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Cognitive impairment in type 2 diabetic patients treated with metformin in comparison with those taking glibenclamide

Abstract

Introduction: Metformin and sulfonylureas are different in their mechanism of action whether they manipulate insulin levels for diabetes treatment. We compared the cognitive impairment among type II diabetic patients treated with metformin or glibenclamide (from sulfonylureas group).

Method: Within a randomized cross-sectional study, 314 subjects were recruited from Isfahan Endocrine and Metabolism Research Center, consisting of 4 groups. Group 1 was treated exclusively by metformin and Group 2 with glibenclamide, Group 3 was patients treated by diet and Group 4 was healthy individuals. Cognitive function was estimated among patients with Mini Mental State Examination (MMSE).

Results: In diabetic groups mean MMS was significantly lower than healthy individuals (27.46±0.197 vs. 28.31±2.24, P-value=0.000). No difference was observed among diabetic groups. (Group1: 27.44±0.415, Group2: 27.61±0.405, Group3: 27.34±0.403, P-value=0.899).

Conclusion: All three groups of diabetic patients were similar statistically in cognitive function evaluated by MMS, which means metformin and glibenclamide regardless of their mechanism of action may not differs the patient's vulnerability to cognitive problems.

Keywords: Dementia, Diabetes, Glibenclamide, Metformin, Mini Mental State Examination (MMSE), Sulfunylurea

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Mohammad Saadatnia,[1,2] Mansour Siavash,[3] Kiandokht Keyhanian,[1,4,6] Adel Hamid,[5] Arash Amini,[5] Vahid Davoudi,[1,4,7]

[1]Isfahan Neurosciences Research Center, Isfahan University of Medical Sciences, Iran
[2]Isfahan Medical Education Research Center, Isfahan University of Medical Sciences, Iran
[3]Isfahan Endocrine & Metabolism Research Center, Isfahan University of Medical Sciences, Iran
[4]Isfahan Physiology Research Center, Isfahan University of Medical Sciences, Iran
[5]Isfahan University of Medical Sciences, Iran
[6]Isfahan Medical Students Committee, Isfahan University of Medical Sciences, Iran
[7]Sina Trauma and Surgery Research Center, Tehran University of Medical Sciences, Iran

Correspondence: Mohammad Saadatnia, Isfahan Neurosciences Research Center, Isfahan Medical Education Research Center, Isfahan University of Medical Sciences, Azzahra Hospital, Isfahan-8158695954, Iran, Tel 989131147179, Email mosaadatnia@yahoo.com

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Abbreviations: AD, Alzheimer's Disease; DM, Diabetes Mellitus; MMSE, Mini Mental State Examination; IEMRC, Isfahan Endocrine and Metabolism Research Center

Introduction

Poor cognitive function is reported to be associated with Type 2 diabetes, although the etiology of this phenomenon is still unclear.[1-3] Comparing with non-diabetic individuals, the incidence of dementia in diabetic patients has increased about 50-100%, in both Alzheimer disease (AD) and vascular dementia.[4] There are still debates whether cognitive impairment is a consequence of high blood glucose level or is due to diabetes induced hyperinsulinemia. However, hyperinsulinemia has attracted more attention for playing an essential role in diabetes effects on cognition.[5-8] To conquer receptor insensitivity, during diabetes induced insulin resistance, hyperinsulinemia is provoked as a compensatory adjustment.[9,10] Neurotoxic effects of hyperinsulinemia could be responsible for further cognitive impairment during diabetes. High amounts of insulin may threat survival of neurons in culture as well as sensitizing them to toxins and stress related damages.[11] On the other hand, insulin-degrading enzyme acts as a linkage between hyperinsulinemia and AD by degrading insulin, along with amyloid-beta peptide (Abeta). Abeta is a short peptide found predominantly in the brain affected by AD. When there is hyperinsulinemia, through this competition, Abeta may rise in the brain and cause AD.[12,13]

Several anti-diabetic drugs are available to decrease blood glucose levels, even though their mechanisms of action are variable. Gelibenclamide also known as glyburide is a second generation of sulfonylureas that control hyperglycemia through insulin secretagogues. Their action is performed on b cells through blocking ATP dependent potassium channels.[14] Metformin which is another common anti-diabetic drug lowers hepatic glucose production by decreasing insulin resistance and reducing carbohydrate uptake within intestine, without inducing hyperinsulinemia and hypoglycemia.[15-20] Considering that these two drugs are different in their mechanism of action in their way of manipulating insulin levels, we performed this study to compare cognitive impairment among type II diabetic patients treating with metformin with those taking glibenclamide, a drug categorized in sulfonylureas group.

Materials and methods

Patients

Within a randomized cross-sectional study, 314 subjects were recruited from Isfahan Endocrine and Metabolism Research Center (IEMRC) from June 2007 to September 2007. IEMRC gathers almost all information concerning disease onset and progression of diabetes and other endocrine diseases. Subjects were ordered in 4 groups. Group 1 and 2, were consisting of 79 patients each with well-controlled type 2 diabetes who were treated exclusively by metformin (Group 1) or glibenclamide (Group 2). Group 3 contained 78 well-controlled diabetic patients on diet and group 4 consisted healthy subjects without diabetes who came to the clinic for the evaluation of their health status and were considered healthy according to our exclusion criteria.

The quality of the diabetic control was assessed according to Hemoglobin A_{1c} levels. HbA_{1c} level of 4.3-5.8% was considered as well controlled diabetes. Subjects who were treated with any drug other than metformin and glibenclamide were not enrolled. In addition, subjects affected by malignancy, inflammatory diseases (such as collagen disease, thyroid disease and viral hepatitis), severe micro and macro-vascular complications of diabetes (such as renal failure), and severe cardiovascular diseases (such as myocardial infarction and unstable angina) were excluded during subject's retrieval. Patients with history of recurrent Hypoglycemia and dementia not due to diabetes were not contributed to the study. Subjects with audio-visual problems were also excluded for preventing any trouble during assessment of cognition. VitB12 is doubted to participate in pathogenesis of dementia.[21] Metformin is also known to reduce VitB12 levels. Consequently, the serum level of VitB12 was measured in all subjects to exclude patients with VitB12 deficiency.

The Ethical committee in Isfahan University of Medical Sciences approved the study design and all subjects had fulfilled informed consent prior to investigation.

Subjects were evaluated for common physical check-up by a general physician in the morning. They were asked to complete a questionnaire about their demographic characteristics, level of education and duration of diabetes. Serum levels of HbA_{1c}, HDL, LDL, cholesterol and FBS were determined in all subjects as well.

Cognitive assessments

Cognitive function was estimated with Mini Mental State Examination (MMSE).[22] Well-trained psychological examiners examined each subject by a same test in a same order. Dementia was defined as MMS<20 for illiterates and MMS<24 for educated subjects.

Statistical analysis

SPSS version 13 was employed and data were reported as mean± standard deviation. Chi square was performed for comparing prevalence of dementia (MMS>24) within 4 groups. ANOVA, T-test and Univariate Test were carried out to analyse and compare MMS mean values.

Results

Among 314 subjects enrolled in our survey, 215 were females vs. 99 males. Sex and age distribution for all 4 groups were defined in Table 1.

There was no significant difference among four groups regarding sex distribution (Pvalue=0.33). Subjects were 31 to 80 years old. Three patients in group 1 were younger than 40. However, Group 2 was significantly older than group 1 and 3 and mean age of group 4 was also higher than group 3 (Group2 vs. Group1, P=0.004, Group2 vs. Group3, P=0.00, Group4 vs. Group3, P=0.003). Mean age of group 1, 2 and 4 was quite similar (Group1 vs. Group4, P=0.11, Group2 vs. Group4, P=0.38). No difference was found between groups 1 and 3 as well (Group1 vs. Group3, P=0.18).

Among diabetic patients treated with metformin (Group 1), one patient had a low level of vitB12 and subsequently was excluded from further analysis. Basic information obtained in the day of neurologic examination is displayed in Table 2. Serum levels of FBS, HbA_{1c}, and BMI and disease duration were not matched within four groups (P-values are reported in Table 2). MMS score was adjusted accordingly by means of R square and adjusted R square (R square: 0.213, Adjusted R square: 0.152). Diabetic patients had significantly lower MMS than healthy individuals (27.46±0.197 vs. 28.31±2.24, P-value=0.000). No difference was found among diabetic groups. (Group 1:27.44±0.415, Group 2:27.61±0.405 and Group 3:27.34±0.403, P-value=0.899). Serum level of FBS, duration of diabetes and level of education were also associated with MMS Score (Table 3). ANCOVA was employed for further adjustment among four groups. The results are shown in Table 4. MMS score was not associated with any of four groups using ANCOVA (P-value=0.25), however the same analysis with ANOVA showed significance (P-value=0.000).

Table 1 Sex and age distribution within 4 groups. Group1: Diabetic patients treated with metformin, Group2: Diabetic patients treated with glibenclamide, Group3: Diabetic patients who were on diet, Group4: Normal subjects without diabetes

	Group 1	Group 2	Group 3	Group 4
Age	53.02±8.5 Min:35, Max:80	57.11±9.08 Min:40, Max:76	50.74±12.23 Min:31, Max:76	55.89±9.1 Min:35, Max:78
Male	N=58, 73.4%	N=49, 62%	N=61, 78.2%	N=31, 60.3%
Female	N=21, 26.6%	N=30, 38%	N=17, 21.8%	N=47, 39.7%
Highly Educated Subject	N=36,45.6%	N=38,48.1%	N=39, 50.0%	N=52,66.7%
Low Educated Subject	N=38,48.1%	N=35,44.3%	N=37,47.4%	N=23,29.5%
Non Educated Subjects	N=5, 6.3%	N=6, 7.6%	N=2, 2.6%	N=3, 3.8%
Mean Years of Education ± SD	9.18±4.19	9.50±4.14	9.47±3.96	10.70±3.81

Table 2 Risk factors for dementia among first 3 groups under study. Group 1: Diabetic patients treated with metformin, Group 2: Diabetic patients treated with glibenclamide, Group3: Diabetic patients who were on diet, MMS: Mini Mental State

	Group1	Group2	Group3	P value
Sex	Male; n:58, 73.4% Female;n:58,73.4%	Male; n:49, 62% Female; n:30, 38%	Male; n:61, 78.2% Female;n:17,21.8%	0.33
Age	53.02 ± 8.5	57.11 ± 9.08	50.74 ± 12.23	0.01
FBS (mg/dl)	136±38.5	144±43.6	131±15.3	0.000
HbA_{1c} (%)	6.69±1.41	8.26±9.14	5.44±0.57	0.005
HDL (mg/dl)	46±10.4	44±8.6	48±7	0.021
LDL (mg/dl)	97±32.18	103±28.1	136±40.14	0.000
Cholesterol (mg/dl)	189±54.42	181±44.29	167±33.45	0.010
Weight (kg)	70.11±11	68.55±13	82.35±10	0.000
Height (cm)	158.51±8.1	160.41±7.5	159.96±7.5	0.282

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Table Continued...

	Group1	Group2	Group3	P value
Systolic Blood Pressure	120±11.5	121±10.5	119±10	0.126
Disease Duration (Years)	6±3.9	7±3	5±1.7	0.000
Level of Education (Years)	9.18±4.19	9.50±4.14	9.47±3.96	0.062
BMI	28.97±4.09	26.56±3.59	28.38±4.07	0.002
MMS Score	26.89±3.61	26.67±2.99	28.20±2.02	0.000

Table 3 Association of MMS scores with risk factors for dementia

	FBS	HbA_{1c}	HDL	LDL	Cholesterol	Disease Duration	Level of Education	Age	Sex	Weight
P value	0.005	0.63	0.76	0.96	0.78	0.02	0.000	0.48	0.37	0.95
R square	-2.84	-0.47	0.29	0.04	6.26	-5.70	5.943	-5.70	0.89	-0.06

Table 4 Association of MMS scores with risk factors for dementia using ANCOVA model

	P value
Groups Under Study	0.25
Age	0. 82
Sex	0.84
Years of Education	0.000
Disease Duration	0.139
FBS	0.004
HbA_1C	0.63
Blood Pressure	0.62
Cholesterol	0.94
LDL	0.96
HDL	0.60
Triglyceride	0.62
BMI	0.89

Dementia scoring was also not associated to the type of medications. Among different risk factors only the level of education showed significant relationship with dementia (P-value<0.05).

Discussion

All three groups of our patients were similar statistically in cognitive function concerning MMS, which means metformin and glibenclamide regardless of their mechanism of action are not differently associated with vulnerability to cognitive decline. Quite identical to previously reported data,[1-4] we found diabetes to be associated with increased risk of cognitive impairment comparing healthy individuals. We evaluated the possible role of hyperinsulinemia in inducing dementia by comparing two drugs that differ in their mechanism of lowering blood glucose. Glibenclamide a subclass of sulphonylurea provokes hyperinsulinemia, while metformin acts in lowering hepatic glucose production and decreases insulin resistance, without changing insulin levels.[14-20] Sulphonylureas appear to increase the cardiovascular problems by blocking ATP dependent potassium channels. Among sulphonylurea subclasses glibenclamide has been associated with the risk of cardiovascular all-cause mortality[23-25] and is also reported to be associated with an elevated cancer-related mortality in diabetic patients.[26] However, Sulphonylureas have shown potentials in improving outcome after an acute ischemic stroke.[27-29] Metformin, in addition to its glycemic effects, seems to result in improvement on lipid profile and weight control.[30,31] Patients treated with metformin, are less frequently diagnosed with cancer and they have a lower risk of mortality from solid tumors comparing with patients treated with either insulin or Sulphonylureas.[26,32]

We found no difference in cognitive function among diabetic patients on diet or patients treated with drugs, when diabetes is controlled. Furthermore, among potential risk factors for dementia, FBS, disease duration and level of education were also associated with MMS score. While cholesterol, HDL and LDL levels were not accompanied with lower MMS scores. This result was in line with previous studies.[33,34] Elevated levels of FBS known as hyperglycemia, has toxic effects on neurons and makes them more vulnerable toward toxins.[35,36] Therefore, it might be the underlying mechanism for cognitive impairment detected in patients with high levels of FBS. Moreover, lower cognitive function seems to be associated with longer duration of diabetes as previously reported in most surveys.[37-39] Educated patients were less at risk for developing cognitive disturbance which could be caused by increased neurogenesis, synaptogenesis and brain vascularization associated with the high brain function.[40] DM has lots of destructive effects on multiple body organs. Diabetes affects both small and large vessels leading to major complications. The most common micro-vascular complications are kidney involvement, peripheral neuropathy and blindness. When affecting large vessels, cardiovascular diseases, myocardial infarction and stroke are most devastating consequences.[41] Diabetic patients are also more at risk for developing Alzheimer's disease as well as vascular dementia and also cognitive dysfunction without dementia.[42,43] Subjects in our study were 31 to 80 years old and this range contains also young subjects who were less than 40. But in the first two groups (treated with metformin or glibenclamide), only three patients in Group 1 were younger than 40. Moreover, our diabetic patients were statistically different regarding their BMI. Group 2 who were treated with glibenclamide were leaner than two other groups and may have less endogenous insulin production due to their lower BMI.[44]

Worldwide, AD is the most prevalent neurodegenerative disease that is predicted to double every 20 years if we cannot stop it by a preventive treatment.[45] Disturbed insulin actions in AD, has attracted more interest in insulin and insulin signaling mechanisms which are essential for AD-type neuro-degeneration and led to the term ''Brain Diabetes" instead of AD.[46,47] Thus pharmacological agents that can alter neuronal insulin resistance gathered a growing attention. Recent studies proposed controversial evidences about metformin action including for or against AD. In one way metformin improves insulin resistance in the brain in line with other parts of the body and does not influence higher hyperinsulinemia.[48] In other way there are still evidences that condemn metformin for increasing Aβ generation and secretion that can have potential side-effects in accelerating clinical manifestation of AD among patients affected by type-2 diabetes.[49] Our study protects the theory that even if metformin may have protective effects against cognitive decline caused by diabetes, it may also devastate the cognitive function itself. These two mechanisms may neutralize the whole effect of metformin on cognition that can elucidate our results which showed that metformin resulted in no improvement in MMS comparing glibenclamide or diet. However, our study was limited by numerous ways. The sample size is low and our study groups are rather young and not similar in age, FBS, HbA_{1c}, BMI and disease duration. Still we could not perform tests for measuring insulin levels.

Conclusion

All three groups of diabetic patients were similar statistically in cognitive function, which means metformin and glibenclamide regardless of their mechanism of action are not differently associated with patient's vulnerability toward cognitive impairment.

Acknowledgments

None.

Conflicts of interest

None.

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