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 ORIGINAL PAPERS

Preliminary Data on the Interactions Between Dementia and Some Metabolic Disfunctions

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Abstract. *Alzheimer's disease is a progressive neurodegenerative condition correlated with the aging process, characterized by the progressive decline of cognitive functions and behavioral and personality changes. We assessed here the sample of 33 subjects and each of them was submitted to the mini–mental state examination (MMSE) to assess the severity of dementia. Our results showed that Type 1 diabetes is caused by the destruction of beta cells resulting in absolute insulin deficiency, and type 2 diabetes is caused by the continuous progression of insulin secretory deficiency and insulin resistance. The present study showed how insulin resistance and high insulin levels in type 2 diabetes, factors outside the CNS, were reported to induce a decrease in brain insulin, with subsequent impairment of signaling pathways associated with learning and memory, neural survival, energy metabolism and plasticity, thereby affecting cognition.*

Keywords: Alzheimer, dementia, diabetes, insulin resistance.

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1. Introduction

Alzheimer's disease (named after the German psychiatrist Alois Alzheimer) is the most well-known type of dementia and can be defined as a slowly progressive neurodegenerative disease characterized by neuritic plaques and neurofibrillary tangles and accumulation of beta-amyloid peptide in the most affected area of the brain, medial temporal lobe and neocortical structures [1].

Alois Alzheimer described the first case of the disease, which would later bear his name, at a congress in Tübingen, Germany, in 1906 [2]. He described "miliary bodies"

as amyloid plaques and "dense bundles of fibrils" as neurofibrillary tangles, which we now recognize as the neuropathological hallmarks of Alzheimer's disease (AD). In 1985, researchers were able to purify amyloid plaque cores and, in doing so, identified amyloid β peptide (Aβ) as the major component of these extracellular deposits [3]. This discovery led to the cloning of the gene encoding the amyloid precursor protein (APP) [4] the molecule from which Aβ is derived. In 1986, it was shown that neurofibrillary tangles are composed of abnormally hyperphosphorylated forms of the tau protein [5].

These important achievements in the 1980s marked the beginning of modern AD research and led to a detailed knowledge of APP metabolism, Aβ generation and tau homeostasis. While examining the brain of his first patient, who was described as having progressive memory loss and dual personality, before he died, Alois Alzheimer noted the presence of amyloid plaques and massive loss of neurons, and described the condition as a severe disease of the cerebral cortex. Emil Kraeplin, who was the first German psychiatrist, considered the founder of modern scientific psychiatry, named this condition, Alzheimer's disease, for the first time in his textbook of psychiatry, in the 7th edition [6].

There is evidence that hyperglycemia is a possible risk factor for the development of mild cognitive impairment, even Alzheimer's disease (AD) [7, 8, 9, 10]. Studies of the brains of patients with AD, that were not diagnosed with type 1 or type 2 diabetes, found similar symptoms as those of diabetes patients [11]. The installation of abnormal glycemic levels was linked to progressive long-term deterioration of the brain's ability in using and metabolizing glucose, simultaneously with a cognitive decline of the brain, including memory loss, difficulty in finding words, various changes in behavior and personality [12]. Some studies have demonstrated that insulin can cross the blood-brain barrier, emphasizing its role in controlling tau phosphorylation and protecting the CNS against β-amyloid accumulation through a mechanism involving the insulin-degrading enzyme downregulation [13]. Reduced insulin signaling may increase the activity of the enzyme glycogen synthase kinase 3, which may promote tau and NFT formation [14].

These findings have led to the theory that drugs used in diabetes may alter the pathophysiology of AD [15]. Insulin itself was proposed to control neurotransmitters releasing at the level of synapses, and the signaling pathways responsible for learning and long-term memory [16]. Interestingly, neurotoxins such as amyloid-beta-derived diffusible ligands can affect insulin signaling [17]. The final glycation products present in hyperglycemic states, which generate oxidative stress and implicitly cellular damage, were also detected in patients with AD [18]. There are also reports of patients with AD with symptoms characteristic of metabolic syndrome, such as greatly increased lipid profile parameters, obesity quantified by large waist circumference and high blood sugar [19, 20].

2. Material and Methods

2.1. Selection of human patients

The sample of subjects selected from the database of the Socola Institute of Psychiatry, Iasi, Romania, between January and July 2022, included 33 patients diagnosed with various forms of dementia, Alzheimer's disease (AD) and diabetes mellitus (DM). Diagnoses of dementia and Alzheimer's were based on standard criteria. Each of the patients underwent a mini-mental state examination (MMSE) to assess the severity of dementia.

2.2. Identification of parameters in order to correlate the degree of cognitive degradation with the severity of diabetes

In the patients in the current study, the following parameters were taken into account: form of dementia, MMSE score, diagnosis of diabetes, blood glucose value, cholesterol value, triglyceride value, psychiatric medication, medication for the type of diabetes discovered. The MMSE score (minimum mental state examination) is an exam to assess cognitive deterioration. It is a test used to screen cognitive function as a whole; It also includes items that can assess orientation, the possibility of recalling words, the assessment of attention and calculation, the assessment of language and visuospatial skills [27].

2.3. Studies in human patients to correlate cognitive impairment with diabetes severity.

In these patients, the following parameters were considered: form of dementia, MMSE score, diagnosis of diabetes, blood glucose value, cholesterol value, triglyceride value, psychotropic medication, medication for the type of diabetes discovered, in order to correlate the degree of cognitive degradation with the severity of diabetes as well as studying how specific medication for Alzheimer's disease and diabetes influences the pathological picture of these diseases and interactions of them.

3.Results

3.1. Distribution of dementia types in the patients sample

Following the evaluation of the sample of 33 patients, these were divided into the following categories: - mixed dementia medium form 43%; - mixed dementia, AD and vascular dementia 18%; - vascular dementia 15%; - severe form mixed dementia 9%; - mild dementia 6%; - medium form dementia 6%; - mixed dementia, epilepsy 3% (fig. 1).

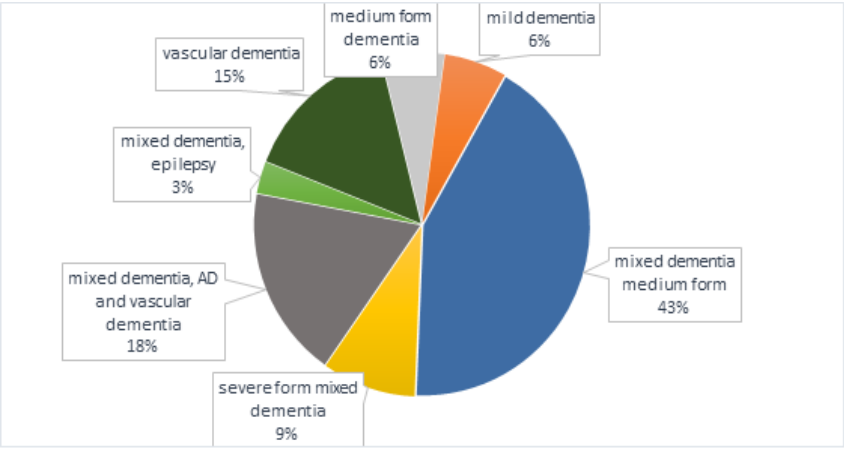


Fig. 1. Distribution of dementia types in the patients sample

3.2. Prevalence of pathologies associated with Alzheimer's disease, diabetes and obesity

Among the associated pathologies, those that are the subject of the present study are diabetes and obesity. Analyzing the prevalence of patients who presented these pathologies from the total number of patients, we found the following data: - in the medium form of mixed dementia group, 7% of patients presented diabetes; - in the group of mixed dementia, Alzheimer's disease and vascular dementia, 16.6% of patients had diabetes; - in the vascular dementia group, 60% of patients had diabetes; - for the other types of dementia, no cases of diabetes were registered (fig. 2); - in the mild dementia group, 50% of patients were obese; - in the medium-form mixed dementia group, 14.2% of patients had obesity; - for the other types of dementia, no cases of obesity were registered (fig. 3).

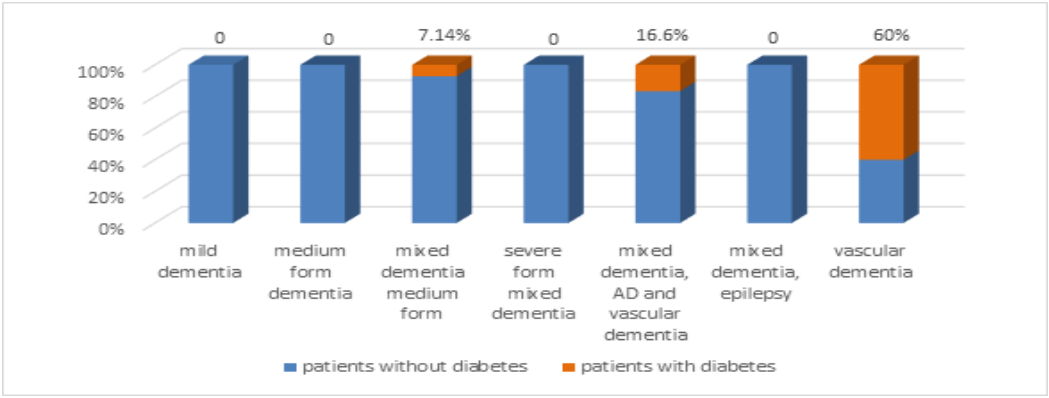


Fig. 2. Prevalence of diabetes cases in the sample of patients

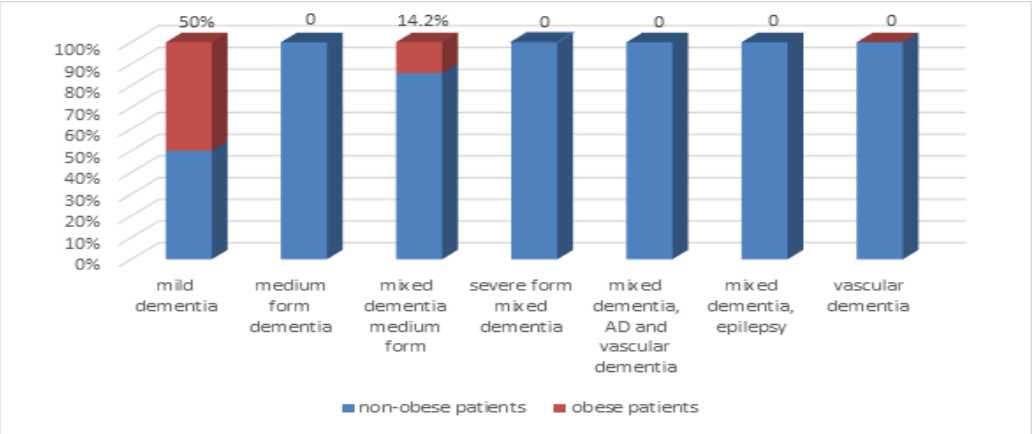


Fig. 3. Prevalence of obesity cases in the sample of patients

3.3. Severity of dementia according to the MMSE score

Each of the patients was submitted to the mini–mental state examination (MMSE) or Folstein test questionnaire to assess the severity of dementia. The results of the 30-point questionnaire reflecting the degree of cognitive impairment are showed in fig.4.

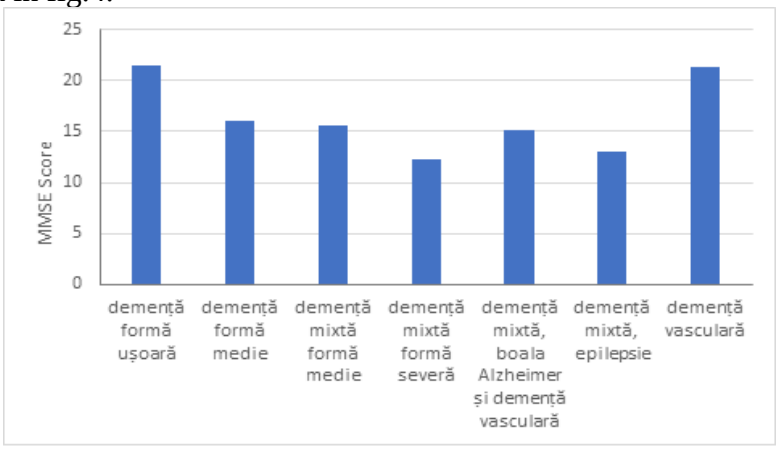
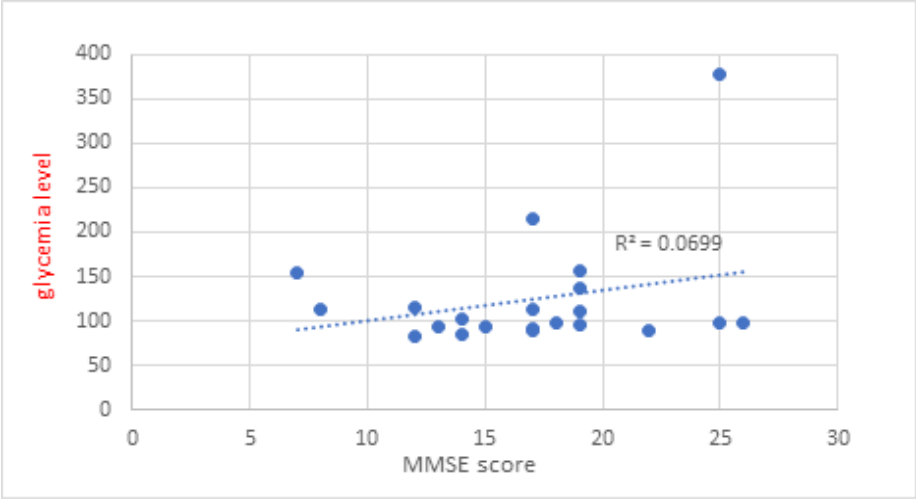


Fig. 4. Severity of dementia according to MMSE score

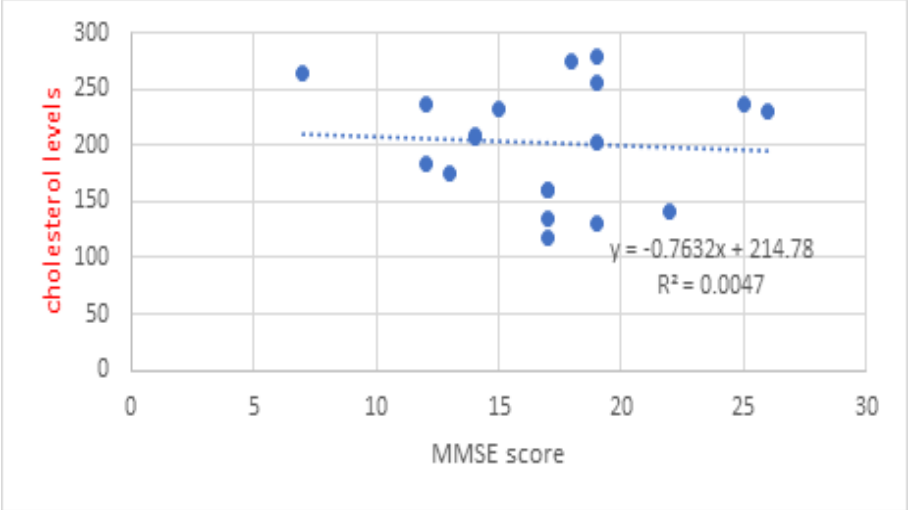
3.4. Correlations between MMSE scores and blood sugar, cholesterol and triglycerides levels of the patients in the analyzed sample

The levels of blood sugar, cholesterol and triglycerides for most of the patients were collected from the patients database and correlations were made with the respective individual MMSE score, *i.e.* the severity of dementia. Pearson correlation between the MMSE scores and blood sugar values (figure 5.A) showed a weak to moderate statistical relevance (Pearson corel. = 0.3), if all

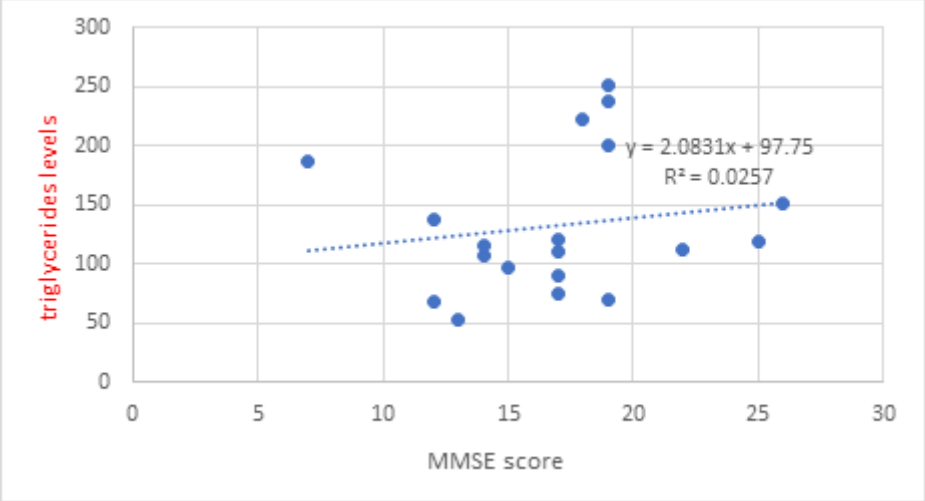
individual values were correlated. Similarly, in the case of correlations between the MMSE indices and cholesterol levels (figure 5.B), and between the MMSE indices and triglycerides levels (figure 5.C) weak Pearson correlations were obtained (Pearson correl. = -0.01 and respectively 0.16) (fig. 41). A possible influence of the medication administered to improve the symptoms of dementia or glycemia cannot be excluded when considering these unconvincing results, that would lower the MMSE scores in the more severe cases.



A. Correlations between MMSE score and sugar levels



B. Correlations between MMSE score and cholesterol levels



C. Correlations between MMSE score and triglycerides levels

Fig. 5. Pearson correlations between the MMSE scores and metabolic markers

29 patients of the total sample of 33, i.e. 88% from the patients, received psychotropic medication: 18 patients received memantine, 6 received piracetam, 4 received donepezil, 4 pramistar, 2 cerebrolysin, 2 cavinton, 1 betaserc, 1 rivastigmine, 1 galantamine. Four patients out of the 33 studied, i.e. 12% from the total, required medication for diabetes (insulin, metfogamma, glucovance, siofor, lipantil, forxiga).

Another method of statistical analysis was applied based on the comparison of parameter averages per subgroups of pacients. The correlations between the percentage averages of patients with diabetes according to the type of dementia and the average glycemia levels showed a strong correlation between the type of dementia and the blood glycemia at a value of 0.76 (fig 6.A).

These correlations were very strong for only certain groups of dementia (the mixed dementia, Alzheimer's disease and vascular dementia group), which could suggest a glycemic vulnerability of only certain subtypes of patients. Analysis of the correlations between the percentage averages of patients with diabetes according to the type of dementia and cholesterol level averages also showed a very strong positive Pearson correlation between the two variables at a value of 0.84 (fig. 6.B). Analyzing the correlations between the percentage averages of patients with diabetes according to the type of dementia and the averages of triglycerides levels, we observed again strong significant correlations between the two variables at a value of 0.70 (fig. 6.C).

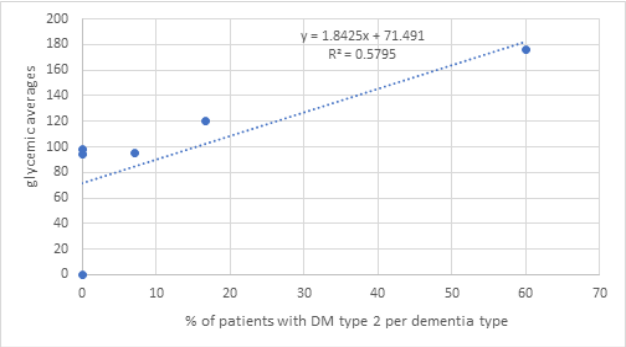


Fig. 6.A. Correlations between the percentage of patients with DM type 2 per dementia type and glycemic averages

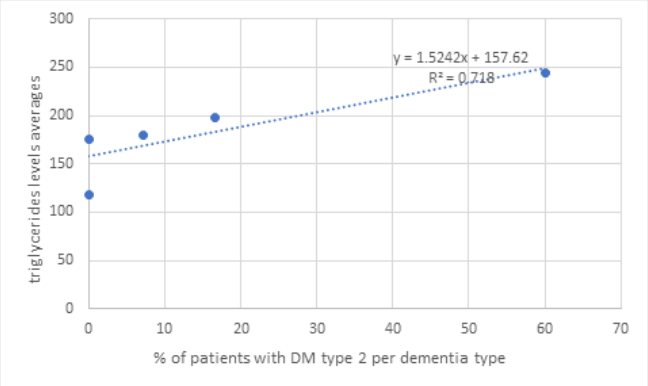


Fig. 6.B. Correlations between the percentage of patients with DM type 2 per dementia type and cholesterol levels averages

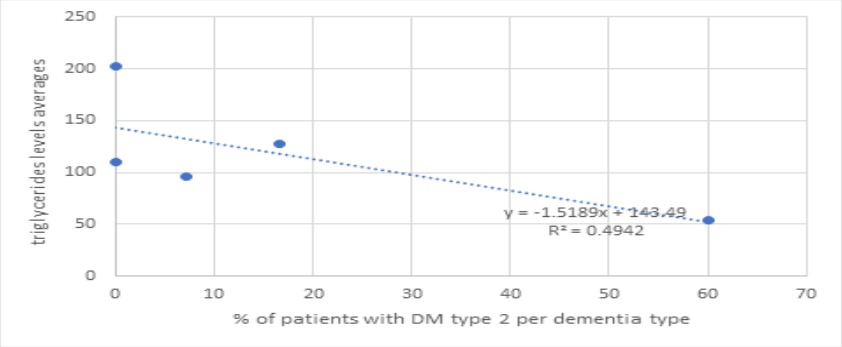


Fig. 6.C. Correlations between the percentage of patients with DM type 2 per dementia type and triglycerides levels averages

Fig. 6. Pearson correlations between the percentage of patients with DM type 2 per dementia type and metabolic markers averages

3.5. Incidence of elevated glycemic values by type of dementia

The incidence of abnormally elevated blood sugar levels, was overall high in the analysed sample. Out of the 29 patients for whom blood sugar levels were registered in the database, 11 had abnormal blood sugar fluctuations: 7 patients with values above average (110-160 mg/dl) and respectively 4 patients with very high values (over 200 mg/dl) (fig.6).

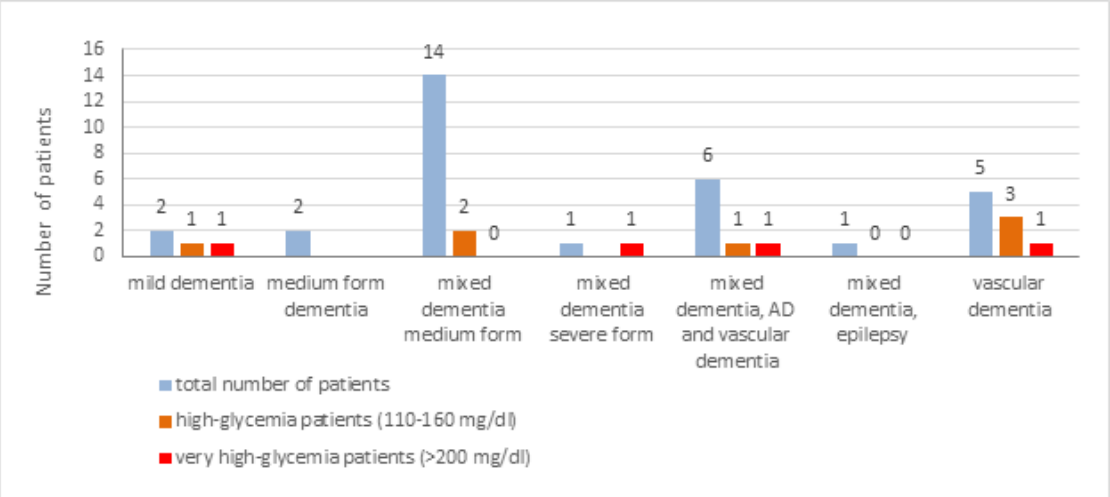


Fig. 7. Incidence of high glycemic values according to the type of dementia

3.6. Correlations between psychotropic medication and MMSE scores

The correlations between psychotropic medication and diabetes were difficult to assess for the provided data sets, requiring much larger samples and also data collecting at different intervals. Given these limitations, on the available data, the MMSE scores (gray dots, figure 8) are generally higher/better when patients followed psychotropic drug treatment. An exception occurs in the case of vascular type dementia where the MMSE score is very high (close to normal values); it should be noted at the same time that this is also the type of dementia with the highest incidence of DM.

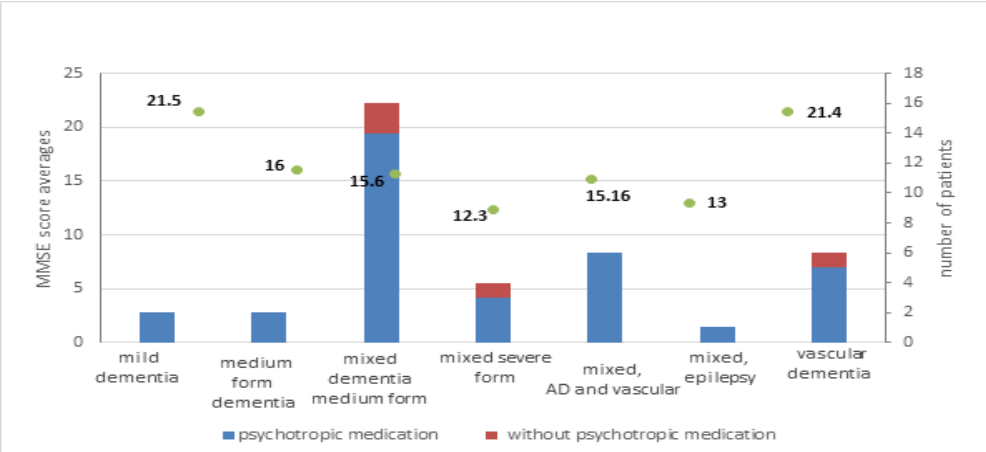


Fig.8. Psychotropic medication and MMSE scores

Concluding remarks

Type 1 diabetes is caused by the destruction of beta cells resulting in absolute insulin deficiency, and type 2 diabetes is caused by the continuous progression of insulin secretory deficiency and insulin resistance. Insulin resistance is associated with obesity and is characterized by the inability of target tissues to respond to insulin. Type 1 diabetes is characteristic of children and young adults, and type 2 diabetes for the other population categories [22]. More recently, a new form of diabetes, type 3 diabetes, closely related to metabolic syndrome is described, that alters memory processing, by mechanisms related to insulin resistance of the brain, defects in insulin signaling pathways, accumulation of neurotoxins, and neurodegeneration [23, 24]. Regarding the insulin resistance, peripheral insulin resistance could be involved in deficiencies in hippocampal insulin signaling pathways and dysregulation of brain metabolism, while central insulin resistance is reported to be linked to specific symptoms of Alzheimer's disease, hyperphosphorylation of tau protein, increased oxidative stress, neuroinflammation, and potentiation of Aβ toxicity [25, 26].

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