RESEARCH ARTICLE

T2DM patients with depression have higher levels of hyperglycemia and cognitive decline than T2DM patients

Savitree Thummasorn[1], Sopida Apichai[1], Supat Chupradit[1], Pornpen Sirisattayawong[1], Pachpilai Chaiwong[1], Sirawit Sriwichaiin[2,3], Wasana Pratchayasakul[2,3], Nipon Chattipakorn[2,3], Siriporn C. Chattipakorn[2,3,4] *

1 Department of Occupational Therapy, Faculty of Associated Medical Sciences, Chiang Mai University, Chiang Mai, Thailand, 2 Neurophysiology Unit, Cardiac Electrophysiology Research and Training Center, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand, 3 Center of Excellence in Cardiac Electrophysiology Research, Chiang Mai University, Chiang Mai, Thailand, 4 Department of Oral Biology and Diagnostic Sciences, Faculty of Dentistry, Chiang Mai University, Chiang Mai, Thailand

* siriporn.c@cmu.ac.th, scchattipakorn@gmail.com

Abstract

The cognitive impairment, depression, a decrease in the ability to perform activities of daily living (ADLs), and salivary gland dysfunction, as indicated by the reduction of alpha-amylase activity, have been reported in patients with type 2 diabetes (T2DM). However, the effects of depression on cognitive function, salivary alpha-amylase activity, and ADLs in T2DM patients have never been investigated. In this study, 115 participants were divided into three groups, including 30 healthy people, 50 T2DM patients without depression, and 35 T2DM patients with depression. Then, the cognitive function, the level of depression, salivary-alpha amylase activity, ADLs, and metabolic parameters were determined. Results showed that T2DM patients had hyperglycemia and cognitive impairment. A decrease in the salivary alpha-amylase activity was observed in T2DM patients. Interestingly, T2DM patients with depression had higher level of hyperglycemia and cognitive impairment than T2DM patients. Additionally, cognitive function was associated with the salivary-alpha amylase activity in T2DM without depression, while the severity of depression was associated with the salivary-alpha amylase activity in T2DM patients with depression. Therefore, we concluded that T2DM caused the impairment of metabolism, decreased salivary alpha-amylase activity, and cognitive impairment. Furthermore, T2DM patients with depression had higher level of hyperglycemia and cognitive decline than T2DM patients.

Introduction

It has been established that type 2 diabetes mellitus (T2DM) causes several complications, such as cardiovascular disease, systemic inflammation, and neurodegenerative disease [1–3]. Previous studies have demonstrated that T2DM is a risk factor for mild cognitive impairment (MCI) [4], increased learning and memory deficits [5] as well as accelerated rate of cognitive

decline in patients with mild dementia [6]. Furthermore, T2DM causes neuropathy and leads to poor quality of life by decreasing one's ability to perform activities of daily living (ADLs) [1, 2] via increased the severity and progressive abnormalities in brain structures and cognitive function [7].

In addition to cognitive decline, recent clinical studies showed that the prevalence of depression was increased in the patients with T2DM [8, 9]. The studies showed that the symptoms of a major depressive episode included sadness combined with decreased energy, changes in thinking, and appetite changes [10], symptoms which may occur in T2DM patients with or without depression [11]. Accordingly, the studies reported that depression was associated with adverse effects for people suffering from T2DM, including impairment of glycemic control, eating habits, and exercise [12, 13]. However, the effects of depression on cognitive function and ability to perform ADLs in T2DM patients have never been investigated.

In addition to the impairment of cognition and ADLs, previous studies also found that the concentration of salivary alpha-amylase was increased under both physical stress, such as treadmill exercise, running, bicycle exercise [14] and psychological stress such as depression, and anxiety [15, 16]. Furthermore, it was established that the hyperglycemia and systemic inflammation in T2DM patients causes changes in the microvasculature and basal membrane of the salivary gland [17, 18], which lead to salivary dysfunction [17, 18]. Previous studies showed that salivary-alpha amylase activity decreased in diabetic rats, diabetic dogs [19, 20] and rats treated long-term with a high-fat diet [13]. Moreover, a recent clinical study demonstrated that low serum amylase levels were observed in patients with obesity, type 1 and 2 diabetes, and metabolic syndrome (MetS) [21]. However, the level of salivary alpha-amylase activity and its correlation with cognitive function or level of depression in T2DM patients with depression have never been investigated. All of those findings lead to our research hypotheses that 1) T2DM decreases the cognition and ability to perform ADLs as well as the salivary alpha-amylase activity; 2) T2DM patients with depression had higher level of these impairments than T2DM patient; and 3) the salivary alpha-amylase activity is correlated with cognition both in T2DM patients with and without depression.

Materials and methods

The study protocol was reviewed and approved by the Institutional Ethics Committee of the Faculty of Associated Medical Sciences, Chiang Mai University, Chiang Mai, Thailand (Ethic number: AMSEC-62EX-010). All participants gave written informed consent for participation in this study. All methods were performed in accordance with the relevant guidelines and regulations. In this study, 130 participants aged 45–70 years, both male and female, were divided into two groups: 30 healthy people (control group) and 100 diabetic patients. Of these, 85 diabetic patients met eligibility criteria and were included in the study. The eligibility criteria used in this study included a diagnosis of type 2 diabetes by a medical doctor, at least 1 year of drug treatment for T2DM, no physical disability, and the ability to sit for 90 minutes for all study protocols. Level of depression was assessed for all participants using the Thai version of the Patient Health Questionnaire (PHQ-9) as a screening tool for major depression [22]. 85 diabetic patients were then divided into two groups: diabetic without depression (n = 50) and diabetic with depression (n = 35). Metabolic function, cognitive function, salivary-alpha amylase activity, and ADL function were determined for each patient in all three groups.

Data collection

Researchers took history, sampled blood and saliva and assessed cognitive function, ADL, and depression level on the same day.

Biochemical measurements

For the measurement of glycemic indices in diabetic patients, blood samples were collected after a minimum of 12 h of fasting since the last meal or snack in order to measure biomedical indicators including HbA1c and fasting blood glucose (FBG) [23]. Blood samples were collected by licensed medical technologists and measured at the clinical analysis laboratory.

The cognitive function assessment

In this study, the Montreal Cognitive Assessment-Basic (MoCA-B) was used to detect cognitive impairment [24]. This questionnaire can detect mild cognitive impairment in individuals with limited education and can assess the different cognitive domains including visual perception, executive functioning, language, attention, memory, and orientation [24]. Test-retest reliability of MoCA-B was 0.91 (P < .001) and internal consistency was 0.82 [24]. The maximum score is 30 points; a score of 25 or above is considered normal. In this study, MoCA-B was administered by one occupational therapist and the time administered ranged between 15 and 20 min.

The assessment of depression

The Thai version the Patient Health Questionnaire (PHQ-9) was used to detect depression in patients with T2DM [22]. The Thai version of the PHQ-9 has acceptable psychometric properties for screening for major depression [22]. In the present study, depression was assessed based on the PHQ-9 scores. The maximum score is 27 points; a total score of 0 to 4 points is classified as "normal," 5 to 9 points as "mild depression," and 10 to 27 points as "Moderate to severe depression" [22]. In this study, the group of diabetic patients with depression included both mild and severe depression levels. In this study, PHQ-9 was administered by one occupational therapist and the time taken to administer the assessment ranged from 10 to 15 min.

Assessment of ability to perform activities of daily living (ADLs)

The Barthel Index (BI) is an assessment tool used to measure performance of the basic activities of daily living (B-ADL) or self-care. The BI assessment tool is divided into 10 items: feeding, personal toileting, bathing, dressing, grooming, controlling bladder, controlling bowel, transferring, mobility, and ascending and descending stairs [25]. The maximum score is 100 points; a total score of 0 to 20 points is classified as "total dependence", 21 to 60 points as "severe dependence", 61 to 90 points as "Moderate dependence", and 91 to 99 points as "independence" [25]. In this study, BI was administered by one occupational therapist and the time taken to administer the assessment ranged from 10 to 15 min.

The Lawton Instrumental Activities of Daily Living Scale (I-ADL) is an assessment tool used to measure ability to perform more complex ADLs necessary for living in a community [26]. Because I-ADL function is usually lost before B-ADL function, I-ADL assessment can identify the decline of physical and cognitive functions in older adults [26]. The I-ADL assessment tool is divided into 8 items: using a telephone, shopping, preparing food, housekeeping, doing laundry, transportation, being responsible for one's own medications, and handling finances [26]. The Lawton I-ADL scale scores each item as 0 ("less able") or 1 ("more able"), so the summary score ranges from 0 (low functioning, dependent) to 8 (high functioning, independent) [26]. In this study, this assessment tool was administered by one occupational therapist and the time taken to administer the assessment ranged from 10 to 15 min.

The assessment of salivary alpha-amylase activity

The saliva samples were collected in the morning. Participants were instructed not to eat, drink, or exercise before collection. To collect saliva samples, the passive drooling method was used [27]. Saliva was stored at −20˚C until the analysis of salivary-alpha amylase activity [27]. The salivary-alpha amylase activity was measured by using a commercial salivary alpha amylase kinetic enzyme assay kit [28]. This kit was specifically designed and validated for the kinetic measurement of salivary-alpha amylase activity [28]. The salivary-alpha amylase activity then was detected by using microplate reader at 405 nm [28].

Data analysis

All data were presented as mean value ± SEM. Comparisons were made using the one way ANOVA followed by the Fisher post-hoc test. Categorical variables were expressed as frequencies and comparison between groups was analyzed by using the Pearson χ^2 test. The correlation between each factor with the salivary-alpha amylase activity was analyzed using the linear regressions. A P value < 0.05 was considered to be statistically significant.

Results

General characteristics of the control, T2DM, and T2DM with depression groups

The general characteristics of participants are shown in Table 1. Our data show that gender, age, education, and occupation had no significant differences among the three groups (Table 1). Additionally, the duration of T2DM and duration of T2DM treatment showed no significant difference between the T2DM with depression and T2DM without depression at the time of this study (Table 1). Also, the underlying diseases, such as hyperlipidemia and

Table 1. General characteristics of the control, type 2 diabetes, and type 2 diabetes with depression groups.

General characteristics	Control	T2DM without depression	T2DM with depression
Gender (Frequency)			
Male/Female	12/18	12/38	10/25
Age (years)			
Average (SD)	61.37±0.72	59.88±1.04	61.54±1.63
Education (Frequency)			
Uneducated/Educated	6/24	14/36	15/20
Occupation (Frequency)			
Unemployed/Employee	8/22	10/40	15/20
Underlying disease (Frequency)			
Yes/No	4/26	44/6*	32/3*
T2DM Duration			
Average (SD)	-	18.82±3.32	14.14±4.27
Duration of T2DM treatment			
Average (SD)	-	15.54±2.23	12.34±2.83
PHQ9 score			
Average (SD)	0.80±0.85	1.50±1.27	7.54±2.86*,†

T2DM: Type 2 diabetes, SD: The standard deviation, PHQ9: the Patient Health Questionnaire-9

* p < 0.05 vs. control group,

† p < 0.05 vs. T2DM without depression

hypertension, had no significant differences among the three groups at the time of this study. Level of depression was determined by using a PHQ-9 screening. An increase of PHQ-9 score indicates an increase in the severity of depression [22]. Our results showed no significant difference in the level of depression between the T2DM without depression group and the control group (Table 1). The PHQ-9 screening also showed a significantly higher level of depression for the T2DM with depression group than for the control and T2DM without depression groups (p<0.05, Table 1).

The comparison of metabolic function between T2DM patients with depression and those without depression

Body weight, body mass index (BMI), fasting blood glucose (FBG) level, and HbA1c in both the T2DM with or without depression groups were significantly higher than the control group (p<0.05, Table 2). Interestingly, FBG level in the T2DM with depression group was significantly higher when compared with the T2DM without depression group (p<0.05, Table 2).

The comparison of cognitive function between T2DM patients with depression and those without depression

In this study, cognitive function was determined by using the MoCA screening and was represented in the data as a MoCA score, with 25 or above considered normal cognitive function [24]. Thus, the decreased MoCA score represents the decline of cognitive function. Our results showed that the MoCA scores of both T2DM group with or without depression group were significantly lower than the control group (p<0.05, Fig 1A). Interestingly, the MoCA scores in the T2DM patients with depression was significantly lower than T2DM patients without depression (p<0.05, Fig 1A).

In this study, ADL function was divided into two categories including basic ADLs (B-ADL) and instrumental ADLs (I-ADL). Our results show that the B-ADL function scores in both T2DM with or without depression groups were not significantly different when compared with control group (Fig 1B). In addition, our results demonstrated that I-ADL function scores in both T2DM with or without depression groups were not significantly different when compared with control group (Fig 1C). All of these findings indicated that depression did not affect the impairment of ability to perform ADLs in T2DM patient.

Table 2. Metabolic function of the control, type 2 diabetes, and type 2 diabetes with depression groups.

Glycemic indices	Control	T2DM without depression	T2DM with depression
Weight (kg)			
Average (SE)	68.53±1.18	77.42±1.41*	73.49±1.71*
BMI (kg/m^2)			
Average (SE)	19.41±0.26	29.55±0.62*	27.48±0.71*
Fasting blood glucose (mg/dl)			
Average (SE)	90.77 ± 0.99	119.58±3.91*	155.94±11.04*,†
HbA1c (%)			
Average (SE)	5.23±0.03	7.54±0.03*	6.66±0.06*

T2DM: Type 2 diabetes, SE: The standard error; HbA1c: Hemoglobin A1C; BMI: Body mass index

* p < 0.05 vs. control group,

† p < 0.05 vs. T2DM without depression
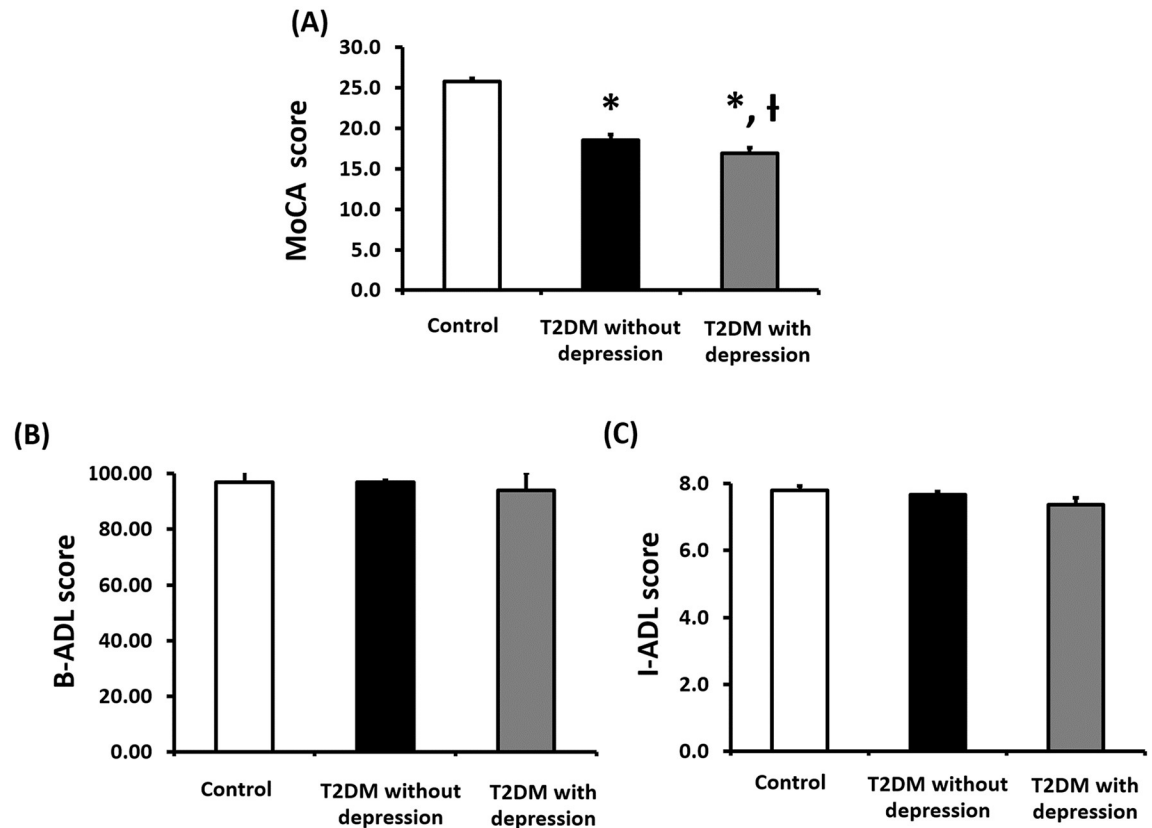
Fig 1. Effects of depression on the cognitive function and the ability to perform ADLs in T2DM patients. Effects of depression on the cognitive function (MoCA score (A)) and ability to perform ADLs (B-ADL score (B) and I-ADL score (C)) in T2DM patients. * $p < 0.05$ vs. control group, † $p < 0.05$ vs. T2DM without depression group. Abbreviation: MoCA = Montreal cognitive assessment, B-ADL = Basic activities of daily living, I-ADL = Lawton instrumental activities of daily living, T2DM = Type 2 diabetes.

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The comparison of salivary alpha-amylase activity between T2DM patients with depression and those without depression

Our results show that salivary alpha-amylase activity in both T2DM with or without depression groups were significantly decreased when compared with control group ($p<0.05$, Fig 2). However, the levels of salivary alpha-amylase activity in the T2DM patients with depression were not significantly different when compared with T2DM patients without depression (Fig 2). All of these findings indicated that depression did not affect the decrement of salivary alpha-amylase activity in T2DM patient.

The correlation between salivary alpha-amylase activity, MoCA score and PHQ-9 score

In this study, the associations between salivary alpha-amylase activity and cognitive function or depression level were assessed by linear regression analysis. The FBG, BMI, age, and gender, which can influence the change of salivary-alpha amylase activity, were considered as covariates. Our result showed that MoCA scores and PHQ-9 scores were not correlated with salivary-alpha amylase activity in control group (Table 3). However, the result in the T2DM patients without depression showed that MoCA score, but not PHQ-9 score, was positively
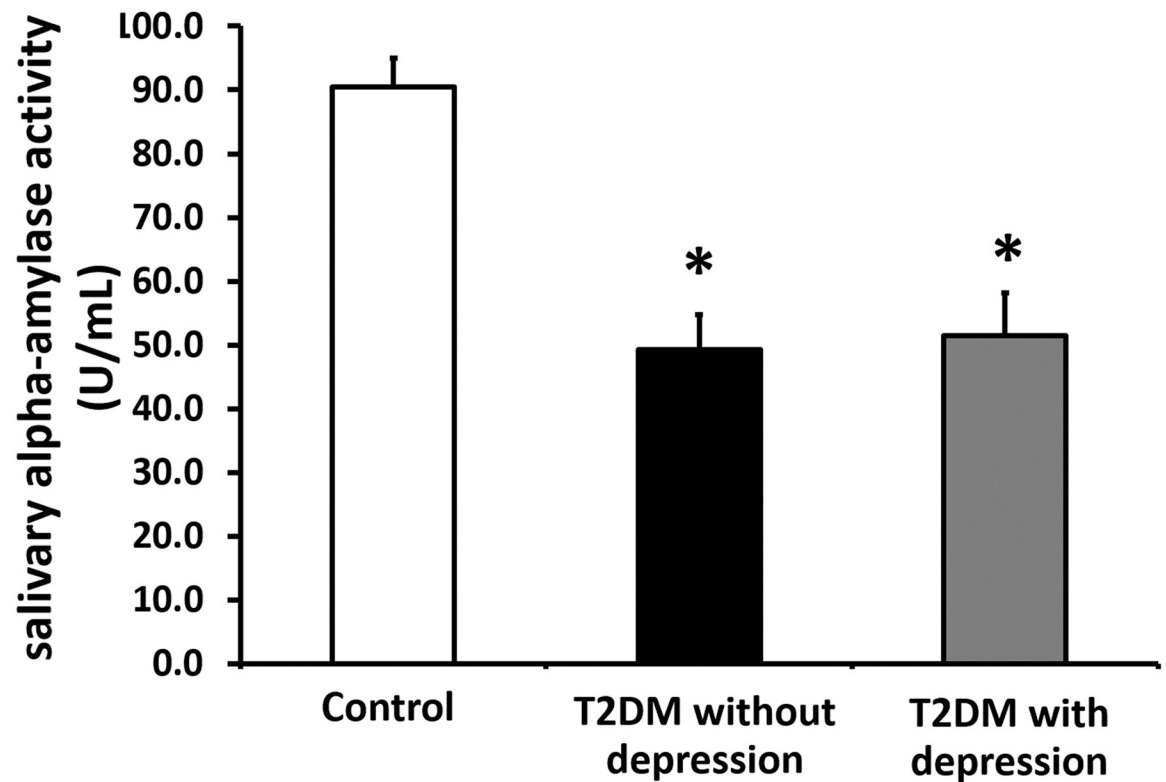
Fig 2. Effect of depression on salivary alpha-amylase activity in T2DM patients. * $p < 0.05$ vs. control group, T2DM = Type 2 diabetes.

associated with salivary-alpha amylase activity. On the other hand, PHQ-9 score was positively correlated with salivary-alpha amylase activity in T2DM patients with depression while there was no association between MoCA score and salivary-alpha amylase activity in this group. All of these findings suggested that cognitive function was associated with the salivary-alpha amylase activity in T2DM patients without depression, while the depression was associated with the salivary-alpha amylase activity in T2DM with depression.

Table 3. Correlation between salivary-alpha amylase activity and MoCA and PHQ-9.

Variables	Control group			T2DM without depression			T2DM with depression		
	B	95%CI	p-value	B	95%CI	p-value	B	95%CI	p-value
MoCA score									
Amylase	-1.310	(-6.711, 4.092)	NS	**3.592**	**(2.219, 4.964)**	**<0.01**	-0.147	(-3.885, 3.591)	NS
Amylase + covariates	-1.570	(-7.303, 4.163)	NS	**3.329**	**(1.850, 4.807)**	**<0.01**	-0.207	(-4.349, 3.936)	NS
PHQ-9 score									
Amylase	6.715	(-4.446, 17.876)	NS	6.630	(-2.114, 15.374)	NS	**9.732**	**(6.242, 13.222)**	**<0.01**
Amylase + covariates	6.284	(-6.591, 19.159)	NS	4.461	(-4.197, 13.119)	NS	**9.793**	**(6.151, 13.436)**	**<0.01**

T2DM: Type 2 diabetes; MoCA: Montreal Cognitive Assessment; PHQ9: the Patient Health Questionnaire-9

Covariates = body mass index, age, and fasting blood glucose

Discussion

The major findings of this study are as follows: 1) the metabolic disturbance and cognitive decline were observed in T2DM patients; 2) T2DM patients with depression had higher hyperglycemia and cognitive decline levels than those without depression; 3) both T2DM patients with and without depression did not impair activities of daily living (ADLs); 4) both T2DM patients with and without depression equally decreased salivary-alpha amylase activity; and 5) cognitive function was correlated with salivary-alpha amylase activity in T2DM patients without depression, while depression was correlated with salivary-alpha amylase activity in T2DM patients with depression.

In this study, the general characteristics within each group showed no significant difference from the other groups. Metabolic dysfunctions of the T2DM patients with and without depression were significantly higher than those of healthy people, as indicated by increased body weight, BMI, fasting blood glucose (FBG), and HbA1c. Consistency, several previous studies also demonstrated that metabolic dysfunction was also observed in T2DM patients [29, 30]. Interestingly, FBG levels in the T2DM patients with depression were significantly higher than those of T2DM patients without depression. This is consistent with the previous studies showing that depression was associated with hyperglycemia and glycemic disturbance in patients with T2DM [31, 32]. It is possible that the increase of mental stress can increase blood glucose levels in depressed patients due to poor self-care behaviors. This is consistent with previous studies that showed that depressive symptoms and mental stress were associated with poor diet, low levels of physical activity, and high levels of blood glucose [31, 32]. The previous study also showed that depression correlated with metabolic diseases and diabetes involving pro-inflammatory cytokine and insulin resistance [33]. Therefore, the higher level of hyperglycemia in T2DM patients with depression may be caused by the induction of mental stress and poor self-care behaviors during depression.

Regarding cognitive function, our results demonstrated that cognitive function in the T2DM patients with and without depression was significantly lower than that of healthy people. Decline of cognitive function has been observed in patients with diabetes [34]. Similarly, another study suggested that T2DM is associated with an impairment of episodic memory and decreased executive function [6]. Interestingly, the decline of cognitive function in the T2DM patients with depression was significantly increased when compared with T2DM patients without depression. This finding is supported by the previous studies showing that depression is a risk factor for MCI and promotes the development of MCI into dementia [35, 36]. Moreover, the depression was shown to increase cognitive decline via reducing synaptic plasticity and increasing pro-inflammatory cytokines [37]. Thus, it is possible that depression may affect cognitive impairment in T2DM patients.

ADLs are routine activities people do every day, and ability to perform ADLs is one of the factors that contribute to quality of life [38]. It has been established that one of the worst effects of diabetes was the cognitive decline that can lead to ADL disability [1, 2]. Thus, reduction of cognitive decline should increase the ability to perform ADLs. Although our results demonstrated that T2DM with or without depression increased the levels of cognitive impairment, the ability to perform ADLs in these patients showed no change when compared to that of healthy people. It is possible that the severity of cognitive impairment in our patients with T2DM may not be high enough to reach to a critical threshold level for the impairment of ADL activity. Thus, no change of ADL function scores in T2DM patients with or without depression was found in this study. This possibility is consistent with previous studies suggesting that the optimal level of cognition function for completing ADLs can be observed in patients with dementia and MCI [39, 40]. So, it is possible that the severity of cognitive

impairment of T2DM patients in this study was not enough to trigger an impairment of ADL function, when compared to healthy people.

In this study, we studied the activity of salivary α-amylase in T2DM patients with and without depression. Our results demonstrated that salivary-alpha amylase activity in T2DM patients without depression was significantly lower than that of healthy individuals. This finding corresponds with animal studies showing that salivary α-amylase activity decreased in diabetic rats and diabetic dogs [19, 20]. Moreover, we investigated the salivary α-amylase activity of T2DM patients with depression. Previous studies have shown that salivary α-amylase was increased under both physical stress, such as treadmill exercise, running, bicycle exercise, cold exposure [41] and psychological stress such as depression, and anxiety [15, 16].

Our study is the first study demonstrated that salivary-alpha amylase activity in T2DM patients with depression was significantly lower than that of healthy people. However, our results showed that salivary-alpha amylase activity in the T2DM patients with depression showed no difference when compared with T2DM patients without depression. It is possible that a decline of salivary-alpha amylase activity in our study was caused by diabetic condition. In the future study, the mechanistic insight of the decline of salivary-alpha amylase activity in the T2DM patients needs to be further investigated.

We also found that cognitive function and the level of depression associated with salivary-alpha amylase activity in all T2DM patients. However, we found that only cognitive function was positively associated with the salivary-alpha amylase activity in T2DM patients without depression, while the depression level was not associated with the salivary-alpha amylase activity in T2DM patients without depression. These results were adjusted with FBG, BMI, and age. Thus, we suggested that salivary-alpha amylase activity was independently associated with cognitive function in T2DM patients without depression. Regarding T2DM patients with depression, the results demonstrated that only depression level was associated with salivary-alpha amylase activity. This finding is consistent with the studies showing that the elevated salivary-alpha amylase level was associated with depression severity in the major depressive disorder patients [42, 43]. According to other studies, elevated secretion of salivary-alpha amylase was associated with a higher prevalence of psychiatric disorders [15, 27]. Thus, we suggested that salivary-alpha amylase activity was correlated with depression in T2DM patients with depression in this study.

Conclusion

T2DM patients with depression had higher hyperglycemia and cognitive decline levels than those without depression. Both T2DM patients with and without depression equally decreased salivary-alpha amylase activity. Moreover, we found that cognitive function was associated with the salivary-alpha amylase activity in T2DM without depression, while the severity of depression was associated with the salivary-alpha amylase activity in T2DM patients with depression.

Study limitation

The results of our study are valid only for the Thai population and may not extent to other countries.

Supporting information

S1 File. The supporting information file in this study.
(XLSX)

Acknowledgments

Author Contributions

Conceptualization: Savitree Thummasorn, Nipon Chattipakorn, Siriporn C. Chattipakorn.

Data curation: Savitree Thummasorn, Nipon Chattipakorn, Siriporn C. Chattipakorn.

Formal analysis: Savitree Thummasorn, Sopida Apichai, Supat Chupradit, Pornpen Sirisattayawong, Pachpilai Chaiwong, Sirawit Sriwichaiin, Wasana Pratchayasakul, Nipon Chattipakorn.

Funding acquisition: Siriporn C. Chattipakorn.

Investigation: Savitree Thummasorn, Sopida Apichai, Supat Chupradit, Pornpen Sirisattayawong, Pachpilai Chaiwong, Sirawit Sriwichaiin, Wasana Pratchayasakul.

Methodology: Savitree Thummasorn, Sopida Apichai, Supat Chupradit, Pornpen Sirisattayawong, Pachpilai Chaiwong, Sirawit Sriwichaiin, Wasana Pratchayasakul.

Validation: Savitree Thummasorn, Sirawit Sriwichaiin, Wasana Pratchayasakul, Nipon Chattipakorn, Siriporn C. Chattipakorn.

Writing – original draft: Savitree Thummasorn.

Writing – review & editing: Savitree Thummasorn, Wasana Pratchayasakul, Nipon Chattipakorn, Siriporn C. Chattipakorn.

References

1. Manfredi M, McCullough MJ, Vescovi P, Al-Kaarawi ZM, Porter SR. Update on diabetes mellitus and related oral diseases. Oral diseases. 2004 Jul; 10(4):187–200. https://doi.org/10.1111/j.1601-0825.2004.01019.x PMID: 15196139

2. Kanazawa I, Takeno A, Tanaka KI, Yamane Y, Sugimoto T. Osteoporosis and vertebral fracture are associated with deterioration of activities of daily living and quality of life in patients with type 2 diabetes mellitus. Journal of bone and mineral metabolism. 2019 May; 37(3):503–11. https://doi.org/10.1007/s00774-018-0948-6 PMID: 30191456

3. Madhusudhanan J, Suresh G, Devanathan V. Neurodegeneration in type 2 diabetes: Alzheimer's as a case study. Brain Behav. 2020 May; 10(5):e01577. https://doi.org/10.1002/brb3.1577 PMID: 32170854

4. Li W, Wang T, Xiao S. Type 2 diabetes mellitus might be a risk factor for mild cognitive impairment progressing to Alzheimer's disease. Neuropsychiatric disease and treatment. 2016; 12:2489–95. https://doi.org/10.2147/NDT.S111298 PMID: 27729793

5. Wang XK, Sun T, Li YJ, Wang YH, Li YJ, Yang LD, et al. A novel thiazolidinediones ATZD2 rescues memory deficits in a rat model of type 2 diabetes through antioxidant and antiinflammation. Oncotarget. 2017 Dec 8; 8(64):107409–22. https://doi.org/10.18632/oncotarget.22467 PMID: 29296174

6. Groeneveld O, Reijmer Y, Heinen R, Kuijf H, Koekkoek P, Janssen J, et al. Brain imaging correlates of mild cognitive impairment and early dementia in patients with type 2 diabetes mellitus. Nutrition, metabolism, and cardiovascular diseases: NMCD. 2018 Aug 2. https://doi.org/10.1016/j.numecd.2018.07.008 PMID: 30355471

7. Yoon S, Cho H, Kim J, Lee DW, Kim GH, Hong YS, et al. Brain changes in overweight/obese and normal-weight adults with type 2 diabetes mellitus. Diabetologia. 2017 Jul; 60(7):1207–17. https://doi.org/10.1007/s00125-017-4266-7 PMID: 28447116

8. Ding X, Rong S, Wang Y, Li D, Wen L, Zou B, et al. The Association of the Prevalence of Depression in Type 2 Diabetes Mellitus with Visual-Related Quality of Life and Social Support. Diabetes Metab Syndr Obes. 2022; 15:535–44. https://doi.org/10.2147/DMSO.S343926 PMID: 35237054

9. Sestile CC, Maraschin JC, Rangel MP, Cuman RK, Audi EA. Antidepressant-like Effect of Insulin in Streptozotocin-induced Type 2 Diabetes Mellitus Rats. Basic Clin Pharmacol Toxicol. 2016 Sep; 119 (3):243–8. https://doi.org/10.1111/bcpt.12563 PMID: 26857652

10. Maxwell MA, Cole DA. Weight change and appetite disturbance as symptoms of adolescent depression: toward an integrative biopsychosocial model. Clinical psychology review. 2009 Apr; 29(3):260–73. https://doi.org/10.1016/j.cpr.2009.01.007 PMID: 19250729

11. Chen S, Zhang Q, Dai G, Hu J, Zhu C, Su L, et al. Association of depression with pre-diabetes, undiagnosed diabetes, and previously diagnosed diabetes: a meta-analysis. Endocrine. 2016 Jul; 53(1):35–46. https://doi.org/10.1007/s12020-016-0869-x PMID: 26832340

12. Braithwaite EC, Murphy SE, Ramchandani PG, Hill J. Associations between biological markers of prenatal stress and infant negative emotionality are specific to sex. Psychoneuroendocrinology. 2017 Dec; 86:1–7. https://doi.org/10.1016/j.psyneuen.2017.09.004 PMID: 28888992

13. Zalewska A, Ziembicka D, Zendzian-Piotrowska M, Maciejczyk M. The Impact of High-Fat Diet on Mitochondrial Function, Free Radical Production, and Nitrosative Stress in the Salivary Glands of Wistar Rats. Oxidative medicine and cellular longevity. 2019; 2019:2606120. https://doi.org/10.1155/2019/2606120 PMID: 31354904

14. Tanaka Y, Maruyama Y, Ishitobi Y, Kawano A, Ando T, Ikeda R, et al. Salivary alpha-amylase and cortisol responsiveness following electrically stimulated physical stress in bipolar disorder patients. Neuropsychiatr Dis Treat. 2013; 9:1899–905. https://doi.org/10.2147/NDT.S48722 PMID: 24353422

15. Jung JY, Nam JY, Kim HA, Suh CH. Elevated Salivary Alpha-Amylase Level, Association Between Depression and Disease Activity, and Stress as a Predictor of Disease Flare in Systemic Lupus Erythematosus: A Prospective Case-Control Study. Medicine. 2015 Jul; 94(30):e1184. https://doi.org/10.1097/MD.0000000000001184 PMID: 26222848

16. Altamura M, Iuso S, Balzotti A, Francavilla G, Dimitri A, Cibelli G, et al. Salivary alpha-amylase and cortisol responsiveness to stress in first episode, drug-naive patients with panic disorder. Neuroscience research. 2018 Mar 14. https://doi.org/10.1016/j.neures.2018.03.003 PMID: 29550536

17. Yamazawa T, Nakamura N, Sato M, Sato C. Secretory glands and microvascular systems imaged in aqueous solution by atmospheric scanning electron microscopy (ASEM). Microscopy research and technique. 2016 Dec; 79(12):1179–87. https://doi.org/10.1002/jemt.22773 PMID: 27696606

18. Garrett JR, Winston DC, Proctor GB, Schulte BA, Anderson LC. Changes in the lectin-binding of capillaries in rat salivary glands after streptozotocin-induced diabetes. Archives of oral biology. 1992 Sep; 37(9):759–61. https://doi.org/10.1016/0003-9969(92)90084-l PMID: 1417525

19. Muratsu K, Morioka T. Levels of salivary lysozyme, lactoperoxidase, and lactoferrin in diabetic hamsters. Infection and immunity. 1985 May; 48(2):389–94. https://doi.org/10.1128/iai.48.2.389-394.1985 PMID: 2580790

20. Arendt M, Fall T, Lindblad-Toh K, Axelsson E. Amylase activity is associated with AMY2B copy numbers in dog: implications for dog domestication, diet and diabetes. Animal genetics. 2014 Oct; 45(5): 716–22. https://doi.org/10.1111/age.12179 PMID: 24975239

21. Nakajima K, Nemoto T, Muneyuki T, Kakei M, Fuchigami H, Munakata H. Low serum amylase in association with metabolic syndrome and diabetes: A community-based study. Cardiovasc Diabetol. 2011 Apr 17; 10:34. https://doi.org/10.1186/1475-2840-10-34 PMID: 21496338

22. Lotrakul M, Sumrithe S, Saipanish R. Reliability and validity of the Thai version of the PHQ-9. BMC psychiatry. 2008 Jun 20; 8:46. https://doi.org/10.1186/1471-244X-8-46 PMID: 18570645

23. Phrommintikul A, Sa-Nguanmoo P, Sripetchwandee J, Vathesatogkit P, Chattipakorn N, Chattipakorn SC. Factors associated with cognitive impairment in elderly versus nonelderly patients with metabolic syndrome: the different roles of FGF21. Scientific reports. 2018 Mar 26; 8(1):5174. https://doi.org/10.1038/s41598-018-23550-9 PMID: 29581470

24. Julayanont P, Tangwongchai S, Hemrungrojn S, Tunvirachaisakul C, Phanthumchinda K, Hongsawat J, et al. The Montreal Cognitive Assessment-Basic: A Screening Tool for Mild Cognitive Impairment in Illiterate and Low-Educated Elderly Adults. Journal of the American Geriatrics Society. 2015 Dec; 63(12):2550–4. https://doi.org/10.1111/jgs.13820 PMID: 26648041

25. Shah S, Vanclay F, Cooper B. Improving the sensitivity of the Barthel Index for stroke rehabilitation. Journal of clinical epidemiology. 1989; 42(8):703–9. https://doi.org/10.1016/0895-4356(89)90065-6 PMID: 2760661

26. Cornelis E, Gorus E, Beyer I, Bautmans I, De Vriendt P. Early diagnosis of mild cognitive impairment and mild dementia through basic and instrumental activities of daily living: Development of a new evaluation tool. PLoS medicine. 2017 Mar; 14(3):e1002250. https://doi.org/10.1371/journal.pmed.1002250 PMID: 28291801

27. Xu Z, Wei B, Qiu Y, Zhang T. Altered Salivary Alpha-Amylase Secretion in Patients with Ulcerative Colitis. Gastroenterology research and practice. 2018; 2018:4203737. https://doi.org/10.1155/2018/4203737 PMID: 29977288

28. Granger DA, Kivlighan KT, el-Sheikh M, Gordis EB, Stroud LR. Salivary alpha-amylase in biobehavioral research: recent developments and applications. Annals of the New York Academy of Sciences. 2007 Mar; 1098:122–44. https://doi.org/10.1196/annals.1384.008 PMID: 17332070

29. Dhas Y, Banerjee J, Mishra N. Blood Viscosity, Glycemic Markers and Blood Pressure: A Study in Middle-Aged Normotensive and Hypertensive Type 2 Diabetics. Indian journal of clinical biochemistry: IJCB. 2020 Jan; 35(1):102–8. https://doi.org/10.1007/s12291-018-0798-y PMID: 32071502

30. Zulfania, Khan A, Ghaffar T, Kainat A, Arabdin M, Rehman Orakzai SU. Correlation between serum leptin level and Body mass index (BMI) in patients with type 2 diabetes Mellitus. JPMA The Journal of the Pakistan Medical Association. 2020 Jan; 70(1):3–6. https://doi.org/10.5455/JPMA.301135 PMID: 31954015

31. Katon WJ, Lin EH, Russo J, Von Korff M, Ciechanowski P, Simon G, et al. Cardiac risk factors in patients with diabetes mellitus and major depression. Journal of general internal medicine. 2004 Dec; 19(12):1192–9. https://doi.org/10.1111/j.1525-1497.2004.30405.x PMID: 15610329

32. Sancini A, Ricci S, Tomei F, Sacco C, Pacchiarotti A, Nardone N, et al. Work related stress and blood glucose levels. Annali di igiene: medicina preventiva e di comunita. 2017 Mar-Apr; 29(2):123–33. https://doi.org/10.7416/ai.2017.2139 PMID: 28244581

33. Felger JC, Lotrich FE. Inflammatory cytokines in depression: neurobiological mechanisms and therapeutic implications. Neuroscience. 2013 Aug 29; 246:199–229. https://doi.org/10.1016/j.neuroscience.2013.04.060 PMID: 23644052

34. Bains GS, Berk LS, Lohman E, Daher N, Petrofsky J, Schwab E, et al. Humors Effect on Short-term Memory in Healthy and Diabetic Older Adults. Alternative therapies in health and medicine. 2015 May-Jun; 21(3):16–25. PMID: 26026141

35. Li W, Sun L, Li G, Xiao S. Prevalence, Influence Factors and Cognitive Characteristics of Mild Cognitive Impairment in Type 2 Diabetes Mellitus. Frontiers in aging neuroscience. 2019; 11:180. https://doi.org/10.3389/fnagi.2019.00180 PMID: 31417393

36. Van der Mussele S, Fransen E, Struyfs H, Luyckx J, Marien P, Saerens J, et al. Depression in mild cognitive impairment is associated with progression to Alzheimer's disease: a longitudinal study. Journal of Alzheimer's disease: JAD. 2014; 42(4):1239–50. https://doi.org/10.3233/JAD-140405 PMID: 25024328

37. You Z, Luo C, Zhang W, Chen Y, He J, Zhao Q, et al. Pro- and anti-inflammatory cytokines expression in rat's brain and spleen exposed to chronic mild stress: involvement in depression. Behavioural brain research. 2011 Nov 20; 225(1):135–41. https://doi.org/10.1016/j.bbr.2011.07.006 PMID: 21767575

38. Bordne S, Schulz RJ, Zank S. Effects of inpatient geriatric interventions in a German geriatric hospital: Impact on ADL, mobility and cognitive status. Zeitschrift fur Gerontologie und Geriatrie. 2015 Jun; 48(4):370–5. https://doi.org/10.1007/s00391-015-0870-7 PMID: 25801512

39. Reppermund S, Brodaty H, Crawford JD, Kochan NA, Draper B, Slavin MJ, et al. Impairment in instrumental activities of daily living with high cognitive demand is an early marker of mild cognitive impairment: the Sydney memory and ageing study. Psychological medicine. 2013 Nov; 43(11):2437–45. https://doi.org/10.1017/S003329171200308X PMID: 23308393

40. Amieva H, Le Goff M, Millet X, Orgogozo JM, Peres K, Barberger-Gateau P, et al. Prodromal Alzheimer's disease: successive emergence of the clinical symptoms. Annals of neurology. 2008 Nov; 64(5):492–8. https://doi.org/10.1002/ana.21509 PMID: 19067364

41. Walsh NP, Blannin AK, Clark AM, Cook L, Robson PJ, Gleeson M. The effects of high-intensity intermittent exercise on saliva IgA, total protein and alpha-amylase. Journal of sports sciences. 1999 Feb; 17(2):129–34. https://doi.org/10.1080/026404199366226 PMID: 10069269

42. Ishitobi Y, Akiyoshi J, Tanaka Y, Ando T, Okamoto S, Kanehisa M, et al. Elevated salivary alpha-amylase and cortisol levels in unremitted and remitted depressed patients. International journal of psychiatry in clinical practice. 2010 Nov; 14(4):268–73. https://doi.org/10.3109/13651501.2010.500737 PMID: 24917438

43. Tanaka Y, Ishitobi Y, Maruyama Y, Kawano A, Ando T, Okamoto S, et al. Salivary alpha-amylase and cortisol responsiveness following electrical stimulation stress in major depressive disorder patients. Progress in neuro-psychopharmacology & biological psychiatry. 2012 Mar 30; 36(2):220–4. https://doi.org/10.1016/j.pnpbp.2011.10.005 PMID: 22063648