LIVER FIBROSIS AS ASSESSED BY THE FIB-4 INDEX AND METABOLIC MARKERS IN SUBJECTS WITH TYPE 2 DIABETES

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INTRODUCTION

• Prevalence of type 2 diabetes (T2DM) and diabetes-associated health burden is increasing worldwide. Diabetic patients are at high risk of developing cirrhosis and liver outcomes, in most cases due to non-alcoholic liver disease (NAFLD). However, liver disease remains a neglected late complication of diabetes and data on the prevalence of advanced hepatic fibrosis in T2DM remain scarce.
• Recent data suggest that the majority (~75%) of patients with NAFLD cirrhosis (referred to a tertiary hospital clinic) had a diagnosis of cirrhosis obtained incidentally and had not previously undergone fibrosis assessment.
• Subjects diagnosed incidentally had more severe liver disease with higher INR and MELD levels and lower platelet counts and were more likely to have HCC at the time of diagnosis.

• Numerous non-invasive panels of tests have been developed to stage liver disease, including combinations of routine laboratory parameters as well as specialized tests such as direct markers of fibrosis and imaging tests using elastography.
• The FIB-4 index was developed as a non-invasive panel to stage liver disease in subjects with HIV-1 infection or cirrhosis.
• The FIB-4 index has also been validated in patients with HCV infection and has shown to be superior to seven other non-invasive markers of fibrosis in patients with NAFLD.
• More recently, FIB-4 values have been investigated in patients with T2DM as assessed by advanced liver fibrosis and imaging tests using elastography.

The aim of the present study was to assess the prevalence of advanced liver fibrosis in patients with T2DM as assessed by FIB-4 values.

MATERIAL & METHODS

• Patients with ICD-10 E11 (T2DM) diagnostic code whose laboratory assessments were completed between January and December 2016 at LabCorp and included data for AST, ALT, age and platelet counts were evaluated.
• The earliest complete assessment per patient was included in the analysis if more than one was present.

FIB-4 Formula

\[
\text{FIB-4} = \frac{(\text{Age} \times \text{AST} \times 10^{3})}{\text{ALT} \times \text{platelet count}}
\]

Results

• The study sample included a total of 3,070,277 subjects (mean age SD 59.6±12.64 y; 47% males)
• The median (IQR) FIB-4 score was 1.10 (0.79-1.49)
• As expected, subjects with a higher FIB-4 score were older and had higher AST and ALT levels (Table 1)
• Lower platelet counts were observed in the highest category of FIB-4
• No difference in the evaluated metabolic risk factors was observed in this sample
  – Mean plasma triglycerides (TG), HDL-cholesterol (HDL-C) and HbA1C were similar among the different FIB-4 range groups.
  – The proportion of patients with high FIB-4 was similar in patients with and without high TG (TG >150 mg/dL) and/or low or high HDL-C (threshold HDL-C <40 and 50 mg/dL in males and females, respectively)

Table 1. Patients’ Characteristics

<table>
<thead>
<tr>
<th>N (males %)</th>
<th>&lt;1.45</th>
<th>1.45 – 2.67</th>
<th>2.67 – 3.25</th>
<th>&gt;3.25</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>2,235,423 (44)</td>
<td>762,098 (54)</td>
<td>495,511 (36)</td>
<td>483,349 (30)</td>
<td>570,377 (67)</td>
<td></td>
</tr>
</tbody>
</table>

Age (y)* | 56.3 (12.50) | 60.1 (8.30) | 67.7 (3.60) | 57.3 (9.08) | 59.6 (12.64) |

AST (U/L)* | 23.5 (14.6) | 26.6 (14.9) | 38.3 (31.7) | 24.2 (17.5) |

ALT (U/L)* | 24.6 (19.3) | 31.9 (31.7) | 43.5 (44.6) | 24.2 (17.5) |

Platelet count (x10^3/µL) | 276.4 (68.39) | 206.8 (62.00) | 163.9 (40.40) | 134.4 (47.40) |

Triglycerides (mg/dL)* | 157.6 (130.8) | 142.3 (107.3) | 142.2 (114.3) | 146.4 (158.5) |

HbA1C* | 6.4 (1.73) | 6.7 (3.35) | 7.1 (3.0) | 6.8 (3.0) |

HDL-C (mg/dL)* | 51.9 (16.72) | 53.7 (18.02) | 56.6 (18.13) | 51.7 (21.65) |

*Mean (SD)

Figure 1. Distribution of FIB-4 Range

<table>
<thead>
<tr>
<th>N (%)</th>
<th>FIB 4</th>
<th>1.45 – 2.67</th>
<th>2.67 – 3.25</th>
<th>&gt;3.25</th>
</tr>
</thead>
<tbody>
<tr>
<td>71%</td>
<td>26</td>
<td>1.45 – 2.67</td>
<td>0.00</td>
<td>6.3</td>
</tr>
<tr>
<td>16%</td>
<td>28</td>
<td>2.67 – 3.25</td>
<td>1.00</td>
<td>1.7</td>
</tr>
<tr>
<td>3%</td>
<td>1.8</td>
<td>&gt;3.25</td>
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CONCLUSION

• The present study shows that patients with T2DM have high prevalence of advanced fibrosis (assessed by FIB-4 panel).
• More than 3% of them have a FIB-4 score in the range that has been reported to be associated with a high risk of adverse liver outcomes.
• Proactive screening of diabetic patients with FIB-4 or other inexpensive methods might help identify patients with un-diagnosed advanced liver fibrosis and it may reduce incidental diagnoses of cirrhosis in the future.

Limitations of the Study

• Using database as a source has several limitations: the lack of detailed clinical information and absence of causal descriptions, potential treatment bias and systemic sampling errors. However, the main advantage is the very large numbers of patients that can be evaluated.

ACKNOWLEDGEMENTS

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REFERENCES

Sterling RK et al. Hepatology 2006;43:1317-1325
Bertot LC et al. Hepatology Communications 2017; 1:53-60

CONTACT INFORMATION

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