Correlation of HbA1c level with electrodiagnostic parameters of diabetic autonomic neuropathy

Korelasi kadar HbA1c dengan parameter elektrodiagnostik neuropati otonom diabetikum

Isnaini Ashar*, Yudiyanta**, Ahmad Asmedi**
*Department of Neurology, Pringsewu Hospital, Lampung
**Department of Neurology, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Yogyakarta

Keyword:
HbA1c, sympathetic skin response, R-R interval, diabetic autonomic neuropathy

ABSTRACT

Diabetic autonomic neuropathy (DAN) is a frequent complication of diabetes mellitus (DM). Serious consequences of DAN are diabetic ulcer and silent myocardial infarction, both can be assessed by examining the sympathetic skin response (SSR) and the R-R interval. The progression of DAN increases the complications and this condition is influenced by glycemic control (HbA1c). The aim of this study was to find the correlation between HbA1c levels and SSR and R-R intervals. This was a cross-sectional study. The HbA1c levels, SSR latency and amplitude and R-R interval at lower extremities in DM patients were assessed. The correlation between HbA1c levels, demographic and laboratory variables with SSR latency, SSR amplitude, and R-R interval were tested with Pearson/Spearman correlation test followed by linear regression test.
There were 41 subjects, whose mean levels HbA1c, SSR latency, SSR amplitude, and R-R interval ratio were 8.7±3.02%, 2586.58±778.69 ms, 0.51±0.61 mV, 0.96±0.28, respectively. Significant bivariate correlations were found between HbA1c with SSR latency (r =0.312; p =0.047), HbA1c with R-R interval ratio (r =-0.392; p =0.011), duration of DM with SSR latency (r =0.524; p =0.000), duration of DM with SSR amplitude (r =-0.444; p =0.003), and duration of DM with interval R-R ratio (r =-0.320; p =0.041). In the multivariate test, duration of DM correlated with SSR latency (β =0.417; p =0.008) and SSR amplitude (β =-0.351; p =0.021), HbA1c with SSR latency (β =0.175; p =0.248) and HbA1c with the R-R interval ratio (β =-0.298; p =0.063). In conclusion, both of HbA1c and duration of DM were positively correlated with SSR latency, and negatively correlated with the R-R interval.

Kata kunci:
HbA1c, sympathetic skin response, interval R-R, neuropati otonom diabetikum

ABSTRAK

Neuropati otonom diabetikum merupakan komplikasi diabetes melitus (DM) cukup sering. Komplikasi neuropati otonom diabetikum yang cukup serius adalah ulkus diabetikum dan silent myocard infarction. Risiko kedua komplikasi tersebut dapat dinilai dengan pemeriksaan sympathetic skin response (SSR) dan interval R-R. Progresivitas neuropati otonom diabetikum meningkatkan komplikasi dan hal itu dipengaruhi oleh kontrol glikemik (HbA1c). Penelitian ini bertujuan menentukan korelasi antara kadar HbA1c dengan SSR dan interval R-R.
Penelitian ini merupakan penelitian potong lintang. Subjek tersebut dilakukan pemeriksaan kadar HbA1c, pemeriksaan latensi dan amplitudo SSR ekstremitas bawah serta interval R-R. Korelasi antara kadar HbA1c, variabel demografi dan laboratorium dengan latensi SSR, amplitudo SSR dan interval R-R dengan uji korelasi Pearson/Spearman dilanjutkan uji regresi linier.
Didapatkan 41 subjek dengan rerata kadar HbA1c 8,7±3,02 %, latensi SSR 2586,58±778,69 ms, amplitudo SSR 0,51±0,61 mV, dan rasio interval R-R 0,96±0,28. Hasil uji korelasi bivariat yang signifikan adalah HbA1c dengan latensi SSR (r =0,312; p =0,047), HbA1c dengan rasio interval R-R (r =-0,392; p =0,011), durasi DM dengan latensi SSR (r =0,524; p =0,000), durasi DM dengan amplitudo SSR (r =-0,447; p =0,003) dan durasi DM dengan rasio interval R-R (r =-0,320; p =0,041.) Pada uji multivariat, durasi DM berkorelasi signifikan dengan latensi SSR (β =0,417; p =0,008) dan amplitudo SSR (β =-0,351; p =0,021), untuk HbA1c dengan latensi SSR (β =0,175; p =0,248) dan untuk HbA1c dengan rasio interval R-R (β =-0,298; p =0,063). Kesimpulan penelitian ini, HbA1c dan durasi DM berkorelasi positif dengan latensi SSR dan berkorelasi negatif dengan interval R-R.

Correspondence:
isnainiashar@gmail.com

INTRODUCTION

Diabetic autonomic neuropathy (DAN) is a serious complication of diabetes mellitus (DM) but is less recognized and understood.[1] Its complication affects the autonomic nervous system and includes many organs, including cardiovascular, gastrointestinal, urogenital, and sudomotor which results in increased morbidity and mortality.[1] Diabetic autonomic neuropathy can be a predictor of morbidity and mortality in providing prognostic information for death or disability due to impaired cardiovascular perfusion.[2,3] Mortality in DM increase three times in patients who had cardiovascular autonomic neuropathy compared to those who did not.[4]

The prevalence of DAN reaches 90% in DM patients, with 60% of them being cardiovascular autonomic neuropathy.[5] The prevalence of cardiovascular autonomic neuropathy increases 35%-44% at the age of 40-70 years and 35%-65% in patients with prolonged diabetes.[6] In neuropathy gastrointestinal, almost 10-20% of people with DM suffer gastrointestinal symptoms.[7]

The most frequent observed manifestation of DAN is cardiovascular autonomic neuropathy due to its life-threatening complications such as arrhythmia, silent myocardial ischemia, sudden death, and associated microangiopathy.[6] In gastrointestinal neuropathy, the signs and symptoms are delayed gastric emptying, constipation, diarrhea, and abdominal pain.[7] Neurogenic bladder or cystopathy can also be caused by DAN. Symptoms such as hesitancy, weak stream, and decreased detrussor activity (areflexia).[1,8]

Peripheral sympathetic autonomic neuropathy is a distal neuropathy caused by microvascular dysfunction, with its clinical manifestations being loss of sweating (sudomotor) causing dry skin, increased callus formation, and ulcer risk.[9] Sudomotor dysfunction as measured by sympathetic skin response (SSR) is associated with increased risk of diabetic foot ulcer. SSR loss increases 13.4 times the occurrence of diabetic ulcers in 4 years compared to diabetic patients whose normal SSR.[10]

The progression of autonomic neuropathy is influenced by glycemic control status, age, duration of DM, hypertension, and smoking.[11] HbA1c is an examination used for glycemic control markers in DM patients. The American Diabetic Association (ADA) recommends achieving HbA1c levels <7 as good blood glucose control in DM patients.[12] HbA1c levels in the blood describes glycemic control from 120 days before. Therefore, HbA1C levels are recommended to be measured every 3 months.[13]

Several studies that assessed the HbA1c correlation with DAN found that HbA1c significantly increased the risk of a decrease of heart rate variability.[14,15,16] The early clinical indicator of DAN is a decrease in heart rate variability. Parasympathetic which regulates the functional heart response due to changes in metabolic activity.[17]

There are many examinations to assess autonomic nerve function, for instance electrodiagnostic examination that can assess sudomotor and cardiovascular functions. Sudomotor autonomic functions can be assessed by sympathetic skin response (SSR) that records potential changes in the skin surface and represents sudomotor sympathetic activity.[18] Electrodiagnostic examination can assess cardiovascular autonomic nerves based on variability in heart rate with interval examination R-R.[19]

The purpose of this study was to investigate the correlation between HbA1c levels and electrodiagnostic parameters of DAN, SSR and R-R intervals.

METHOD

This was a cross-sectional observational analytic study to find the correlation between HbA1c levels and the autonomic neuropathy that measured by SSR and R-R interval in type 2 DM patients. The independent variables in this study were HbA1c levels, age, duration of DM, BMI, systolic blood pressure, diastolic blood pressure, cholesterol, low density lipoprotein (LDL), high density lipoprotein (HDL), and triglycerides level. The dependent variables were SSR latency, SSR amplitude, and R-R interval ratio.

Inclusion criteria were DM patients, ≥20 years-old, and willing to participate in this study. Subjects were DM patients who checked up in the Outpatient Department of Neurology at Dr Sardjito General Hospital, Yogyakarta. Exclusion criteria were subjects who had been diagnosed with neuropathy due to other previous causes (alcoholism, chemotherapy, chronic kidney disease), patients with arrhythmia, active lung disease, and taking anti-cholinergic drugs. This research had received approval from the Ethics Committee for Research in humans, Faculty of Medicine, Public Health and Nursing, Gadjah Mada University.

Subjects who met the above criteria were then recorded for gender, age, duration of DM, medications, and smoking status. Furthermore, examination of blood pressure, height, weight, and body mass index (BMI) were recorded. Laboratory tests, including HbA1c levels, total cholesterol levels, HDL levels, LDL levels, and triglyceride levels, were obtained from blood tests at the Clinical Pathology Laboratory Dr Sardjito Hospital.

Electrodiagnostic examinations were performed at the Electromedic Polyclinic of Dr Sardjito General Hospital. SSR latency and amplitude of lower extremity, along with R-R interval ratio by comparing interval R-R at rest and deep breathing were measured. In the SSR examination, the subject was in supine position. In this study only examination of the lower extremities was performed. Negative electrodes were placed on the soles

of the feet, positive electrodes were placed on the dorsum of the foot, grounding electrodes were placed on the legs. Short electrical stimuli, with a wave duration of 0.2 millisecond (ms) and an intensity of 15-25 milliamperes (mA) were given. Stimulations were given four times with 30 seconds interstimulus interval, latency was recorded. The stimulated nerve were the tibial nerve.

The R-R interval was recorded by placing a negative electrode in the right parasternal intercostal space 1 or 2, a positive electrode in the left anterior axillary line of the lowest rib, and a ground electrode in the right anterior axillary line at the lowest rib. The patient was in supine position. The recording was performed twice, during rest and deep breathing (breathing frequency 6 times/minute). Each recording was carried out for one minute, then the shortest R-R and the longest R-R were measured. The maximum R-R interval proportion to the minimum R-R interval was expressed as the expiration:inspiration (E:I), and this proportion was calculated separately at rest and during breathing using the formula: maximum R-R interval/minimum R-R interval (automatically measured by the device). The interval ratio R-R was calculated using the formula (value at deep breathing)D%/(value at rest)R%.

Data analysis and statistical calculations were computerized. Pearson/Spearman correlation test was used for bivariate analysis. Multivariate analysis with linear regression was performed to assess the correlation of several independent variables to dependent variables.

RESULT

The subjects of this study were 41 DM patients. In subject characteristics (table 1), it was found that the number of male subjects (56.10%) was higher than female (43.90%), and most subjects were nonsmokers (65.85%). The mean age of the subjects was 64.26±7.61 years, which was included in the elderly category. The average duration of suffering from DM was 10.05±6.90 years. The mean body mass index was 24.60±3.36% (normal category). There were 10 subjects suffering from hypertension in therapy, with a mean systolic blood pressure of 135.85±18.26 mmHg and a diastolic blood pressure of 81.82±8.27 mmHg.

The average subject had an HbA1c level of 8.7±3.02%. Hence, the average subject had not achieved good glycemic control. On examination of lipid profiles, the average total cholesterol and HDL levels were found in the normal range, but LDL and triglycerides were increased. The results of SSR examination on the lower extremities shown in Table 1, obtained a mean subject lengthening latency, but for normal amplitude. For R-R interval, the average subject had a low R-R interval ratio.

Table 1. Characteristics of subjects

Variable	n (%)	Average (SD)
Men	23 (56.1)	
Women	14 (34.15)	
Age		64.26±7.61 y.o
Duration of DM		10.05±6.90 y.o
Body mass index		24.60±3.36 %
Systolic blood pressure		135.85±18.26 mmHg
Diastolic blood pressure		81.82±8.27 mmHg
HbA1c		8.7±3.02 %
Total cholesterol		190.41±45.74 mg/dl
LDL		123.14±44.10 mg/dl
HDL		40.83±10.99 mg/dl
Triglyceride		168.17±83.86 mg/dl
R-R interval ratio		0.96±0.28
SSR latency lower extremity		2586.58±778.69 ms
SSR amplitude lower extremity		0.51±0.61 mV

Note: DM =diabetes mellitus, HDL =high density lipoprotein, LDL =low density lipoprotein, SSR =sympathetic skin response

From the results of the bivariate analysis (table 2), it was found that HbA1c was positively correlated with lower limb SSR latency (r =0.312; p =0.047). HbA1c also had a negative correlation with ratio of R-R interval (r =-0.392; p =0.011). There was a significant positive correlation between DM duration and lower limb SSR latency (r =0.524; p =0,000), and a significant negative correlation was found between the duration of DM and lower extremity SSR amplitude (r =-0.447; p =0.003) as well as R-R interval ratio (r =-0.320; p =0.041). No significant correlation was found between age, BMI, systolic blood pressure, diastolic blood pressure, total cholesterol, LDL, HDL, triglycerides and electrodiagnostic parameters of DAN, namely SSR latency, SSR amplitude and R-R interval (table 2). There was no sex differences in normal and abnormal electrodiagnostic results on SSR latency (p =0.631), SSR amplitude (p =0.571), and R-R interval ratio (p =0.380). In the smoking status variable, no difference was found between normal and abnormal groups with SSR latency (p =0.386), SSR amplitude (p =0.588), and R-R interval ratio (p =0.944).

In multivariate analysis (table 3), it was found that only the duration of DM was independently correlated with lower extremity SSR latency (β =0.417; p =0.008), while HbA1c did not significantly correlate with SSR latency (β =0.175; p =0.248). In Table 3 it was found that the duration of DM was independently correlated with lower extremity SSR amplitude (β =-0.351; p =0.021), while HDL did not correlate with lower extremity SSR amplitude (β =-0.252; p =0.092). Table 3 also shows that there are no independent variables correlated with R-R interval ratios, namely HbA1c (β =-0.298; p =0.063), DM duration (β =-0.247; p =0.121) and SBP (β =- 0.097; p =0.521).

Table 2. Independent variable bivariate analysis with electrodiagnostic parameter of DAN

Independent Variable	SSR latency		SSR amplitude		R-R interval ratio	
	r	p	r	p	r	p
Age	-0.009	0.955	-0.141	0.380	-0.018	0.910
HbA1c	0.312	0.047*	-0.133	0.408	-0.392	0.011*
DM duration	0.524	0.000*	-0.447	0.003*	-0.320	0.041*
BMI	-0.112	0.486	0.108	0.502	0.078	0.626
SBP	0.114	0.478	-0.066	0.683	-0.216	0.174
DBP	0.002	0.990	0.033	0.836	0.012	0.942
Cholesterol	-0.036	0.822	0.101	0.531	0.082	0.612
LDL	-0.058	0.718	0.035	0.825	0.031	0.846
HDL	0.075	0.640	-0.263	0.097	-0.118	0.463
Triglyceride	0.072	0.656	0.079	0.625	0.032	0.842

*significant, p-value <0.05

Table 3. Bivariate analysis of independent variables with electrodiagnostic parameter of DAN

Independent Variables	SSR latency		SSR amplitude		R-R interval ratio	
	β	*p*	β	*p*	β	*p*
HbA1c	0.175	0.248			-0.298	0.063
DM duration	0.417	0.008*	-0.351	0.021*	-0.247	0.121
HDL			-0.252	0.092		
SBP					-0.097	0.521

*significant, *p*-value < 0.05

DISCUSSION

Bivariate analysis showed that HbA1c was correlated with increasing SSR latency and decreasing R-R interval ratio. It was found that DM patients with normal SSR results were lower in HbA1c levels compared with DM patients who had absent SSR.[20] Prolongation of SSR latency is an early sign of sympathetic small nerve fiber dysfunction in diabetic neuropathy.[21]

The high level of HbA1c which indicates poor glycemic control is proportional to the decrease of nerve fibers innervation in the sweat glands causing sudomotor dysfunction in diabetic neuropathy.[22] Symptoms of sudomotor denervation in diabetic neuropathy is decreased sweat production due to postganglionic nerve degeneration. Pathological changes in sudomotor innervation is followed by sudomotor symptoms.[22] Hsiao et al. [23] studied heart rate variability measured with R-R intervals in DM patients. This study found that the higher the HbA1c level, the lower the heart rate variability. HbA1c is a glycemic control marker in patients with DM.[14] High levels of HbA1c increase the formation of advanced glycation end-product (AGE).[23] AGE can deposit in each peripheral nerve component, such as collagen stroma, endothelial cells, pericytes, axonal basement membrane, and Schwann cells. The intensity of AGE deposition correlates with a decrease in myelin density, due to direct toxicity to nerve tissue along with endoneurial microangiopathy.[24]

Previous study showed that BMI and total cholesterol levels had significant effect on heart rate variability.[14] In this study, BMI did not significantly correlate with electrodiagnostic parameters of autonomic neuropathy. Overweight and obesity category in body mass index becomes a factor of DAN.[25] In contrary, the mean BMI in this study was in the normal category. No correlation in BMI variable was found in the this study. Hyperlipidemia causes an increase in oxidative stress and high LDL oxidation triggers an inflammatory reaction in the microvascular endothelium, thus developing neuropathy in the peripheral nervous system. In addition, the increase in oxidative stress also increases the local inflammatory reaction in peripheral nerves.[26] In this study, mean cholesterol level was in normal range and no correlation was found between the parameters of autonomic neuropathy.

In the multivariate test, only the duration of DM significantly affected SSR latency and SSR amplitude, while HbA1c did not significantly correlate with SSR latency, SSR amplitude and R-R interval. Although the results of multivariate analysis HbA1c did not significantly correlate with SSR latency, SSR amplitude and R-R interval, but HbA1c has an influence with SSR latency and R-R interval indicated by the strength of the bivariate analysis correlation. The results of this study indicate that DM patients with high HbA1c levels or poor glycemic control with a duration of DM more than 10 years correlate with the occurrence of autonomic sudomotor and cardiovascular diabetic neuropathy.

The duration of DM was positively correlated with SSR latency and negatively correlated with SSR amplitude. In addition, the duration of DM was also negatively correlated with the ratio of the interval R-R. The duration of DM is an independent factor in macrovascular and microvascular complications.[27] Another study found a very strong negative correlation between the duration of DM and changes in heart rate during normal breathing and deep breath (r = -0,908;

p <0.001).[28] Variability in heart rate has a strong relationship with the duration of DM. In 5-10 years duration of DM, it showed loss of parasympathetic modulation, whereas in the 10-15 year period it showed a loss of sympathetic modulation.[15]

In the previous study, the duration of DM and age were risk factors for microvascular complications in DM, such as neuropathy and retinopathy.[27] Increasing age caused a decrease in noradrenergic neurotransmitters which are autonomic neurotransmitters in the cardiovascular system, resulting in a decrease in electrical stimulation and decreased cardiovascular innervation.[29] Hyperglycemia is the strongest hypothesis of diabetic neuropathy. Hyperglycemia leads to activation of protein kinase C, activation of the polyol pathway, and increased oxidative stress, resulting in a decrease in blood flow of neurons.[6] Increasing exposure to hyperglycemia increases neuronal damage. Glycemic control (HbA1c) and the duration of DM are predictors of DM neuropathy, and nervous system changes have occurred from the initial diagnosis of DM which correlates with the severity of the disease and chronicity, so this is the target of therapy to prevent the development of neuropathy.[30] This explains the results of the a study in whice the duration of DM and HbA1c levels were positively correlated with DAN.

CONCLUSION

HbA1c levels were positively correlated with SSR latency, and negatively correlated with the ratio of interval R-R. There is a tendency for an increase in HbA1c levels with a decrease in SSR amplitude, although not statistically significant.

LIMITATION

This study only found the correlation and the direction of correlation at one time. We could not explain the causative mechanism underlying the findings. Hence, causative research with a case-control or cohort design is needed.

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