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*Original Article*

# The Relationship between the Duration of Suffering from Diabetes and HbA1c Levels with the Degree of Liver Stiffness in Type 2 Diabetes Mellitus Patients

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## Abstract

**Background :** Type 2 diabetes mellitus (DM) is one of the main problems faced by the health carae system. Diabetes is a multifactorial, chronic and progressive metabolic disorder characterized by chronic hyperglycemia. Persistent hyperglycemia is associated with long-term damage to the liver. Ultrasound elastography is an imaging modality that can assess liver stiffness and can help clinicians in determining therapy, evaluating and predicting disease progression. This study aims to determine the relationship between the degree of liver stiffness using ultrasound elastography with the duration of suffering from type 2 diabetes mellitus and HbA1c levels.
**Methods :** This research is an observational analytic with a cross-sectional approach. This research was carried out from September 2021 to September 2022 at the radiology installation of RSUP Dr. Kariadi Semarang, then 50 research subjects were obtained who met the inclusion criteria. The Rank–Spearman correlation test was used to assess the relationship between the degree of liver stiffness and the duration of suffering from type 2 DM and HbA1c levels.
**Results :** The average value of liver stiffness assessed using ultrasound elastography is 7.92 ± 6.72 kPa. The average value of HbA1c levels is 8.55 ± 2.63%. The average duration of suffering from type 2 DM is 9.10 ± 6.50 years. The results of the Rank-Spearman test shows a significant relationship between HbA1c levels and the degree of liver stiffness ($p < 0.001$) with a correlation coefficient (r) of 0.68. The results of the Rank–Spearman test shows no significant relationship between the duration of suffering from type DM 2 and degree of liver stiffness ($p = 0.052$).
**Conclusion :** There is a relationship between liver stiffness and HbA1c levels but there is no relationship between liver stiffness and the duration of suffering from type 2 DM.

**Keywords :** Diabetes mellitus type 2, duration of suffering from diabetes, HbA1c level, ultrasound elastography, liver stiffness

## INTRODUCTION

Diabetes mellitus (DM) is a multifactorial, chronic and progressive metabolic disorder characterized by chronic hyperglycemia. Persistent hyperglycemia is associated with long-term damage, dysfunction, and failure of the liver.[1,2] Diabetes is one of the main problems and biggest challenge faced by the health care system. Data from the International Diabetes Federation (IDF) in 2017 found that the number of diabetes sufferers in Indonesia reached 10.3 million people. The global prevalence of diabetes in adults is currently estimated at around 382 million, with 175 million undiagnosed and the greatest incidence occuring between the ages of 40 and 59 years.[3,4]

The main goal in managing diabetes therapy is to control blood sugar. High levels of HbA1c greatly influence the emergence of complications in diabetes sufferers in the form of liver damage. In theory, the long duration of suffering from diabetes mellitus is also related to the process of liver stiffness. The duration of suffering from DM is directly proportional to the risk of developing liver stiffness.[5,6]

Liver biopsy is currently considered as the gold standard for assessing liver stiffness. However, this procedure has several disadvantages involving invasive, painful, and limited to patients who are asymptomatic. In addition, the accuracy of this procedure in assessing liver stiffness can be questioned as potential for errors in sampling location and variability between examiners.[7,8]

Ultrasound elastography is an imaging modality that can be used to diagnose liver stiffness, the results of which can help clinicians in determining therapy, evaluating therapy, and predicting disease progression.[8,9] Therefore, this research was conducted to examine the relationship between the degree of liver stiffness and the duration of suffering diabetes and HbA1c levels in type 2 diabetes mellitus patients.

## METHODS

This research is an observational analytical study coducted prospectively with a cross-sectional design. This study was carried out after obtaining approval from the Health Research Ethics Committee of RSUP Dr. Kariadi. Data was collected from September 2021 to September 2022 by carrying out examinations using an ultrasound elastography and medical record data from type 2 DM sufferers at Dr. RSUP. Kariadi. The sample used in this research was 50 subjects. The inclusion criteria involve type 2 DM sufferers who were over 18 years old, had an HbA1c examination and an

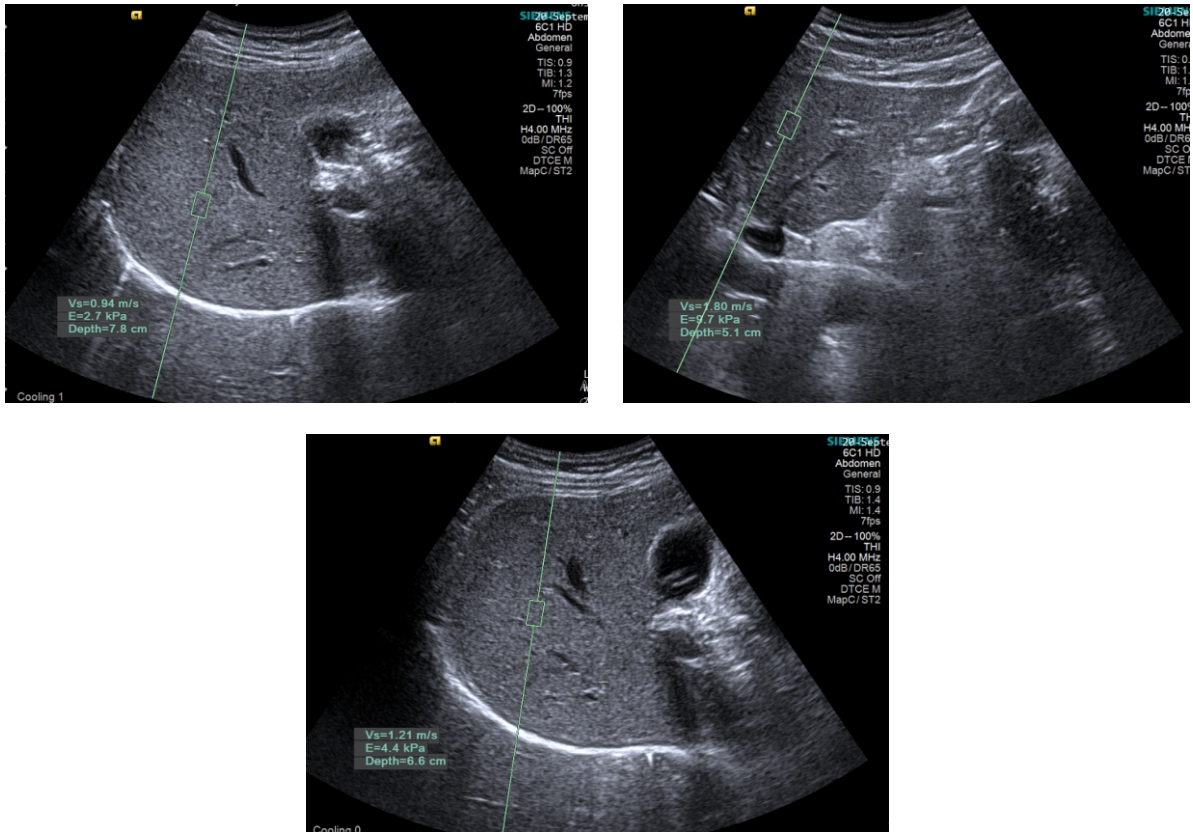


**Figure 1.** Elastography examination of the liver

ultrasound elastography examination. The exclusion criteria involve patients with comorbidities such as heart disease, hepatitis, biliary obstruction, liver cirrhosis, liver malignancies and alcohol-related liver disease.

This research uses Siemens Acuson S2000® ultrasound elastography. The independent variables in this study are the duration of diabetes and HbA1c levels. The dependent variable in this study is the degree of liver stiffness based on ultrasound elastography examination.

Data analysis used statistical programs consisting of descriptive analysis and statistical analysis. Descriptive analysis was carried out to examine the distribution characteristics of the number and percentage of gender, age, duration of suffering from type 2 DM, HbA1c levels and degree of liver stiffness. The Rank-Spearman correlation test was then used to assess the relationship between the degree of liver stiffness and the duration of suffering from type 2 DM and HbA1c levels.

## RESULTS

Of the 50 subjects, it was found that the number of female patients is greater than male consisting of 30 (60%) female patients and 20 (40%) male patients, with a ratio of 3:2. The average age of subjects is 56.94 ± 9.28 years, the youngest patient is 40 years old and the oldest patient is 79 years old. Furthermore, the average duration of suffering from type 2 DM is 9.10 ± 6.50 years with the shortest duration of suffering from type 2 DM is 1 year while the longest duration of suffering is 27 years. The average HbA1c level is 8.55 ± 2.63%, the lowest HbA1c level is 5.5% and the highest HbA1c level is 15.8%. Examination using ultrasound elastography found the average value of liver stiffness is 7.92 ± 6.72 kPa (Table 1).

HbA1c levels are a reflection of blood glucose control in the last 10–12 weeks. Thus, HbA1c levels are a reliable parameter to reflect chronic glycemia conditions and are strongly correlated with the risk of type 2 DM-related complications, especially cardiovascular disease and stroke. HbA1c levels correlate proportionally with blood glucose levels.[11]

The examination of liver stiffness using ultrasound elastography found the majority of subjects (40%) experienced minimal fibrosis with liver stiffness values categorized at the F1: <5.7 kPa. As many as 26% patients are included in the significant fibrosis category (F2: 5.7–7.3 kPa), 20% subject are included in the cirrhosis category (F4: > 10 kPa), while the fewest number of patients is in the severe fibrosis category (F3: 7.3 – 10 kPa) involving 14% patients. The prevalence of liver stiffness is significantly higher in patients with type 2 DM. Type 2 DM is a significant risk factor for liver fibrosis in both subjects with and without liver disease.[12] Hyperglycemia is known to have a negative effect on liver cells which can initiate the progression of Non-Alcoholic Fatty Liver Disease (NAFLD) into steatosis, non-alcoholic steatohepatitis (NASH), and cirrhosis respectively. Untreated liver cirrhosis can cause irreversible cirrhosis

TABLE 1
**Characteristics of research subjects based on age, duration of suffering, HbA1c levels and liver stiffness**

| | N | Mean | SD | Median | Min | Max |
|---|---|---|---|---|---|---|
| Age (years) | 50 | 56.94 | 9.28 | 57.0 | 40 | 79 |
| Duration of suffering DM (years) | 50 | 9.10 | 6.50 | 8.0 | 1 | 27 |
| HbA1c levels (%) | 50 | 8.55 | 2.63 | 8.50 | 5,5 | 15.80 |
| Liver stiffness (kPa) | 50 | 7.92 | 6.72 | 6.55 | 2.60 | 14.80 |

TABLE 2
**Characteristics of research subjects based on body weight, height, BMI and type of anti-diabetes mellitus therapies**

| Variable | Classification | Number | % |
|---|---|---|---|
| Body weight | < 40 | 0 | 0 |
| | 40 – 49 | 2 | 4 |
| | 50 – 59 | 12 | 24 |
| | 60 – 69 | 20 | 40 |
| | 70 – 79 | 10 | 20 |
| | ≥ 80 | 6 | 12 |

*TABLE 2. Continued.*

| Variable | Classification | Number | % |
|---|---|---|---|
| Height (cm) | < 150 | 5 | 10 |
| | 150 – 159 | 21 | 42 |
| | 160 – 169 | 22 | 44 |
| | ≥ 170 | 4 | 4 |
| IMT (Kg/m$^2$) | < 18.5 | 0 | 0 |
| | 18.5 – 25 | 19 | 38 |
| | 25 – 29.9 | 23 | 46 |
| | 30.0 – 34.9 | 7 | 14 |
| | 35 – 39.9 | 1 | 2 |
| | > 40 | 0 | 0 |
| Types of anti-diabetes mellitus therapies | Insulin, Glimepiride | 8 | 16 |
| | Insulin, Gliclazide | 4 | 8 |
| | Insulin, Glibenclamide | 1 | 2 |
| | Insulin, Metformin | 3 | 6 |
| | Insulin, Gliquidon | 4 | 8 |
| | Insulin | 13 | 26 |
| | Glimepiride, Metformin | 8 | 16 |
| | Gliquidon, Metformin | 3 | 6 |
| | Insulin, Glimepiride, Metformin | 6 | 12 |

TABLE 3
**Relationship between duration of suffering from DM and HbA1c levels with liver stiffness in type 2 diabetes mellitus patients**

| | | HbA1c levels | Duration of suffering from type 2 DM |
|---|---|---|---|
| Liver stiffness | *p-value* | 0,000 | 0,052 |
| | Correlation coefficient | 0,688 | 0,276 |

*Spearman's rank coefficient correlation test

and Hepatocellular Carcinoma (HCC) which will ultimately increase mortality.[13,14]

The subject characteristics (Table 2) show the frequency and percentage of subjects based on body weight, which is the highest number of patient's weight is in the range of 60–69 kg (40%) while the lowest number of patient's weight is in the range of 40–49 kg (4%). Based on body height, the highest number of patient's height is in the range of 160–169 cm (44%) while the lowest number of patient's height is in the range of ≥170 cm (4%). Based on Body Mass Index (BMI), the highest number patient's BMI is in the range of 25.0-29.9 Kg/m$^2$ (46%) while the lowest number patient's BMI is in the range of 35.0–39.9 Kg/m$^2$ (2%). Based on the type of anti-diabetes mellitus therapies, it was found that the highest number of patients (26%) used insulin, while the lowest of number patients (2%) used insulin and glibenclamide.

The liver stiffness value is obtained by measuring the Region of Interest (ROI) which is carried out in a neutral position as the patient is asked to take a deep breath followed by holding breath. The examination was repeated 10 times. Subsequently, the median value of the repeated examinations is used as the final result of ultrasound elastography examination presented in kilopascals (kPa).

The Kolmogorov-Smirnov test was used to determine the normal distribution of the research data. The test shows the variables of liver stiffness and duration

of suffering from type 2 DM is not normally distributed ($p < 0.05$), while the variable of HbA1c levels is normally distributed ($p \geq 0.05$), thus the statistical analysis between these variables used the Spearman's rank correlation coefficient test.

The Spearman's rank correlation coefficient test analyzed relationship between duration of suffering from DM and HbA1c levels with the degree of liver stiffness in patients with type 2 diabetes mellitus (Table 3).

The results of the Spearman's rank coefficient correlation test showed a significant correlation between HbA1c levels and the degree of liver stiffness ($p < 0.001$). The results of this study are in accordance with research conducted by Watt *et al*. (2020) on 774 Mexican–American subjects showing that HbA1c levels are parameter that have the closest relationship with liver stiffness compared with fasting glucose levels, insulin levels, and insulin resistance.[15] Apart from having a close relationship with liver stiffness, superiority HbA1c in stratifying the risk of liver stiffness also lies in the better stability of HbA1c compared to other parameters. The relationship between HbA1c and liver stiffness is also known to be unaffected by the patient's waist circumference or other confounding factors.[13,15] Similar results were also found in the study of Fernando *et al*. (2019) showing a relationship between HbA1c levels > 7% and liver fibrosis and cirrhosis.[16] In this study, the correlation shown by HbA1c levels and the degree of liver stiffness has a positive tendency (correlation coefficient of 0.688) in which increased HbA1c levels corresponds with increased degree of liver stiffness. This is in accordance with the research results of Watt *et al*. (2020) finding increased HbA1c by 10% would increase liver stiffness by 4% (positive correlation).[15] Research by Tewari *et al*. (2021) also showed positive correlation of HbA1c levels and the degree of liver stiffness with correlation coefficient of 0.820.[17]

The results of the Rank-Spearman test show no significant correlation between the duration of suffering from type 2 DM and the degree of liver stiffness ($p = 0.052$). The main goal in managing diabetes therapy is controlling blood sugar by assessing the HbA1c examination parameter. This condition will not affect the appearance of liver stiffness if HbA1c level is controlled properly regardless the duration of suffering from diabetes. This study is in contrast with previous study by Fernando *et al*. (2019) examining 121 type 2 DM patients diagnosed with NAFLD in the Philippines which found that the duration of suffering from type 2 DM for more than 5 years is related to liver fibrosis and cirrhosis.[16] Similarly, another research conducted by Tewari *et al*. (2021) shows that the duration of suffering from type 2 DM (average 10.98 years) is significantly and positively correlated with advanced fibrosis (liver stiffness >9.6 kPa) with a correlation coefficient of 0.596.[17]

## CONCLUSION

There is a significant correlation between HbA1c levels and the degree of liver stiffness. The correlation shown by HbA1c levels and the degree of liver stiffness has a positive tendency with a correlation coefficient of 0.688. Secondly, there is no significant correlation between the duration of suffering from type 2 DM and the degree of liver stiffness. The main goal in managing diabetes therapy is controlling blood sugar by assessing the HbA1c examination parameter. This condition will not affect the appearance of liver stiffness if HbA1c levels is controlled properly regardless the duration of suffering from diabetes.

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