Glucose fluctuations reduce quality of sleep and of life in patients with liver cirrhosis

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Abstract

Background:

Sleep disturbance and decreased health-related quality of life (HRQOL) are significant complaints in patients with liver cirrhosis. Although the etiology of these complications is unclear, we propose that glucose intolerance may be a predisposing factor. Therefore, our aim was to investigate the relationship between glucose intolerance and these complications.

Methods:

We assessed continuous glucose monitoring (CGM) in 43 patients with chronic liver disease. Among these patients, 36 completed the Pittsburgh Sleep Quality Index (PSQI), the 36-item short-form health survey (SF-36), and the Neuropsychological Test (NPT). We also assessed the change in glucose fluctuations between preoperative periods and 1 year after liver transplantation in 13 patients.

Results:

Standard deviation (SD) of blood glucose was 24.15 ± 13.52. SD values correlated to glucose metabolism measures, including HbA1c, glycoalbumin. SD values also correlated to markers of liver fibrosis, including type IV collagen.

Twenty-one patients (58.3%) were classified as “poor” sleepers, with a global PSQI

score ≥ 6. Glucose fluctuations correlated with the global PSQI score (r = 0.456, *p* = 0.008) and the SF-36 score (r = 0.434, *p* = 0.013). Multivariate regression analysis identified SD values as an independent risk factor for sleep disturbance (r = 0.12, *p* = 0.039) and decreased HRQOL (r = -0.32, *p* = 0.024). SD values did not correlate with the NPT.

SD values were also improved in 11 (84.6%) patients 1 year after liver transplantation.

Conclusion:

Abnormal glucose fluctuations are a risk factor for sleep disturbance and decrease of HRQOL in patients with cirrhosis.

Word count of Abstract: 249

Keywords

Cirrhosis – Glucose fluctuations – Sleep disturbance – Health related quality of life

Introduction

Sleep disturbance is a common chronic disorder[1]. It is estimated that 50% to 65% of patients with liver cirrhosis experience sleep disturbance [2-4], which manifests as disordered sleep, delayed sleep phases, and excessive day-time sleepiness [2, 4]. However, the mechanisms underlying sleep disturbance in patients with liver cirrhosis are unclear.

Liver cirrhosis also negatively influences health-related quality of life (HRQOL), with patients reporting fatigue, inability to function at work, depression, and loss of dignity among other problems that significantly decrease overall quality of life [5-9].

In addition to sleep disturbance and reduced quality of life, many patients with chronic liver disease have glucose intolerance [10, 11]. The possibility of sleep disturbances being independently associated with glucose intolerance and insulin resistance has been raised in previous research [12]. Therefore, it is plausible that glucose tolerance may contribute to sleep disturbance and decreased HRQOL in patients with liver cirrhosis. The aim of our study was to investigate the relationship between glucose intolerance measured as fluctuations in glucose levels over 3 consecutive days, and sleep disturbance, HRQOL, and minimal hepatic encephalopathy in patients with liver cirrhosis.

Methods

Patients

Our study group consisted 43 patients with chronic liver disease admitted to the Department of Gastroenterology and Hepatology at Nagasaki University Hospital between April 2013 and June 2015. Patients with renal dysfunction, defined by a creatinine concentration >2.0 mg/dL (reference interval, 0.40-1.10 mg/dL), gastroesophageal reflux disease, psychiatric disorder, chronic obstructive pulmonary disease, severe anemia, defined by a hemoglobin concentration <7.0 g/dL (reference interval, 11.3-15.2 g/dL), overt hepatic encephalopathy, and major portosystemic shunt, such as gastrorenal shunt were excluded from the study. Relevant characteristics of our patient group are reported in Table 1. All patients provided informed consent, and our study protocol conformed to the guidelines of the Declaration of Helsinki and was approved by the Nagasaki University Ethics Committee (approval no. 13120201).

Subcutaneous interstitial glucose levels were monitored over a period of 3 consecutive days using a continuous glucose monitoring system (CGM; iPro2: Medtronic, Northridge, CA, U.S.A.). Recorded data were downloaded to a computer to evaluate glucose fluctuations, quantified as the time-dependent standard deviation (SD) around the mean level. Glucose metabolism was evaluated using a 75 g oral glucose tolerance

test (OGTT) with plasma levels of glucose measured at 120 min after intake. Concentrations of glycohemoglobin A1c (HbA1c, mmol/mol) and glycoalbumin (%) were also measured. The etiology of the liver disease was determined through a combination of clinical, laboratory, radiological, and histological variables. Liver function was evaluated using the Child-Pugh score and the Model for End-Stage Liver Disease (MELD) score. Concentrations of albumin (g/dL; reference interval, 3.9-4.9 g/dL) and ammonia (NH3, μg/dL; reference interval, 30-86μg/dL) were also measured. The following markers of liver fibrosis were evaluated: virtual touch tissue quantification (VTQ), ultrasound imaging and concentration of type IV collagen. VTQ measurements were performed using an Acuson S2000 ultrasound system (Siemens Healthcare, Erlangen, Germany).

Sleep quality, HRQOL, and the presence or absence of minimal hepatic encephalopathy was evaluated in 36 of the 43 patients in our study group. Sleep disturbance was identified using the Japanese version of the Pittsburgh Sleep Quality Index (PSQI). Questionnaire responses were used to evaluate 7 components of sleep, with each component scored on a Likert scale from “0” to “3”, with a score >1 indicative of sleep abnormalities. The component scores were added to provide the global PSQI score, ranging can range between “0” and “21”, with a cutoff score >5

identifying individuals as “poor” sleepers.

HRQOL was assessed using the Japanese version of the SF-36 Health Survey, version 2 (Medical Outcomes Trust, Health Assessment Lab, Quality Metric and Shunichi Fukuhara). On the SF-36, 1 item globally evaluates perceived change in health status, with the remaining 35 items used to generate eight subscales, with the score on each subscale ranging between “0” and “100”. The following subscales are evaluated: physical functioning (PF); role limitations due to poor physical health (RP); bodily pain (BP); general health perception (GH); vitality (VT); social functioning (SF); role limitations due to poor emotional health (RE); and role limitations due to mental health (MH). Individual subscale scores were standardized using the general Japanese population to generate a corresponding *z*-score. Aggregate physical and mental component summary scores (PCS; physical component summary, and MCS; mental component summary, respectively) were obtained by multiplying each *z*-score by its respective physical and mental factor score coefficient and summing these eight products.

The Neuropsychological Test (NPT) was designed to evaluate psychomotor, attention, memory, and special brain functions using the following eight cognitive tests: number connection tests A and B; figure position test; digit symbol test; block design test; and

reaction time tests A, B, and C. The NPT is used clinically to screen for minimal hepatic encephalopathy. To simplify the assessment, two-dimensional operations are performed on a computer. The NPT can be completed in about 20 min, which included the time required to read the operation guide and practice. The software for the NPT was developed by Otsuka Pharmaceutical Co, Ltd, Kokuyo Co, Ltd, and ISB Co, Ltd.

Furthermore, living donor liver transplantation (LDLT) was performed in 13 of the 43 patients in our study group and we assessed the change in SD values between preoperative periods and 1 year after LDLT.

All analyses were performed using Stat Flex (ver. 6.0; Artec, Osaka, Japan). Data were presented as a mean and standard deviation (SD). Correlations were evaluated using Pearson's correlation coefficient. Multivariate regression analysis was used to identify variables that independently predicted sleep disturbance and decreased HRQOL. Pairwise comparisons were evaluated using Student's *t*-test. A p-value <0.05 was considered statistically significant.

Results

Relevant clinical and laboratory characteristics of our patient group are presented in Table 1, with key features summarized as follows: age, 57.1±13.0 years; 22 (51.2%) male and 21 (48.8%) female; HbA1c (NGSP) levels of 5.1±0.8%; and diabetes mellitus identified in 7 (16.3%) patients, with 4 of these patients using insulin. The distribution of underlying liver diseases was as follows: hepatitis C virus (HCV) in 17 (39.5%) patients; hepatitis B virus (HBV) in 2 (4.6%) patients; chronic alcoholism in 8 (18.6%) patients; and non-alcoholic liver disease (NASH) in 4 (9.3%) patients. Forty of the 43 patients in our study group had a clinical diagnosis of liver cirrhosis, with a mean Child-Pugh score 8.89±2.59 (Grade A, 7 patients; Grade B, 15 patients; and Grade C, 18 patients).

Concerning CGM, the SD values were 24.15 ± 13.52, with mean glucose level of 127.85 ± 29.36 mg/dL. Nocturnal hypoglycemia (BS <70 mg/dL) was identified 7 (16.3%) patients (Table 1).

A Summary of the results of assessment questionnaires and the NPT was provided in Table 2. According to the global PSQI scores, 21 (58.3%) patients were classified as being “poor” sleepers (the global PSQI score ≥6), with all “poor” sleepers having a clinical diagnosis of liver cirrhosis.

SD values of glucose fluctuation correlated to glucose metabolism measures (HbA1c, r = 0.438, $p = 0.005$; glycoalbumin, r = 0.761, $p < 0.001$; OGTT plasma glucose levels at 120 min, r = 0.775, $p < 0.001$). Although SD values did not correlate with liver function test results, including the Child-Pugh and MELD scores, a correlation with markers of liver fibrosis was identified (VTQ, r = 0.360, p = 0.026; and type IV collagen, r = 0.423, p = 0.008; Fig. 1).

SD values correlated with the global PSQI score (r = 0.456, $p = 0.008$; Table 3a). The relationship between the global PSQI score and other clinical factors was also reported in Table 3a, with no significant correlation identified to HbA1C, glycoalbumin, NH3, BMI, and the number of abnormalities on the NPT. Multivariate regression analysis identified SD values as an independent risk factor for sleep disturbance (r = 0.12, $p = 0.039$; Table 3b). We have demonstrated the subgroup analysis of the Hepatitis C Virus (HCV) (17 patients) and alcoholic (8 patients) groups. In the HCV group, the SD values correlated with the global PSQI score (r = 0.456), although not significantly. However, the SD values significantly correlated with PCS (r = -0.6559, $p < 0.05$). In the alcoholic group, SD values correlated with neither PSQI score (r = 0.5409) nor PCS (r = -0.4239). The number of patients examined in these groups might be too small to detect any statistical significance.

In terms of HRQOL, SD values correlated with the PCS subscore of the SF-36 (r = 0.434, $p = 0.013$; Table 4a). The relation between PCS and other clinical measures was also reported in Table 4a. The PCS score correlated with the Child-Pugh score. Multivariate regression analysis identified SD values as an independent risk factor for HRQOL (r = -0.32, $p = 0.024$; Table 4b). In terms of NPT, SD values correlated with the 'block design' subtest of the NPT (r = 0.504, $p = 0.006$). However, there was no overall correlation between SD values and NPT.

SD values were also improved in 11 of 13 (84.6%) patients 1 year after LDLT. The mean SD values were significantly decreased 1 year after LDLT (preoperative periods; 27.9 ± 16.7, 1 year after LDLT; 19.5 ± 10.3, $p < 0.05$; Fig. 2).

Discussion

Liver cirrhosis is associated with important morbidity and mortality, usually due to complications that include hepatic encephalopathy, ascites, and variceal bleeding [13]. According to the World Health Organization, about 70% of patients with liver cirrhosis have oral glucose intolerance or diabetes [10], with obvious diabetes identified in 21%-30% of patients with liver cirrhosis [11].

In our study, we used glucose fluctuations, obtained using CGM, in combination with other metabolic markers of glucose metabolism, namely HbA1c, glycoalbumin, and plasma glucose. Compared to standard monitoring methods, CGM systems provide more information, including extent and duration of fluctuation in blood glucose level, from which hyperglycemia and asymptomatic hypoglycemia can be identified, impairments in glucose metabolism which are often difficult to identify using conventional monitoring systems [14]. Therefore, the CGM system is used for patients with diabetes, liver cirrhosis, enteral feeding, or late dumping syndrome [15]. Rizzo et al also demonstrated a significant correlation between glucose fluctuations and Mini Mental Status Examination (MMSE) scores by using the CGM system [16].

A recent study reported a mean ± SD glucose fluctuation of 14.2 ± 5.8 in healthy adults [17]. In our study, the mean ±SD glucose fluctuation in cirrhotic patients was significantly

higher than this reported value in healthy adults. Evidence of insulin resistance and hyperinsulinemia in patients with liver cirrhosis has previously been reported [18, 19]. In our study, SD values of the glucose level measured by CGM, were correlated with glucose metabolism values, including HbA1c, glycoalbumin, and plasma glucose, and therefore, we consider the SD of the glucose level measured by CGM to be a useful index of glucose metabolism.

We identified a correlation between the SD of the glucose level and markers of hepatic fibrosis. Meanwhile, we did not identify a correlation between the SD of the glucose level and liver function tests. A previous study also reported that sleep disturbance was not related to liver function [20]. Therefore, it is possible that the association between SD of the glucose level and sleep disturbances could be mediated by the correlation between SD and markers of hepatic fibrosis, with the progressive hepatic fibrosis gradually increasing glucose tolerance.

In our study, 58.3% of patients were classified as being poor sleepers, which is similar to previously reported rates of poor sleepers among patients with liver cirrhosis [2, 21-24]. We did not identify a correlation between nocturnal hypoglycemia and sleep disturbance measured by the global PSQI score. However, we did identify a significant correlation between the global PSQI score and the SD of the glucose level. The mechanism of sleep

disturbance in patients with cirrhosis is still unclear. Previous studies have related sleep disturbances in patients with liver cirrhosis to MHE, and there are some animal data to support this relationship [25-27]. However, in humans, Cordoba et al. did not identify the prevalence of sleep disturbances as a function of psychometric performance in 44 patients with liver cirrhosis [2]. Similarly, Montagnese et al. did not report a correlation between the sleep disturbance and the severity of encephalopathy in 87 patients, categorized as healthy controls or as having minimal or overt HE [21].

Meanwhile, Sleep disturbance is commonly identified in patients with diabetes mellitus [28]. In fact, the prevalence of sleep disturbance has been reported to range between 23% and 58% of patients with diabetes [28, 29]. A specific relationship between poor quality of sleep and a high degree of insulin resistance and high adiposity measure has been reported [30]. Impaired glucose tolerance is associated with autonomic dysfunction, which may lead to sleep disturbances. One study demonstrated that 30% of diabetic patients with autonomic dysfunction have sleep disturbance, a proportion greater than that of diabetic patients without autonomic dysfunction [31]. In addition, poor glucose control and autonomic dysfunction might cause hormonal imbalances in patients with cirrhosis. One study demonstrated parallel delays in the onset of melatonin and cortisol rhythms in patients with cirrhosis [32]. Our finding of a relationship between

abnormal glucose metabolism and sleep disturbance in patients with chronic liver disease corroborates these previous reports.

We also identified a negative correlation between the SD of the glucose level and the PCS, implying an effect of glucose metabolism on HRQOL. Previous studies have reported lowering in work performance and quality of life with disturbances in sleep [4, 21]. Therefore, sleep disturbance might be associated with reduced HRQOL.

SD values were improved in 11 patients after LDLT. This result raised that glucose fluctuations might be reversible and influenced by liver fibrosis or function. It is desirable to consider whether or not improvement of glucose fluctuations improve quality of sleep and life, in the future.

There are few reports of glucose fluctuations in patients with liver cirrhosis using continuous glucose monitoring (CGM). To our knowledge, this is the first study to evaluate the correlation between sleep disturbances, HRQOL, and glucose fluctuations in Japanese patients with liver cirrhosis.

The limitations of our study should be acknowledged in the interpretation of results. Foremost, our study group was small, including a low representation of patients with HBV-related liver disease. Our evaluation also lacked objective assessments of sleep and HRQOL. A strength of our study is the use of multivariate statistical models for

analysis, controlling for potential confounders, such as age, sex, hemoglobin, and albumin. When controlling for these potential confounding effects, SD of the glucose level remained a significant factor.

In conclusion, impaired glucose tolerance is a risk factor for sleep disturbance and HRQOL in patients with liver cirrhosis. We believe that sleep disturbance and HRQOL could be improved by controlling glucose fluctuations.

Compliance with Ethical Standards:

Conflict of Interest: Author Dr. Haraguchi, Dr. Miyaaki, Dr. Ichikawa, Dr. Shibata, Dr. Honda, Dr. Ozawa, Dr. Miuma, Dr. Taura, Dr. Takeshima and Dr. Nakao declare that they have no conflict of interest.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent: Informed consent was obtained from all individual participants included in the study.

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Tables

Table 1. Clinical characteristics of the study group

Male : Female	22 : 21
Age (years)	57.12 ± 13.00
BMI (kg/m^2)	23.82±4.07
HbA1c (%)	5.18 ± 0.80
Type 2 diabetes	7 cases
Newly diagnosed with DM	9 cases
Antidiabetic agents	oral hypoglycemic agent; 0 case Insulin; 4 cases
LC	40 cases
HCV-related	14 (33%)
HBV-related	2 (4.6%)
Alcohol-related	8 (18.6%)
NASH	4 (9.3%)
PBC	5 (11.6%)
AIH	2 (4.7%)

Others	5 (11.6%)
CH (HCV-related)	3 (7.0%)
Child-Pugh classification (A/B/C)	7/15/18
Child-Pugh score	8.89 ± 2.59
MELD score	13.40 ± 5.26
Hemoglobin (g/dL)	11.04 ± 2.30
Creatinine (mg/dL)	0.94 ± 0.97
NH3 (μg/dL)	68.31 ± 42.18
liver VTQ (m/s)	2.60 ± 0.79
type IV collagen (ng/mL)	340.27 ± 195.29
Continuous Glucose Monitoring (CGM)	
Glucose fluctuations	24.15±13.52
Mean glucose levels	127.85±29.36
Nocturnal hypoglycemia	7 (16.3%)

Notes: BMI, body mass index (kg/m^2); HbA1c, glycohemoglobin A1c; LC, liver cirrhosis; HCV, hepatitis C virus; HBV, hepatitis B virus; NASH, non-alcoholic steatohepatitis; PBC, primary biliary cirrhosis; AIH, autoimmune hepatitis; CH, chronic hepatitis; MELD, Model For End-Stage Liver Disease; NH3, ammonia; VTQ, virtual

touch tissue quantification. The ‘others’ category includes two cases of primary sclerosing cholangitis (PSC), one case of Wilson’s disease and of polycystic liver disease, and one case of unknown etiology.

Table 2. Outcome scores of questionnaires and the Neuropsychological Test

Pittsburgh Sleep Quality Index (PSQI)	7.11 ± 4.08
poor sleeper (PSQI score > 5)	21 (58.3%)
SF-36	
physical functioning (PF)	71.94 ± 16.79
role limitations due to poor physical health (RP)	59.39 ± 25.34
bodily pain (BP)	65.03 ± 22.37
general health perception (GH)	43.04 ± 14.17
vitality (VT)	47.94 ± 20.04
social functioning (SF)	65.88 ± 27.27
role limitations due to poor emotional health (RE)	62.96 ± 27.27
role limitations due to mental health (MH)	61.67 ± 18.40
physical component summary (PCS)	40.15 ± 10.26
mental component summary (MCS)	47.57 ± 7.66
Neuropsychological Test (NPT)	
Number of abnormalities	3.31 ± 2.39

Table 3a. Correlation between the Pittsburgh Sleep Quality Index (PSQI) score and patients' demographics and clinical test scores (Univariate analysis)

Covariate	**Correlation coefficient**	***p*-value**
Age (years)	0.115	0.504
Sex (male)	-0.049	0.557
SD values	0.456	0.008
Hemoglobin	-0.299	0.077
Albumin	-0.290	0.086
HbA1c	0.139	0.42
Glycoalbumin	0.317	0.078
DM (+)		0.35
NH3	0.201	0.23
BMI	0.007	0.96
Child-Pugh score	0.214	0.21
VTQ	0.199	0.255

Number of abnormalities in NPT	0.189	0.34

Notes. *P*-value was based on Pearson product-moment correlation coefficient; HbA1c, glycohemoglobin A1c; NH3, ammonia; BMI, body mass index; VTQ, virtual touch tissue quantification; NPT, Neuropsychological Test

Table 3b. Correlation between the Pittsburgh Sleep Quality Index (PSQI) score and patients' demographics and clinical test scores (Multivariate analysis)

Covariate	**Coefficient (β)**	***t*-ratio**	***p*-value**
Age (years)	0.02	0.33	0.74
Sex (male)	-0.20	0.12	0.91
SD values	0.12	2.17	0.039
Hemoglobin	-0.09	0.79	0.84
Albumin	-1.00	0.21	0.44

Notes. *P*-value was based on multivariate regression analysis.

Table 4a. Correlation between the physical component summary (PCS) of the SF-36 and clinical factors (Univariate analysis)

Covariate	**Correlation coefficient**	***p*-value**
Age (years)	0.116	0.507
Sex (male)	-0.049	0.557
SD values	-0.434	0.013
Hemoglobin	0.176	0.312
Albumin	0.309	0.070
HbA1c	-0.096	0.584
Glycoalbumin	-0.280	0.127
DM (+)		0.077
NH3	-0.318	0.071
BMI	-0.074	0.683
Child-Pugh score	-0.356	0.036
VTQ	-0.059	0.743

Notes. *P*-value was based on Pearson product-moment correlation coefficient.

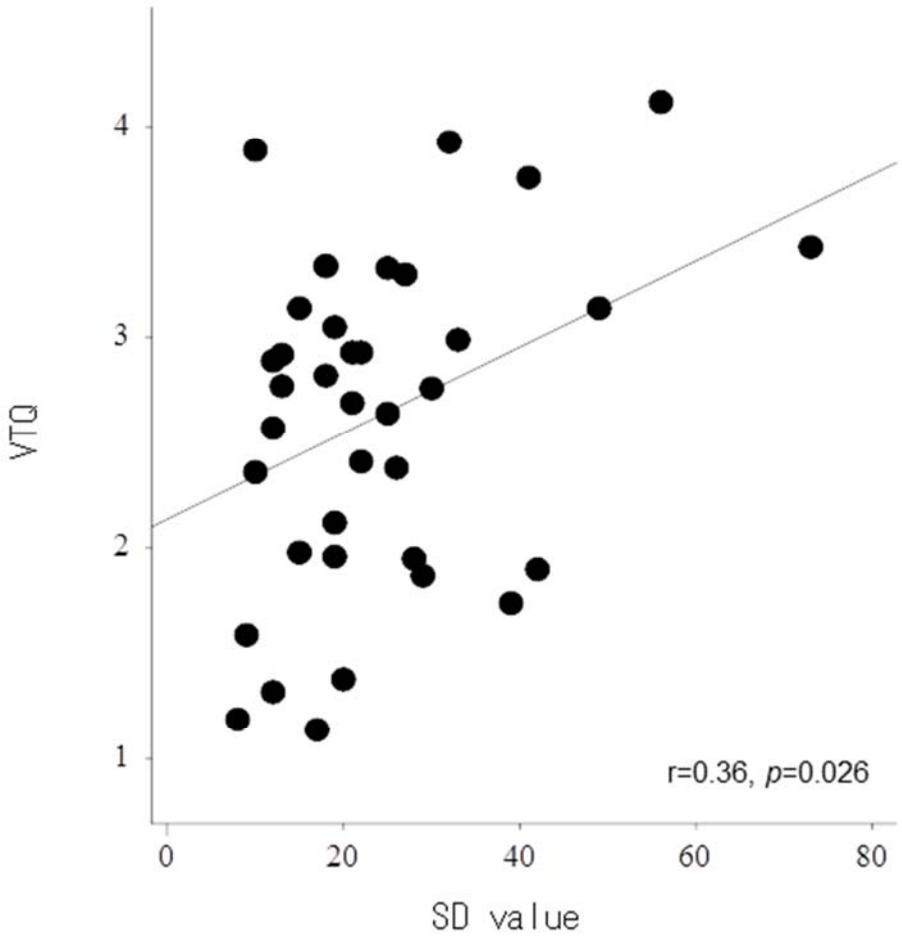
HbA1c, glycohemoglobin A1c; NH3, ammonia; BMI, Body Mass Index; VTQ, virtual touch tissue quantification

Table 4b. Correlation between the physical component summary (PCS) of the SF-36 and clinical factors (Multivariate analysis)

Covariate	**Coefficient (β)**	***t*-ratio**	***p*-value**
Age (years)	-0.048	0.28	0.78
Sex (male)	2.43	0.74	0.47
SD values	-0.32	2.41	0.024
Child-Pugh score	-0.86	1.14	0.27
NH3	-0.07	1.54	0.14

Notes. *P*-value was based on multivariate regression analysis; NH3, ammonia

Fig. 1a.



1b.

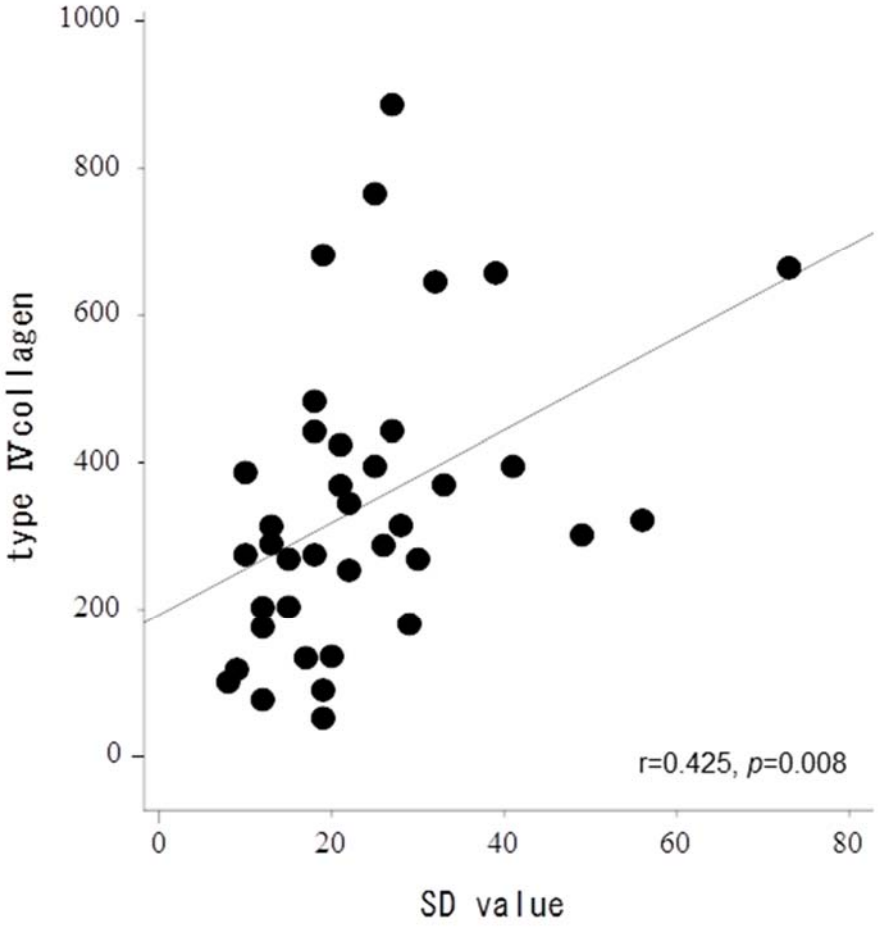


Fig. 1. Correlation between the SD values and liver fibrosis markers, showing a significant correlation to (a) virtual touch tissue quantification (VTTQ), and (b) type IV collagen.

Fig. 2.

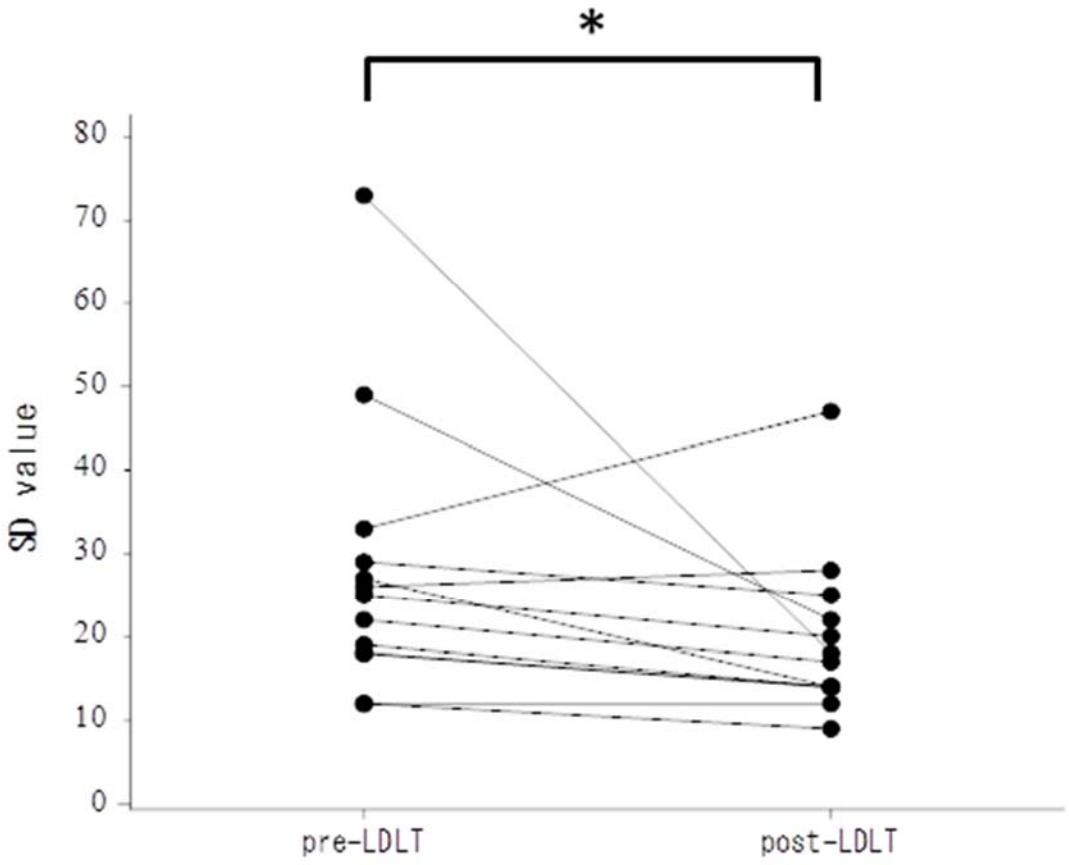


Fig. 2. The Change in SD values of glucose fluctuations. The mean SD values of glucose fluctuations were significantly decreased 1 year after LDLT (preoperative periods; 27.9 ± 16.7, 1 year after LDLT; 19.5 ± 10.3, * $p < 0.05$).

LDLT, living donor liver transplantation.