The prevalence of disorders of the gut-brain axis in type 2 diabetes mellitus patients with metabolic dysfunction-associated fatty liver disease: an observational study

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Abstract

Background and study aim: **Disorders of the gut-brain axis (DGBI) and metabolic dysfunction-associated liver disease (MAFLD) are frequently diagnosed and exhibit pathophysiological similarities. This study aimed to estimate the prevalence of DGBI in type 2 diabetes mellitus (T2DM) patients with MAFLD.**

Patients and methods: **In this single center, observational study, in adults with T2DM demographics, diabetes-related parameters and liver tests were recorded. MAFLD was defined by the presence of hepatic steatosis on imaging. Functional dyspepsia (FD) and irritable bowel syndrome (IBS) were diagnosed based on Rome IV criteria. Quality of life (QOL), anxiety levels and depression levels were documented by validated questionnaires.**

Results: **We included 77 patients, 44 with and 33 without steatosis. There were no significant differences in age, body mass index (BMI), waist circumference, HbA1c levels or metformin use between groups. IBS was significantly more prevalent in the liver steatosis group (9/44 vs. 2/33, p = .037), while a similar trend was observed for FD (9/35 vs. 2/31, p = .103). No differences were found in anxiety, depression and overall QOL. However, QOL subscales for health worry, food avoidance and social reaction were significantly higher in the liver steatosis group.**

Conclusions: **In otherwise comparable T2DM patients, DGBI, and especially IBS, are more prevalent in the presence of MAFLD. This difference could not be attributed to increased levels of anxiety or depression. Future research should target the underlying pathophysiological mechanisms.** (Acta gastroenterol. belg., **2021,** 84**, 541-547**).

Keywords: metabolic dysfunction-associated fatty liver disease, irritable bowel syndrome, type 2 diabetes, disorders of the gut-brain axis

Abbreviations: ALT, Alanine transaminase; BMI, Body mass index; DDP4, Dipeptidylpeptidase-4; DGBI, Disorders of the brain-gut axis; EPS, Epigastric pain syndrome; FD, Functional dyspepsia; FIB-4, Fibrosis-4; FODMAPs, Fermentable oligo-di monosaccharides and polyols; GLP-1, Glucagon-like peptide-1; IBS, Irritable bowel syndrome; IBS-C, Irritable bowel syndrome with constipation; IBS-D, Irritable bowel syndrome with diarrhea; IBS-M, Irritable bowel syndrome, mixed type; IBS-U, Irritable bowel syndrome, unspecified type; HADS, Hospital anxiety and depression scale; LS, Liver steatosis; NLS, No liver steatosis; MAFLD, Metabolic dysfunction-associated fatty liver disease; PDS, Postprandial distress syndrome; QOL, Quality of life; SD, Standard deviation; SGLT-2, Sodium-glucose cotransporter-2; SIBO, Small intestinal bacterial overgrowth; T2DM, Type 2 diabetes mellitus.

Introduction

Diseases of the gut-brain axis (DGBI), previously referred to as functional gastro-intestinal diseases, are common in the general population. They constitute a large group of digestive disorders defined in accordance to the Rome IV criteria (1). Irritable bowel syndrome (IBS) and functional dyspepsia (FD) are the most recognized DGBI. Based on a recent study, it is estimated that 3.8% of the population worldwide suffers from IBS according to the most recent Rome IV criteria (2). A multitude of underlying pathophysiological mechanisms have been postulated, including psychological variables such as anxiety and depression (3), diet (4), low-grade intestinal inflammation (5) and altered intestinal microbial composition (6). However, the exact etiology remains unclear (7).

Metabolic dysfunction-associated fatty liver disease (MAFLD) is another increasingly prevalent condition, correlating with the global obesity pandemic. Recent expert-opinion based consensus defines MAFLD as the presence of accumulation of fat in the liver, referred to as steatosis, in the presence of overweight, diabetes mellitus type 2 and/or evidence of metabolic dysregulation (8). In Western countries, MAFLD has been recognized as a major health concern. Due to the associated hepatic inflammation, patients with liver steatosis are at risk for progressive liver fibrosis and cirrhosis. It has been demonstrated that hepatic complications of MAFLD have become the fastest growing indication for liver transplantation (9).

The possible implication of the intestinal microbiome has also been recognized in MAFLD, resulting in the concept of the gut-liver axis (10). As seen in small intestine bacterial overgrowth (SIBO), increased bowel permeability triggers bacterial translocation. Subsequent activation of the innate immune system increases endotoxin levels in the portal circulation, in turn contributing to steatosis and liver injury (11). Obesity and high-fat containing diets reduce the diversity of intestinal microbiota while favoring unfavorable strains (12). Such dysbiosis is suggested to chronically stimulate the immune system, triggering a cascade of low-grade inflammation, decreased intestinal barrier function, thus contributing to steatohepatitis (13). A correlation between the abundance

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of bacterial taxa and markers of liver steatosis as well as fibrosis has been established (14).

Similarly, in IBS increased circulating levels of tumor necrosis factor alpha and interleukin 6 support the role of a low-grade inflammatory status (15).

Dysbiosis is believed to play a major role in IBS. The existence of post-infectious IBS, in which IBS symptoms develop following gastro-enteritis (16) and the fact that SIBO is more prevalent in diarrhea predominant IBS (17) support this statement. In addition, studies have demonstrated an association between IBS and alterations, reduced diversity and instability of the microbiome (18,19). Furthermore, as summarized by Poortmans et al., prebiotics, probiotics and antibiotic treatment have proven beneficial effects on symptom relief (20).

Pro-inflammatory cytokines and dysbiosis increase gut permeability and change bowel motility patterns, theoretically resulting in a vicious circle (21,22,23). Finally, a bidirectional gut-brain interaction gained attention in recent years, possibly explaining the higher frequency of mood disorders and psychiatric illness in patients with DGBI (24).

Imbalances in gut microbiota have also been observed in T2DM (25). As a result of the increased occurrences of both MAFLD and alterations in intestinal microbiota, T2DM forms an ideal target population to study these disorders with common pathophysiological pathways. Based on the shared observation of intestinal dysbiosis in both diseases, we postulated that DGBI would be more frequently observed in patients diagnosed with MAFLD.

Methods

We conducted this observational study at the diabetes clinic of our institution between August 2020 and January 2021. The study protocol was approved by the local ethics committee in February 2020. Informed consent was obtained from all participants. The study included patients with T2DM between the ages of 18 and 75 years old. We excluded patients with alcohol abuse (defined as > 14 standardized units per week); documented liver disease other than MAFLD; use of steatosis-inciting drugs; use of antibiotics, probiotics and non-steroidal inflammatory drugs within the last four weeks; documentation of current or past gastro-intestinal disease; documentation of current or past psychiatric illness; history of abdominal surgery apart from cholecystectomy and appendectomy; important renal impairment (defined as eGFR < 30ml/kg/1.73m^2); and poor glycemic control (defined as HbA1c > 9.0%).

In accordance with the position statement of the Belgian Association for Study of the Liver (BASL) MAFLD was defined as the documentation of steatosis on recent liver ultrasound, computed tomography or magnetic resonance imaging (26) – thereby distinguishing between a liver steatosis (LS) and a no liver steatosis (NLS) group. Age, sex, ethnicity, body mass index (BMI; kg/m^2) and waist circumference were recorded. Diabetes specific parameters such as disease duration, Hb1Ac values, the presence of microvascular complication and current hypoglycemic treatment regimens were documented. The total number of medications apart from the hypoglycemic treatment was documented as a surrogate marker for comorbid disease. Alanine transaminase (ALT) values (IU/L), fibrosis-4 (FIB-4) scores and the presence of an established cirrhosis (according to the medical record) were obtained. A FIB-4 score of <1.45 was considered as non-significant fibrosis (27). Functional dyspepsia (FD) and irritable bowel syndrome (IBS) were defined according to Rome IV criteria. Quality of life, anxiety and depression scores were assessed by IBS-QOL and the hospital anxiety and depression scale (HADS) respectively.

Statistical analysis was conducted with SPSS (IBM Corp. Released 2020. IBM SPSS Statistics for Windows, Version 27.0. Amonk, NY: IBM Corp). Patient characteristics are referred to as percentages and means ± standard deviation (SD). Prevalences were compared by the Fisher's exact test, while continuous variables were compared by Student's t-test. A p-value of less than .05 was considered statistically significant. Considering a DGBI prevalence of 5% in the NLS group and expecting an increase up to 20% in the SP group, 88 subjects should be recruited in both groups to demonstrate a significant difference between groups with 80% power at the .05 significance level. Expecting 10% of subjects with insufficient data, 100 patients were programmed for recruitment in both groups.

Results

Patient characteristics

During the study period 77 patients were enrolled. Patients were on average 58.7 ± 9.3 years old and a slight male predominance (62.3%) was observed. The majority of participants were of Caucasian ethnicity (43 participants), followed by North-Africans (18), Black Africans (10), Turkish (4), Asian (1) and South American origins (1). Mean BMI and waist circumference were 32.7 ± 5.3 kg/m^2 and 108.4 ± 11.5cm respectively. At the time of our study the mean duration of T2DM was 10 ± 7 years with the majority (72.7%) having no microvascular complications and a mean Hb1AC value of 6.8 ± 0.8%. An established cirrhosis was present in one single patient, with FIB-4 scores in the normal range for the majority of the subjects (54/74, 72.8%). Distinction of steatosis was mainly based on ultrasound results (64/77, 83.1%), followed by computed tomography (10/77, 13%) and magnetic resonance (3/77, 3.9%). Additionally, in a post-hoc analysis, a fatty liver index (FLI) (26) could be calculated for 62/77 (80.5%) patients.

Liver steatosis vs. no liver steatosis group

The liver steatosis (LS) and no liver steatosis (NLS) group consisted of 44 and 33 subjects respectively. As

Table 1. — **Comparison between the LS and NLS group**

	Liver steatosis (N=44)	No liver steatosis (N=33)	P value
Demographics			
Age (years)	56.9 ± 8.7	61.1 ± 9.8	.051
Male sex	27 (61.4%)	21 (63.6%)	1.00
Caucasian	24 (54.5%)	19 (57.6%)	.791
BMI (kg/m^2)	33.0 ± 5.0	32.2 ± 5.9	.518
Waist circumference (cm)	110 ± 11	106 ± 12	.179
Total number of medications	3.8 ± 2.1	4.0 ± 2.5	.710
Diabetes parameters			
T2DM duration (years)	8.2 ± 6.8	9.5 ± 7.7	.974
Microvascular complications	12 (27.3%)	9 (27.3%)	1.00
HbA1c (%)	6.9 ± 0.8	6.6 ± 0.8	.107
Insulin use	25 (56.8%)	19 (56.6%)	1.00
Metformin use	37 (84.1%)	23 (69.7%)	.169
Sulfonylurea use	11 (25%)	5 (15.2%)	.222
SGLT-2 inhibitor use	8 (18.2%)	2 (6.1%)	.109
DDP4 inhibitor use	1 (2.3%)	0 (0%)	.571
GLP1 analogue use	0 (0%)	1 (3.0%)	.429
Liver specifics			
Mean ALT (IU/L)	36 ± 18	24 ± 14	**.003**
Number of FLI > 0.6	9/24 (37.5%)	36/38 (94.7%)	**<.001**
Mean FLI	83.4 ± 17.2	61.8 ± 20.8	**<.001**
Number of FIB-4 < 1.45	33/42 (79%)	21/31 (68%)	.419
Mean FIB-4	1.3 ± 1.0	1.2 ± 0.4	.305
DGBI prevalence			
IBS	9 (20.5%)	1 (3%)	**.037**
FD	9 (20.5%)	2 (6.1%)	.103
Quality of life scores			
Overall	14.5 ± 20.7	7.1 ± 17.0	.100
Health worry	16.1 ± 23.9	5.6 ± 14.5	**.019**
Food avoidance	21.8 ± 25.3	9.6 ± 21.2	**.026**
Social reaction	13.1 ± 23.3	4.4 ± 14.7	**.049**
Dysphonia	13.4 ± 23.1	5.9 ± 15.4	.089
Body image	16.6 ± 21.7	9.3 ± 20.4	.139
Interference with activity	15.9 ± 22.8	9.4 ± 20.1	.197
Sexual	8.0 ± 16.4	4.6 ± 18.4	.395
Relationship	8.7 ± 20.7	6.8 ± 17.7	.674
Anxiety and depression scores			
Anxiety	6.25 ± 4.5	6.58 ± 5.33	.772
Depression	4.32 ± 3.96	3.91 ± 5.22	.697

Prevalences were compared by the Fisher's exact test, while continuous variables were compared by Student's t-test. A p-value of less than .05 was considered statistically significant. Statistically significant differences were highlighted. Abbreviations: ALT: alanine aminotransferase; BMI: body mass index; DDP4: dipeptidylpeptidase-4; DGBI: disorders of the gut-brain axis; FD: functional dyspepsia; FIB-4: fibrosis-4; FLI: fatty liver index; GLP-1: glucagon-like peptide-1; IBS: irritable bowel syndrome; LS: liver steatosis; NLS: no liver steatosis; SGLT-2: sodium-glucose cotransporter-2; T2DM: type 2 diabetes mellitus.

shown in Table 1, there were no significant differences in age; sex; Caucasian vs. non-Caucasian ethnicity; BMI; waist length; T2DM duration; microvascular complications; insulin or oral treatment regimens; HbA1C values; total number of medications; FIB-4 scores or HADS scores between groups. As expected, ALT levels were significantly higher in the LS group (36 ± 18 vs. 24 ± 14 IU/L, p=.03). FLI was significantly higher in the LS group (83.4 ± 17.2 vs. 61.8 ± 17.7, p <.001). An FLI score > 0.6 was significantly associated with the radiological presence of steatosis (36/38 vs. 9/24, 94.7% vs. 37.5%, in the LS vs. NLS group respectively, p<.001). A significantly higher prevalence of IBS was noted in the LS group (9/44 vs. 1/33, 20.5% vs. 3.0%, p=.037), while there was only a trend towards more FD (9/44 vs. 2/33, 20.5% vs. 6.1%, p=.103). All subtypes of IBS (5 IBS-M, 3 IBS-D and 2 IBS-C) and FD (3 FD-EPS, 7 FD-PDS, 1 overlap) were represented. FD was significantly more prevalent in patients with an FLI > 0.6 (0/17 vs. 11/45, 0% vs. 24.4%, p=.026). Despite the fact that no patient with an FLI > 0.6 had IBS, the prevalence of IBS was not significantly different between groups (0/17 vs. 8/45, 0% vs. 17.8%, p = .094). Overall IBS-QOL scores were not significantly different, however scores for subscales of food avoidance (21.78 ± 25.26 vs. 9.6 ± 21.23, p =.026), health worry (16.10 ± 23.94 vs. 5.56 ± 14.53, p=.019) and social reaction (13.07 ± 23.34 vs. 4.36 ± 14.70, p=.049) were higher in the LS group. Other subscale scores remained comparable between both groups.

IBS vs. non-IBS group

When comparing study subjects in respect to the presence of IBS female predominance (8/10 vs. 46/67,

Table 2. — Comparison between the IBS positive and IBS negative group

	IBS positive (N = 10)	IBS negative (N = 67)	P value
Demographics			
Age (years)	55.0 ± 9.0	59.2 ± 9.3	.183
Male sex	2 (20%)	46 (68.7%)	**.005**
BMI (kg/m²)	33.2 ± 4.8	32.6 ± 5.5	.748
Waist Circumference (cm)	107 ± 11	109 ± 12	.745
Total number of medications	4.0 ± 2.4	3.8 ± 2.3	.832
Diabetes parameters			
T2DM duration (years)	7.3 ±7.2	9.0 ± 7.2	.527
Microvascular complications	3 (30%)	18 (26.9%)	.551
HbA1c (%)	6.7 ± 0.6	6.8 ± 0.8	.892
Insulin use	5 (50%)	39 (58.2%)	.737
Metformin use	8 (80%)	53 (79.1%)	1.00
Sulfonylurea use	1 (10%)	15 (22.3%)	.335
SGLT-2 inhibitor use	1 (10%)	9 (13.4%)	.616
DDP4 inhibitor use	1 (10%)	0 (0%)	.130
GLP1 analogue use	0 (0%)	1 (1.5%)	.870
Liver specifics			
ALT (IU/L)	35.8 ± 22.9	30 ± 16.8	.342
Number of FLI > 60	8/8 (100%)	17/54 (31.5%)	.094
Mean FLI	82.8 ± 10.3	73.8 ± 22.0	.091
Number of FIB-4 < 1.45	10 (100%)	44 (69.8 %)	.055
Mean FIB-4	0.9 ± 0.3	1.3 ± 0.8	.221
Quality of life score			
Overall	44.4 ± 26.1	6.4 ± 12.4	**.001**
Dysphonia	42.8 ± 30.0	5.3 ± 13.1	**.003**
Interference with activity	48.2 ± 23.2	7.9 ± 16.1	**.000**
Body Image	46.9+ ± 31.2	8.4 ± 14.0	**.004**
Health worry	47.5 ± 28.3	6.2 ± 13.2	**.001**
Food avoidance	50.8 ± 26.8	11.4 ± 19.8	**<.001**
Social reaction	45.6 ± 30.9	3.9 ± 11.0	**.002**
Sexual	31.3 ± 31.3	2.8 ± 10.2	**.019**
Relationship	34.2 ± 36.3	4.0 ± 11.5	**.028**
Anxiety and depression scores			
Anxiety	9.8 ± 4.7	5.9 ± 4.3	**.016**
Depression	7.3 ± 5.1	3.7 ± 4.3	**.017**

Prevalences were compared by the Fisher's exact test, while continuous variables were compared by Student's t-test. A p-value of less than .05 was considered statistically significant. Statistically significant differences were highlighted. Abbreviations: ALT: alanine aminotransferase; BMI: body mass index; DDP4: dipeptidylpeptidase-4; FIB-4: fibrosis-4; FLI: fatty liver index; GLP-1: glucagon-like peptide-1; IBS: irritable bowel syndrome; QOL: quality of life; SGLT-2: sodium-glucose cotransporter-2; T2DM: type 2 diabetes mellitus.

80% vs. 68.6%, p=.005), lower overall QOL scores (44.41 ± 26.14 vs. 6.40 ± 12.40; p < .001), lower scores for all QOL subscales (all p <.05) and higher HAD scores for anxiety (9.80 ± 4.66 vs. 5.88 ± 4.27; p=.016) as well as depression (7.30 ± 5.06 vs. 3.67 ± 4.27; p=.017) were observed in the IBS-positive group; as shown in table 2. No other statistically significant differences were observed between these groups.

Since there was merely a trend towards more FD, differences between the FD and non-FD patients will not be discussed in further detail.

Discussion

Our observational study demonstrates a higher prevalence of IBS in T2DM patients with steatosis in comparison to their counterparts without steatosis; with a similar trend observed for FD. These results could not be attributed to differences in demographics, T2DM-related parameters, anxiety or depression levels between groups. While QOL scores were consistently lower for all subscales in the presence of IBS, decreased scores for some specific subscales were noted in the steatosis positive group. To the best of our knowledge this is the first study addressing the prevalence of IBS and FD, as assessed by the ROME IV criteria, in MAFLD patients.

It is unclear whether the male predominance influenced the prevalence of DGBI cases. On one hand DGBI are known to occur more frequently in women (28), while on the other male gender is a recognized risk factor for MAFLD development (29), making way for possible bias in both directions. Nonetheless, the expected gender distribution was respected for both MAFLD and IBS in our study. It has been demonstrated that subjects with Caucasian ethnicity are at higher risk for MAFLD (30). However, as Caucasian ethnicity was equally represented in the liver steatosis and no liver steatosis group, ethnicity did not play a confounding role in this study. The increased ALT levels in the MAFLD cohort are to be expected since aminotransferase levels

correlate with the disease spectrum and steatohepatitis in particular (31). Although earlier research suggested that IBS correlated with higher ALT levels and the presence of a metabolic syndrome in an otherwise healthy study population (32), no ALT elevation was observed in the DGBI or IBS subgroup. This could be explained by our study population which solely consists of T2DM patients, implying a metabolic syndrome in virtually every participant. Although visceral adiposity and waist circumference are associated with an increased risk for IBS (33), no statistically significant difference in BMI and waist circumference in relation to the presence of MAFLD or IBS was measured. This could result from the fact that almost every participant had a BMI above 25 kg/m^2 or higher. Anxiety and depression scores, both established associations in accordance to DGBI (3), did not significantly differ between the liver steatosis and no liver steatosis cohort, refuting a baseline bias in these groups. As observed in earlier studies (34) a lower QOL was found in IBS patients. However, comparisons in respect to the presence of steatosis indicated significantly higher QOL scores only for specific subscales. As all subscale scores remained comparable between the IBS negative and the cohort without steatosis, this could simply reflect the increased prevalence of both FD and IBS in the presence of steatosis. Studies indicated that cirrhosis develops in 2.5% of patients with MAFLD after an estimated period of 28 years (35, 36). In our study, an average diabetes duration of less than 10 years was observed. Together with the small sample size, it could explain the comparable proportion of patients with a FIB-4 score < 1.45 between groups.

In a post-hoc analysis the FLI was calculated. An FLI > 0.6 was considered positive for the presence of steatosis, according to recent consensus (26, 37). No patient with an FLI < 0.6 had either FD of IBS according to the ROME IV questionnaire. However, where the radiological diagnosis of steatosis was associated with a higher prevalence of IBS, but not FD, the FLI demonstrated the opposite. As the association of FLI > 0.6 and the radiological presence of steatosis was confirmed, this discrepancy probably reflects the effect of the missing data on FLI, as was seen in 19.5% of our patients.

None of the T2DM-related parameters correlated with the presence of DGBI, suggesting T2DM poses no risk in DGBI occurrence. This in contrast with previous research, stating gastro-intestinal symptoms co-exist more frequently in the presence of microvascular complications (38), and a Chinese study, demonstrating a strong association between gastro-intestinal symptoms and T2DM duration (39). In addition, there is conflicting data in regard to the link between poor glycemic control and digestive symptoms in T2DM, with one study claiming (38) and another study refuting (40) this association. Furthermore, since digestive symptoms constitute established side-effects of metformin, the finding that its use was not observed more frequently in the DGBI group, is all the more surprising. We believe this result may be partially explained by the observation that mild gastrointestinal symptoms subside over time while severe intolerance generally results in discontinuation of the drug (41). The exact reason(s) for these contradicting, inconclusive or even paradoxical findings remain currently unclear. More research is required to further clarify the relationship between T2DM and DGBI.

Some limitations should be taken into consideration. First, the target sample size was not reached. Indeed, as a result of the COVID-19 pandemic, patient recruitment was hampered by replacement of out-patient visits by phone calls, thus delaying the obtention of informed consent for participation. As the study approached its predefined deadline, an interim analysis was conducted. Regardless of the reduced participant numbers, the prevalence of IBS in our study group appeared much higher than initially anticipated, therefore it was decided against prolonging the recruitment period. Given the similar trend observed for FD in the steatosis cohort, and the higher prevalence of FD when diagnosing steatosis was based on FLI, we believe further enrollment would have confirmed the increased prevalence of both IBS and FD symptoms in the presence of steatosis.

Second, other potentially significant cofounders were not included in our questionnaires. For instance, fructose consumption is an established risk factor for MAFLD (42), while belonging to the group of fermentable oligo-, di-, monosaccharides and polyols (FODMAPs) it also constitutes a known trigger for IBS symptoms (43). Further studies should include a dietary assessment to control this potential confounding effect. The role of physical activity similarly remained unassessed. Research indicates that a sedentary lifestyle is inversely related to gastrointestinal symptoms in IBS patients (44), whereas preliminary studies indicate increased physical activity has a beneficial effect on symptom severity (45). Similarly, in MAFLD exercise is considered one of the cornerstones of treatment (46).

Third, since the role of dysbiosis is mainly described in IBS, we chose to limit the questionnaires in our study to IBS and FD, not addressing other DGBI. There is however some circumstantial evidence suggesting several other DGBI occur more frequently in liver disease. An observational study by Fritz et. al demonstrated gastro-intestinal symptoms, mainly bloating and abdominal pain, were not only very common in cirrhotic patients but also associated with liver disease severity and psychological distress (47). In respect to the exploratory nature of the current study, the presence of dysbiosis was not evaluated. In parallel to the increasing amount of evidence for the role of dysbiosis in IBS we mentioned earlier on (6,7), proof of its role in liver disease is growing as well. One study showed dysbiosis occurred more frequently and severely in later stages of cirrhosis (48), whereas Higarza et. al demonstrated dysbiosis affects liver function, which in turn alters psychoneurological functioning through the release of hepatotoxins (49). These results strengthen the hypothesis of the so-called

liver-gut-brain axis, postulating that apart from the bidirectional communication between gut and brain, a third axis is formed through interplay with the liver, in close conjunction with the gut microbiome (50). The role of the gut microbiome is illustrated by the protective effect of Bifidobacteria in both IBS and MAFLD. In IBS, prebiotics promoting the growth of this bacterial strain have a proven favorable effect on symptom burden (51) whereas fecal microbiota transplantation with an abundance of Bifidobacteria in the donor sample correlate with its therapeutic efficacy (52). In MAFLD, Bifidobacteria abundancy is believed to protect against MAFLD development, as suggested by stool sample analysis in children with obesity and fatty liver disease (53). Furthermore, a study by Malagauaerna et al. demonstrated a beneficial effect on steatohepatitis activity in MAFLD patients receiving probiotic treatment with Bifidobacterium longum (54). Therefore, in parallel with IBS, targeting the gut microbiome may become a promising treatment modality for MAFLD in the future.

Fourth, the diagnosis of IBS and FD was defined by the ROME IV questionnaire, with exclusion of other apparent causes of symptoms. However, the applicability of this diagnosis to patients suffering from a metabolic condition could be questioned. Diabetes has been shown to be associated with different gastro-intestinal symptoms such as nausea, bloating, abdominal pain, diarrhea and constipation (55). The observed increased prevalence of IBS could result from more pronounced alterations in gut physiology in diabetic patients with steatosis, resulting from impacted smooth muscle cells or damaged enteric neurons. It remains a matter of debate whether to refer to ensuing symptoms as DGBI as treatment response could be different from non-diabetic patients. Further research on the matter and its underlying pathophysiology is needed.

Finally, and ideally, steatosis should be confirmed at the time of patient inclusion since it can develop or vanish rapidly through life style modification (56). It would be equally rewarding to evaluate the degree of hepatic fibrosis and steatosis in participants at that time. This documentation of hepatic fibrosis deems even more appealing since one study from Fouad et. al demonstrated a higher prevalence of IBS in patients with a chronic hepatitis C infection, especially in those with concurrent significant hepatic fibrosis (57). As literature on the matter is currently lacking, identifying the presence of DGBI in all-cause and all-stage liver disease seems essential to further unravel and comprehend the liver-gut-brain axis.

In conclusion, this study demonstrates that IBS is more frequently observed in T2DM patients with steatosis. It further supports the hypothesis that IBS and MAFLD may be associated conditions sharing multiple similarities on a pathophysiological level. Future research should expand the study population beyond T2DM while evaluating the mechanisms underlying the observed association.

Conflict of interest statement: there is no conflict of interest.

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