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RESEARCH ARTICLE

Factors Involved in Glucose Metabolism in Community-Dwelling Elderly Caregivers and Dementia Patients

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ABSTRACT

Background: **Caregivers of dementia patients are at higher risk of coronary heart disease (CHD) than non-caregivers, and diastolic blood pressure of caregivers is reportedly associated with the frequency of disruptive behaviors in dementia patients. Factors related to the higher risk of CHD in caregivers include the impact of stress on the autonomic nervous system and glucose metabolism, as well as poor blood pressure control. Elevated HbA1c levels have been reported to correlate with the likelihood of developing hyperglycemia under stress. Thus, identifying caregivers' psychological stressors may help control elevated glucose metabolism. The present study aimed to identify factors that influence the levels of HbA1c, an important stress-related health indicator, in caregivers.**

Methods: **This cross-sectional study assessed the association between HbA1c and hallucinatory symptoms (a peripheral symptom of dementia patients). Subjects were caregivers who provided care at home (hereafter, "caregivers") and their care recipients with dementia (hereafter, "patients").**

Results: **Factors significantly associated with caregiver HbA1c were patient sex (OR: 5.423, P = 0.013, 95%CI: 1.435, 20.500), patient age (OR: 0.894, P = 0.049, 95%CI: 0.800, 1.000), and patient hallucinatory symptoms (OR: 0.635, P = 0.070, 95%CI: 0.388, 1.037).**

Discussion: **The proportion of spousal caregivers tended to be higher than other types of caregivers. Caregivers likely felt more difficulty caring for their loved ones and had more anxiety and stress based on their sex. As dementia patients aged, caregivers may have acquired coping skills not only to address physical caregiving but also psychological symptoms associated with dementia.**

Conclusion: **Our findings suggest that monitoring biochemical data is important for understanding the physical condition of and preventing diabetes and cardiovascular disease in caregivers, and highlight the importance of caregivers being aware of their own stress from an early stage.**

Keywords: Elderly caregiver, glucose metabolism, dementia patient, hallucination.

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1. Introduction

Caregivers are at a slightly higher risk of health problems than non-caregivers [1], and caregivers of dementia patients are at higher risk of coronary heart disease (CHD) than non-caregivers [2]. The association between objective stressors and health has been reported to be mediated by caregivers' feelings of overload [3]. D-dimer, a marker of fibrin formation and degradation, is significantly higher in caregivers than in non-caregivers and may contribute to increased cardiovascular risk and overall mortality due to dementia care burden [4]. Chronic stress in caregivers of dementia patients has been reported to negatively affect blood pressure [5], and diastolic blood pressure of caregivers is associated with the frequency of disruptive behaviors in dementia patients [6]. Relevant factors may include the effects of stress on the autonomic nervous system and glucose metabolism, as well as poor blood pressure control. This suggests a potential relationship between

the nervous system and glucose metabolism. Caregivers of dementia patients have been shown to have higher hair cortisol concentration (HCC) [7], indicating that the stress response in these caregivers is associated with increased secretion of glucocorticoids from the adrenal glands.

One cause of elevated glucose is stress [8], which impairs insulin's ability to control blood glucose levels. In particular, chronic stress can affect glucose metabolism by impacting the body's hormonal secretion and autonomic nervous system [9]. Furthermore, stress-induced hyperglycemia is associated with increased morbidity and short-term mortality [10], suggesting that patients with previously undiagnosed diabetes are at greater risk for adverse effects than pre-existing diabetic patients in certain severities of hyperglycemia [11]. Increased IL-6 levels in hyperglycemic individuals with HbA1c >6.5% compared to normoglycemic individuals have been reported to be significantly associated with diurnal cortisol [12], and elevated HbA1c levels correlate with the likelihood of developing hyperglycemia under stress [13].

High levels of HbA1c can be confirmed based on measurements of long-term blood glucose fluctuations, since the amount of glucose bound to hemoglobin increases when blood glucose levels are high due to stress. Cardiovascular disease and renal function are predicted to worsen if hyperglycemia is left unchecked. Furthermore, there is a possible risk of depression due to autonomic deterioration. Identifying caregivers' psychological stressors may contribute to reducing elevated glucose metabolism. Accordingly, this study aimed to identify factors that influence HbA1c, an important stress-related health indicator in caregivers.

2. Methods

2.1. Subjects

Subjects were caregivers providing care at home (hereafter, "caregivers") and their care recipients (i.e., dementia patients; hereafter "patients"). Caregivers were those with well-controlled chronic diseases such as hypertension, diabetes, and dyslipidemia. Those with poorly-controlled chronic diseases were excluded.

2.2. Research Design

This cross-sectional study assessed associations between caregiver HbA1c (a health indicator) and patient hallucinatory symptoms (a peripheral symptom).

2.3. Assessment of Caregivers

Caregivers aged ≥65 years were included in this study and tested for HbA1c [14]. When caregivers are stressed, the sympathetic nervous system is excited, and glucagon, adrenaline, and thyroid hormones, which increase blood glucose levels, increase. Cortisol, which is secreted when stress is high, also increases blood glucose levels. Stress-induced hyperglycemia increases the amount of glucose bound to hemoglobin, resulting in high HbA1c levels. HbA1c is a stable indicator that reflects average glycemic control over a period of time, and thus is not easily influenced by lifestyle factors such as diet and exercise immediately before blood samples are taken.

2.3.1. Assessment of Dementia Patients

The presence and severity of patient hallucinatory symptoms were assessed using the Neuropsychiatric Inventory (NPI) scale [15] based on frequency and severity information. NPI scores ranged from 0 to 12 points.

2.3.2. Statistical Analysis

Spearman's correlation coefficients were used to assess correlations between caregivers' own factors and those of dementia patients. Binomial logistic regression analysis was performed to identify factors associated with caregiver HbA1c. The dependent variable was caregiver HbA1c dichotomized into high and low values based on the median HbA1c level, i.e., HbA1c <5.2% = 0 and HbA1c ≥5.2% = 1. For independent variables, covariates were analyzed by entry into the models. Patient sex, patient age, patient hallucinatory symptoms, caregiver sex, and caregiver age were entered into Model 1.

2.4. Ethical Considerations

This study was approved by the Nagoya University Bioethics Review Committee. Informed consent was obtained from each subject.

3. Results

All caregivers and dementia patients were aged ≥65 years. There were 50 couples of caregivers caring for their cohabitant dementia patients.

Characteristics of caregivers and patients are presented in Table I Twenty-five caregivers had HbA1c <5.2% and 27 had HbA1c ≥5.2%. Twelve patients had hallucinatory symptoms, with six having relatively mild hallucinatory symptoms, four having moderate hallucinatory symptoms, and two having severe hallucinatory symptoms.

Table II shows correlations between caregiver HbA1c and caregiver factors. No correlations were observed between caregiver HbA1c and caregiver sex and age.

Table III shows correlations between caregiver HbA1c and patient factors. There were negative correlations between caregiver HbA1c and patient age ($r = -0.285$, $p = 0.041$), and between caregiver sex and patient sex ($r = -0.962$, $p = 0.000$). There was a positive correlation between caregiver age and patient age ($r = 0.523$, $p = 0.000$).

Table IV shows the results of the binomial logistic regression analysis using the stepwise method with caregiver HbA1c as the dependent variable. Significant factors

TABLE I: Subject Characteristics

	N	Median	IQR (25–75)
Caregivers			
HbA1c <5.2%	25	4.900	4.800–5.100
HbA1c ≥5.2%	27	5.400	5.200–6.000
Dementia patients			
Hallucinatory symptoms	12		
Hallucination score: 1–2 points	6		
Hallucination score: 3–5 points	4		
Hallucination score: 6–12 points	2		

Note: HbA1c (%) reference range: 4.6%–6.2%.

TABLE II: Correlations between Caregiver HbA1c and Caregiver Factors

		1.	2.	3.
1. CG HbA1c	r	1		
	p			
2. CG sex	r	−0.233	1	
	p	0.097		
3. CG age	r	−0.001	−0.172	1
	p	0.994	0.222	

Note: r: Spearman's correlation coefficient; p: significance, †p<0.1, *p<0.05, **p<0.01.
CG: Caregiver.

TABLE III: Correlations between Caregiver HbA1c and Patient Factors

		1. CG HbA1c	2. CG sex	3. CG year	4.	5.	6.
4. Pt sex	r	0.245	−0.962**	0.206	1		
	p	0.080	0.000	0.142			
5. Pt age	r	−0.285*	0.177	0.523**	−0.201	1	
	p	0.041	0.209	0.000	0.153		
6. Pt hallucinatory symptoms	r	−0.118	−0.066	−0.049	0.045	0.011	1
	p	0.403	0.640	0.731	0.750	0.939	

Note: r: Spearman's correlation coefficient; p: significance, †p<0.1, *p<0.05, **p<0.01.
CG: caregiver, Pt: dementia patient.

TABLE IV: Logistic Regression Analysis with Caregiver HbA1c as Dependent Variable

						95%CI	
Dependent variable		Covariate	B	*P*	OR	Lower limit	Upper limit
HbA1c		Patient sex: female	1.691	0.013	5.423	1.435	20.500
		Patient age	−0.112	0.049	0.894	0.800	1.000
		Patient hallucinatory symptoms	−0.455	0.070	0.635	0.388	1.037
	Variable 2	Variables not included in equation	Score	*P*			
		Caregiver sex	0.191	0.662			
		Caregiver age	0.171	0.679			

Note: HbA1c (<5.2% = 0; ≥5.2% = 1) was entered as the dependent variable.
Covariates were analyzed by entering to Model 1. For Model 1, we entered patient sex, patient age, patient hallucinatory symptoms, caregiver sex, and caregiver age.
B: partial regression coefficient, P: significance probability, 95%CI: 95% confidence interval.

TABLE V: Mann-Whitney U Test for Sex Differences in Caregiver HbA1c

Caregiver	Median	IQR		*P*
		25%	75%	
Male	5.200	4.900	5.800	0.96
Female	5.100	5.000	5.200	

associated with caregiver HbA1c were patient sex (OR: 5.423, P = 0.013, 95%CI: 1.435, 20.500), patient age (OR: 0.894, P = 0.049, 95%CI: 0.800, 1.000), and patient hallucinatory symptoms (OR: 0.635, P = 0.070, 95%CI: 0.388, 1.037). Caregiver sex and caregiver age were not associated with caregiver HbA1c.

Table V summarizes the analysis of sex differences in HbA1c among caregivers. Male and female caregivers had median HbA1c values of 5.2% and 5.1%, respectively, with no significant difference between sexes (P = 0.96).

4. Discussion

Factors significantly associated with caregiver HbA1c identified in the present study included patient sex, patient age, and patient hallucinatory symptoms. Caregiver sex and caregiver age were not associated with caregiver HbA1c.

Cahn *et al*. reported that diabetic patients with elevated and stable HbA1c trends have higher mortality only in the elderly group, and concluded that HbA1c variability and trends are important determinants of mortality risk [16]. Normal glucose tolerance in elderly people is 36% impaired glucose tolerance (IGT) or 3% is noted to progress to diabetes [17]. Impaired glucose tolerance, but not impaired fasting glucose, is a risk factor for early stage atherosclerosis [18]. Age-related decreases in skeletal muscle mass and strength are implicated in the etiology of both insulin resistance and type 2 diabetes, especially in elderly people [19]. In the present study, caregiver HbA1c was

within the reference range and did not differ significantly between sexes. It is possible that caregivers themselves had different lifestyles and knowledge and understanding of their health. Although the caregivers of our study were in relatively good health, there were notable differences across individuals and the condition was considered to be at risk of developing due to aging.

In the present study, patient sex was associated with caregiver HbA1c. According to previous studies, hallucinations are one of the most frequent psychiatric symptoms in Alzheimer's disease [20] and a predictor of caregiver burden [21], and the tendency for hallucinations and agitation increases with the severity of dementia [22], with delusional hallucinations reported among all men in one study [23]. In a study of hospitalized patients with behavioral psychological symptoms of dementia, female dementia patients were reported to have significantly more hallucinatory symptoms than their male counterparts [24]. These findings from previous studies suggest that the role of sex in hallucinatory symptoms is not entirely clear. Another previously reported sex difference relates to work-related stress, which was found to be associated with the development of type 2 diabetes in women but not in men [25]. Moreover, a study of elderly husbands who cared for their wives with dementia reported that the husbands were enthusiastic about their caregiving role but may have felt socially isolated [26]. In the present study, a higher percentage of caregivers tended to be spousal caregivers, suggesting that caregivers were more likely to experience difficulties in caregiving and may have experienced more anxiety and stress based on their sex.

Mental stress and anxiety may increase the risk of developing type 2 diabetes [27]. This is due to the secretion of various hormones, such as cortisol [28] and adrenaline [29], in response to excessive stress, which increases blood pressure, heart rate, and blood glucose levels. We speculate that these effects result from the increased secretion of hormones that cause insulin resistance due to mental stress and decreased sensitivity to insulin. Furthermore, in fasted states, gluconeogenesis is dependent on epinephrine alone to increase hepatic glucose output. According to one study, stimulation of the brain of rats in the fasting state leads to an increase in hepatic glucose release due to the breakdown of glycogen in the liver, resulting in a marked increase in hepatic venous blood glucose levels [30]. This suggests that the transmission pathways of substances that stimulate the brain and raise blood glucose vary, and that blood glucose can increase through various mechanisms [31]. Several such studies have gradually elucidated how mental stress affects the body. Similarly, we speculate that stress caused by the excessive strain of caregiving activates the sympathetic nervous system and causes the release of hormones, leading to even higher blood glucose levels. It is also conceivable that hormones may be secreted to raise blood glucose, although the transmission pathways for raising blood glucose are diverse, and blood pressure, heart rate, and blood glucose levels may have increased. The secretion of blood glucose-elevating hormones due to stress from hallucinatory symptoms in dementia patients is predicted to lead to stronger insulin resistance and more hyperglycemia.

Patient hallucinatory symptoms were identified as a factor associated with caregiver HbA1c. In a study of patients with insulin-dependent diabetes mellitus, subjects with type A behavioral pattern personality exhibited a hyperglycemic response to stress. However, subjects with type B personality reported being unaffected by stress [32]. It is possible that caregiver personality types made them less susceptible to stimulation from patient hallucinatory symptoms. The chronic accumulation of stress may lead to a vicious cycle of increased onset of depression and further exacerbation of diabetes. For instance, one study reported an increased incidence of diabetes and frequency of insulin resistance in older women with depression [33]. Thus, we consider a risk factor to be a stress-sensitive personality or a physical condition that is susceptible to stress, combined with genetic factors that predispose caregivers to the development of diabetes due to environmental factors.

According to one study, diabetes was not poorly controlled in subjects under chronic stress conditions [34]. This suggests the possibility that caregivers of the present study who acquired coping skills by interacting with people other than their care recipients, such as by using social services, and who were exposed to chronic stress may not have exhibited changes in HbA1c due to their stress tolerance.

Stress-induced anxiety is a normal human response. In general, stressed caregivers have been reported to have higher levels of fasting plasma glucose and HbA1c compared to non-caregivers [35]. Variations in HbA1c are associated with cardiovascular disease and mortality in diabetic patients [36] and a 1% increase in HbA1c was associated with an increased risk of all-cause mortality [37]. The risk of developing venous thrombosis was similarly found to be 1.4 times higher in the presence of diabetes [38]. In addition, added stress worsens the mental state and increases anxiety symptoms, which in turn leads to a vicious cycle of increased overeating and elevated blood glucose levels. To prevent the increased risk of diabetes caused by stress, effective stress coping strategies are needed.

Prediabetes, defined as impaired glucose tolerance, impaired fasting glucose, or elevated HbA1c, was associated with an increased risk of cardiovascular disease [39]. HbA1c may be a predictive indicator of cardiovascular risk factors in non-diabetic patients and was highly associated with IGT and impaired fasting blood glucose [40]. Stress is a defense response to protect oneself from the environment and therefore is important to address. Although it may be difficult to change the caregiver's environment, caregivers should develop and practice methods that they themselves can easily incorporate into their daily lives, such as reviewing aspects of their lifestyle and ensuring sufficient rest.

Another factor associated with caregiver HbA1c was patient age. It is possible that the older age of dementia patients reduced the physical and emotional stress of entrusting some of the care to medical staff for not only the physical care, but also for mental symptoms associated with dementia. For hallucinations and other symptoms associated with the progression of dementia, it is important for medical staff to be actively involved in patient care to reduce the caregiver's sense of emotional burden.

5. Conclusion

This study identified factors that influence caregiver HbA1c, an important stress-related health indicator. Factors associated with caregiver HbA1c included patient sex, patient age, and patient hallucinatory symptoms. The results suggest that monitoring biochemical data is important for understanding the physical condition of and preventing diabetes and cardiovascular disease in caregivers. Our findings also highlight the importance of caregivers to be aware of their own stress status from an early stage, to identify the content and causes of the stress, and to practice coping strategies to alleviate the stress.

Acknowledgment

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Conflict of Interest

None.

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