOMA-IR and HOMA-β and a significantly lower QUICKI values.

Table 2: Comparison of glycemic parameters between diabetic and non-diabetic groups

Glycemic profile (n=232)	**3MS score**	
	R value	**P value**
FBS (mg/dL)	-0.327	< 0.0001**
HbA1c %	-0.431	< 0.0001**
FSI (mIU/L)	-0.264	< 0.0001**
HOMA-IR	-0.3	< 0.0001**
HOMA-β	-0.039	0.51
QUICKI	0.294	0.0001**

**Statistically highly significant

Table 3: Correlation between 3MS scores and glycemic profile

Glycemic profile	Diabetics (n=126) Mean ± SD	Non-diabetics (n=106) Mean ± SD	P value
FBS (mg/dL) (70 to 100 mg/dL)	119.29 ± 36.15	91.89 ±11.66	0.0001**
HbA1c % (< 5.7 %)	7.21 ± 1.46	5.57±0.30	0.0001**
FSI (mIU/L) (2 to 25 mIU/L)	11.78 ± 6.15	7.03±3.05	0.0001**
HOMA-IR (1-2.5)	3.64 ± 2.49	1.61± 0.77	0.0001**
HOMA-β (<100)	119.22 ± 125.83	100.05±52.04	0.03*
QUICKI (>0.339)	0.33 ± 0.03	0.37± 0.04	0.0001**

* Statistically significant, ** statistically highly significant

The glycemic profile and insulin resistance indices are presented in Table 2. There was a statistically significant difference in these parameters among both the groups. The diabetic group exhibited a higher FBS, HbA1C and FSI values and a higher HOMA-IR and HOMA-β and a significantly lower QUICKI values. Table 3 shows that the 3MS values were negatively correlated with glycaemic status of the subjects and it is statistically significant.

DISCUSSION

In this study, we have found that Insulin resistance plays a pivotal role in cognitive impairment. Insulin possesses a major role in maintenance of normal brain functioning (8, 9). Optimum insulin actions require an interaction with insulin receptors at the target organs that are expressed well in areas like hippocampus and cerebral cortex. The insulin and its receptor complex leads to activation of a unique signaling cascade inside the cells which includes a tyrosine kinase activity in energy metabolism. These even safeguard and support neurons by modulating glucose metabolism and facilitate the learning, long term potentiation and memory consolidation by adjusting the quanta of neurotransmitter flux (10).

As insulin controls glucose metabolism in the neuronal cells of the brain, IR can primarily cause decline in cognitive function on its own. A study has shown that deranged glucose metabolism might significantly elevates the likelihood of cognitive dysfunction especially in stroke patients (11).Chronic hyperglycemic status has said to be associated with dwindling of glucose transporters such as GLUT1 in endothelium that might direct to glucose deprivation along with excitotoxicity and could account for neuro-cognitive complications of T2DM (12).

The consequence of Insulin resistance on cognitive function may involve multiple mechanisms. IR may promote Aβ metabolism and hyperphosphorylation of Tau protein, resulting in neuronal degeneration and metabolic derangements together with cognitive dysfunction under state of hyperinsulinemia (13).
Insulin receptors present in the brain are distributed highly in learning and memory regions (16). It has been shown that IR impair brain tissue oxygen utilization and metabolism, Peroxisome Proliferator-Activated Receptor γ (PPARγ) downregulation, along with upregulation of advanced glycation end products (AGE) and Receptor for Advanced Glycation End product (RAGE) levels, and also increases the phosphorylation process of Nuclear Factor kappa B (NF-κB), thereafter, enhancing the interactions between the AGE-RAGE path and PPARγ in insulin resistance animal models (14). Hyperinsulinemia could raise the levels of inflammatory cytokines like interleukin (IL)-1a, IL-6, and tumor necrosis factor (TNF)-α in cerebrospinal fluid (CSF) and plasma (15, 16) and added oxidative stress leads to early cognitive impairment (17).

The underlying mechanisms linking diabetes and dementia are exposed with continuous studies on it. Undoubtedly, given the well-established process of brain damage involves cerebro-vascular distortion due to vascular complications of T2DM. It is now believed that diabetes and raised HbA1c, the validated biomarker of T2DM, has said to increase the chances of stroke, and thereby, enhances the risk of cognitive decline and dementia, including the commonest vascular dementia (18).

In the present study the fasting serum insulin levels were negatively correlated with the cognition scores which indicate hyperinsulinemia can lead to deterioration of cognition in diabetics early than healthy individuals. It can be explained by the mechanism that, hyperinsulinemia can bring on hypercortisolemia via the hypothalamo-pituitary-adrenal axis, modulating the process of long-term potentiation in hippocampus and long-term depression via inhibition of granule cell regeneration, and ultimately blunting the cognitive function. Insulin resistance in the brain, especially in the hippocampus and the cerebellum, seems to be an early feature of Alzheimer's disease. In addition, accompanied resistance offered by insulin-like growth factor 1 (IGF-1) and conjoined dysfunction of IRS-1-PI3K pathway, triggered by Aβ oligomers, results in cognitive failure (19).

Furthermore, insulin resistance, whether central or peripheral, both could involve increased blood glucose and AGEs, and can even impair adipokine levels like leptin and others (20). Inflammatory changes in the periphery and brain areas may be an additional key factor which explains the connection between T2DM and cognitive dysfunction (21, 22).

QUICKI is derived by computing the inverse of the sum of the logarithmically expressed values of fasting glucose and insulin. A value of less than 0.339 indicates insulin resistance and is associated with a trend towards increasing insulin resistance, obesity, and cardiovascular disease (23).

It has also been postulated that disrupted insulin and IGF-1 signaling pathways may lead to suboptimal neurotransmitter functioning, such as dopamine. Functioning of astroglial cells and brain endothelial cells involved in formation and functioning of blood-brain barrier (BBB), metabolic processes undergoing in mitochondria and associated oxidative stress, modulation of the microtubule-associated tau protein phosphorylation and clearance of Aβ proteins and of amyloid fibrils, synthesis of cholesterol in the brain which is crucial for myelination of neurons and membrane functioning, glucose and fat metabolism in specific areas of the brain, which could relate to overall neurocognitive dysfunction (24).

CONCLUSION

The present study showed that Insulin resistance is a potential risk factor for initiation and progression of cognitive decline in elderly type 2 diabetic patients. Considering these findings, action toward early recognition, diagnosis and effective therapeutic management to reduce IR seems to have major implications in the prevention of cognitive decline.

CONFLICT OF INTEREST

Authors declare no conflicts of interest.

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