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Use of noninvasive fibrosis calculators in an urban diabetes center suggests a large burden of undetected advanced liver disease

Ahmed Ebeid[1], Fatma Mokhtar[1], Valeria Martinez-Lebron[2], Susie Park[2], Seta Degann[2], Jeremy Payano[3], Zahid Vahora[3], Stephen Gray[3], Lynt Johnson[3], Diala El-Maouche[4] and Ameer Abutaleb[3*]

Abstract

Background Metabolic dysfunction associated steatotic liver disease (MASLD) is prevalent in up to 60% of patients with type 2 diabetes mellitus (T2DM). T2DM accelerates the risk of hepatic fibrosis and hepatocellular carcinoma in patients with MASLD. Our goal in this study was to identify patients with suspected MASLD and hepatic fibrosis in a large T2DM clinic by using noninvasive fibrosis scoring systems.

Methods We conducted a retrospective study of patients with T2DM seen by our endocrinologists at the Medical Faculty Associates (MFA) Diabetes Center in Washington, DC, from November 1, 2021, until November 1, 2022. We included all subjects who were over 18 years old with a hemoglobin A1c (HbA1c) of 6.5 or higher. Patients with a history of significant alcohol consumption, decompensated cirrhosis, previous bariatric surgery, or prior chronic liver disease were excluded from the study. We identified patients at risk for hepatic fibrosis by using the Fibrosis-4 (FIB-4) Index, NAFLD Fibrosis Score (NFS) and AST to Platelet Ratio Index (APRI) when lab values were available.

Results A total of 1,411 patients were evaluated for T2DM by an endocrinology provider during the one-year period. Out of these, 336 patients met one or more of the exclusion criteria, leaving a total of 1075 patients included in the analysis. The majority were African American ($n=582$, 54%), 261 were Caucasian (24.3%), and 85 were Hispanic (7.9%). Most patients were females ($n=675$, 62.7%). The mean HbA1c was 8.1 ± 2.3. 643 patients (59.8%) were insulin dependent. Based on FIB-4 scores, we found that 35 (3.9%) patients had a score of >2.67 associated with advanced fibrosis and 257 (29%) patients with scores of 1.3–2.67 had moderate fibrosis. Using the NFS calculator, there were 281 (28%) patients with values of >0.675 consistent with F3-F4 disease. 715 (71.8%) patients with values of <0.675 consistent with F0-F2 fibrosis. A total of 6(< 1%) patients met criteria for advanced fibrosis by APRI scoring.

Conclusion In our urban Diabetes Center, utilizing the NFS calculator may detect many patients with advanced liver disease. Further research is needed to ensure the internal validity of the non-invasive tests in predicting liver fibrosis and to correlate these findings with transient elastography and other imaging evidence of fatty liver disease.

Clinical trial number Non-applicable.

*Correspondence:
Ameer Abutaleb
aabutaleb@mfa.gwu.edu

Full list of author information is available at the end of the article

Keywords Metabolic dysfunction associated steatotic liver disease (MASLD), MASH, Fibrosis scoring systems, Non-invasive tests, Advanced liver fibrosis

Introduction

Metabolic dysfunction associated steatotic liver disease (MASLD) is characterized by the existence of hepatic steatosis in the absence of secondary factors that lead to fat accumulation in hepatocytes, such as excessive alcohol consumption, chronic viral hepatitis, or hereditary metabolic liver disorders [1]. From a clinical perspective, individuals with MASLD frequently exhibit features associated with metabolic syndrome, including obesity, T2DM, hypertension and dyslipidemia [2–4].

Epidemiologic research has demonstrated the bidirectional and reciprocal association between T2DM and MASLD, wherein T2DM increases the risk of MASLD incidence and progression to liver cirrhosis and ultimately hepatocellular carcinoma, and MASLD increases the risk of T2DM incidence [5]. The possible compensatory hyperinsulinemia in response to insulin resistance leads to defective lipid metabolism and subsequent accumulation of hepatic triglycerides (TG) in MASLD, and to dysfunction of beta cells in T2DM [6, 7].

According to the CDC's National Diabetes Statistics Report, 11.6% of the U.S. population, or 38.4 million people, had diabetes in 2021 [8] and MASLD as an often-overlooked complication of T2DM is prevalent in up to 60% of patients with T2DM [9].

Due to higher cardiovascular and cerebrovascular risks in diabetic patients with MASLD [10], it is important to accurately determine how prevalent MASLD is in T2DM to help providers better assess the need for hepatology referral and care.

Given the above, efforts are underway to assess liver disease in diabetes clinics all over the world [11, 12]. In addition, academic institutions have started opening muti-disciplinary clinics to tackle the coordination of care necessary for these patients ensuring an early diagnosis and treatment [13].

The most reliable approach for diagnosis is histopathological examination via biopsy, which is limited due to its invasive nature, amongst other reasons [14]. Although, ultrasonography is the recommended first-line screening methods in clinical practice, it is known with its limited sensitivity [15].

Other methods such as proton magnetic resonance spectroscopy (1 H-MRS), magnetic resonance elastography, and vibration-controlled transient elastography could be used to assess the magnitude of liver stiffness. However, these methods are time-consuming, and not cost-effective for large-scale MASLD screening [16]. Noninvasive scoring systems such as the NAFLD fibrosis score (NFS), fibrosis-4 (FIB-4) index, and aspartate aminotransferase (AST) to platelet ratio index (APRI), have been developed to predict advanced fibrosis. These scores are easy to compute using demographic and laboratory data, making them readily available for use by health care providers and clinical researchers [17–19].

The primary outcome of the study is to assess the prevalence of MASLD and the subsequent advanced liver fibrosis in T2DM patients using these noninvasive fibrosis scoring systems.

Methods

We conducted a single-center retrospective study of patients with T2DM seen by endocrinologists at the Diabetes Center of the GW Medical Faculty Associates (MFA) in Washington DC, from November 1, 2021, until November 1, 2022. We included all subjects who were over 18 years old with a hemoglobin A1c (HbA1c) of 6.5 or higher who were not previously established with hepatology care. Patients with a history of significant alcohol consumption (>14 standard drinks/week in men, >7 standard drinks/week in women), decompensated cirrhosis, previous bariatric surgery, previous liver biopsy, or prior chronic liver disease were excluded from the study. We identified patients at risk for hepatic fibrosis by using noninvasive fibrosis scoring systems such as Fibrosis-4 (FIB-4) Index, NAFLD Fibrosis Score (NFS) and AST to Platelet Ratio Index (APRI) when lab values were available. Additionally, all patients' records were reviewed for any prior abdominal imaging such as ultrasonography, Magnetic Resonance Imaging or Computed Topography to assess the presence of liver fibrosis and/or steatosis over a period of 10 years from 2013 to 2023.

The **FIB-4** Index is based on the following formula: FIB-4 Score = (Age* x AST)/ (Platelets x √(ALT)) and a score of >2.67 is indicative of advanced fibrosis [17].

The **NAFLD Fibrosis Score (NFS)** is based on the following formula: NFS = -1.675 + (0.037*age [years]) + (0.094*BMI [kg/m2]) + (1.13*IFG/diabetes [yes = 1, no = 0]) + (0.99*AST/ALT ratio) – (0.013*platelet count [×109/L]) – (0.66*albumin [g/dl]) and a score of >0.675 is indicative of advanced fibrosis [18].

The AST to Platelet Ratio Index (APRI) is based on (AST in IU/L) / (AST Upper Limit of Normal in IU/L) / (Platelets in 109/L) and score of ≥1.5 is indicative of advanced fibrosis [19]. Low APRI score (<0.5) and FIB – 4 score (<1.3) had a NPV of 98% in predicting future severe liver disease related events.

Table 1 Population demographics and clinical characteristics ($n = 1075$)

Variable	Population ($n = 1075$)
Age (mean ± SD)	58.05 ± 14.61
< 65 (n, %)	699 (65.0%)
≥ 65 (n, %)	376 (35.0%)
Race (n, %)	
White	262 (24.3%)
Black	582 (54.1%)
Other- Asian	51 (4.7%)
Other- Native Hawaiian/Pacific Islander	2 (0.19%)
Other- American Indian/Alaskan Native	5 (0.47%)
Other- Other	93 (8.7%)
Unknown	81 (7.53%)
Ethnicity (n, %)	
Hispanic/Latino	85 (7.9%)
Not Hispanic/Latino	697 (64.8%)
Unknown	293 (27.3%)
Sex (n, %)	
Male	399 (37.1%)
Female	675 (62.8%)
Unknown	1 (0.1%)
BMI (mean ± SD)	31.7 ± 7.8
Aspartate aminotransferase (AST) (mean ± SD)	25.9 ± 68.8
Alanine transaminase (ALT) (mean ± SD)	24.8 ± 34.8
Hemoglobin A1C (mean ± SD)	8.1 ± 2.3
Platelet count (mean ± SD)	268.7 ± 83.0

Table 2 Occurrence of fibrosis via NFS, FIB-4 and APRI fibrosis scores

Fibrosis scoring system	Number of patients, mean score
NFS ($n = 996$)	
≤0.675	$n = 715$ (71.8%), $\bar{x} = -1.129$
>0.675	$n = 281$ (28.2%), $\bar{x} = 2.006$
FIB-4 ($n = 880$)	
<1.3 (low risk)	$n = 588$ (66.9%), $\bar{x} = 0.81$
1.3–2.67 (indeterminate risk)	$n = 257$ (29.2%), $\bar{x} = 1.73$
>2.67 (high risk)	$n = 35$ (4.0%), $\bar{x} = 7.69$
APRI ($n = 900$)	
< 0.5	$n = 844$ (93.8%), $\bar{x} = 0.201$
0.5 ≤ APRI ≤ 1.5	$n = 50$ (5.6%), $\bar{x} = 0.719$
> 1.5	$n = 6$ (0.7%), $\bar{x} = 8.225$

Statistical methodology

A descriptive summary table was calculated for the cohort. Continuous variables were summarized using means and standard deviations, while categorical variables were summarized with percentages. One-way ANOVA was used to calculate differences in continuous laboratory variables by categorical demographic classifications.

Fisher's Exact Tests were used to calculate the differences in the distribution of fibrosis marker values (FIB-4, NFS and APRI) by demographics (age, race, sex and ethnicity).

A binomial multivariable logistic regression model for the NAFLD fibrosis score (NFS) was developed with patient race, sex, and level of diabetes management (quantified by Hemoglobin A1C) used as categorical predictor variables. Adjusted odds ratios were calculated for each categorical predictor.

Results

A total of 1,411 patients were evaluated for T2DM by an endocrinology provider during the one-year date range. 336 patients met one or more of the exclusion criteria, leaving a total of 1075 patients included in the analysis. The majority were African American ($n = 582$, 54%), 261 were Caucasian (24.3%), and 85 were Hispanic (7.9%). Most patients were females ($n = 675$, 62.7%). The mean BMI was 31.7. In terms of the clinical characteristics, the mean HbA1c was 8.1 ± 2.3. 643 patients (59.8%) were insulin dependent. The ALT and AST mean was 24.8 and 25.9 respectively and the platelet count mean was 268.7 (Table 1).

Based on FIB-4 scores, we found that 35 patients had a score of > 2.67 associated with high risk of liver disease and 257 patients with scores of 1.3–2.67 intermediate risk of liver disease. Using the NFS calculator, there were 281 patients (29%) with values of > 0.675 consistent with advanced fibrosis and 715 patients (71%) with values < 0.675. Using the APRI scoring, only 6 patients (< 1%) met the criteria for advanced fibrosis (Table 2).

Using the NFS score, patients who were identified with values < 0.675 (consistent with F0-F2 fibrosis) 513 (71.8%) were 65 years or younger and 202 (28.2%) were more than 65 years old. In terms of race, 403 (56.4%) were black, 168 (23.5%) were white and 144 (20.1%) were either other or unknown races. In terms of sex, 454 (64.5%) were females and 261 (36.5%) were males. 583 (81.7%) had an A1c of less than 10 and 131 (18.3%) had an A1c equal or more than 10. Of those identified with values of > 0.675 (consistent with F3-F4 disease), 153 (54.4%) were 65 or younger and 128 (45.6%) were more than 65 years old. In terms of race, 152 (54.1%) were black, 78 (27.8%) were white and 51 (18.2%) were either other or unknown races. In terms of sex, 172 (61.2%) were females and 109 (38.8%) were males. 232 (82.6%) had an A1c of less than 10 and 49 (17.4%) had an A1c equal or more than 10 (Table 3).

Using multivariable binary logistic regression analysis, adjusted odds ratios were calculated for associations of variables using the NFS score. For white patients, adjusted odds ratio was 0.945 (0.518, 1.771 CI). For black patients, the adjusted odds ratio was 0.785 (0.444, 1.432 CI). For female patients, adjusted odds ratio was 3.702e + 05 (1.558e+-42, N/A). For male patients, adjusted ratio was 3.971e + 05 (1.673e+-42, N/A). For patients with uncontrolled diabetes determined by

Table 3 Differences in covariates amongst NFS ≤ 0.675 and NFS > 0.675

Variable	NFS ≤ 0.675 (*n* = 715)	NFS > 0.675 (*n* = 281)	*p*-value
Age (years)	56.4	63.0	< 0.001
≤65	513 (71.8%)	153 (54.4%)	< 0.001
>65	202 (28.2%)	128 (45.6%)	
Race (n, %)			
White	168 (23.5%)	78 (27.8%)	0.186
Black	403 (56.4%)	152 (54.1%)	0.563
Other	104 (14.5%)	32 (11.4%)	0.229
Unknown	40 (5.6%)	19 (6.8%)	0.580
Ethnicity (n, %)			
Hispanic/Latino	53 (7.4%)	23 (8.2%)	0.779
Not Hispanic/Latino	489 (68.4%)	171 (60.9%)	0.029
Unknown	173 (24.2%)	87 (31.0%)	0.036
Sex (n, %)			
Male	261 (36.5%)	109 (38.8%)	0.549
Female	454 (64.5%)	172 (61.2%)	
Level of DM Control			
A1c < 10.0	583 (81.7%)	232 (82.6%)	0.807
A1c ≥ 10.0	131 (18.3%)	49 (17.4%)	

Table 4 Multivariable binary logistic regression analysis to calculate adjusted odds ratios for associations of variables with the NAFLD fibrosis score

Variable (Level)	Multivariable odds ratio (95% CI)	*P*-value
Race: White	0.945 (0.518, 1.771)	0.856
Race: Black	0.785 (0.444, 1.432)	0.416
Race: Other	0.639 (0.326, 1.271)	0.196
Male	3.971e + 05 (1.673e+-42, N/A)	0.981
Female	3.702e + 05 (1.558e+-42, N/A)	0.981
Uncontrolled DM (A1C ≥ 10.0)	0.960 (0.660, 1.379)	0.828

*Adjusted ORs were calculated using a multivariable binomial logistic regression model for the nonalcoholic fatty liver disease fibrosis score (score of ≤ 0.675 versus > 0.675 as a binary outcome variable). The multivariable binary logistic regression analysis model included race (as categorical factors), sex and level of DM control, quantified by Hemoglobin A1c (≥ 10.0 versus < 10.0)

Table 5 One-way ANOVA for associations of variables with the FIB-4 fibrosis score

Factor	Degrees of freedom	Sum of squares	Mean square	F-value	*P*-value
Race	5	3.55	0.7091	2.307	0.043
Sex	1	2.61	2.6086	8.487	0.004
Hemoglobin A1C	1	1.16	1.1578	3.767	0.053

A1c > 10, adjusted odds ratio was 0.960 (0.660, 1.379 CI). (Table 4)

A one-way analysis of variance for variables associated with the FIB-4 Fibrosis score is now included. Age was not included in either of the regression models to avoid statistical redundancy, as age is a variable in the formula for both fibrosis scores. (Tables 5 and 6)

Table 6 Post-hoc Tukey's comparison of means for levels of variables associated with the FIB-4 fibrosis score

Levels	Difference	*p* adj
Other: American Indian/Native Alaskan – White	0.926	0.048
Other: American Indian/Native Alaskan – Black	0.981	0.028
Other: American Indian/Native Alaskan – Asian	0.956	0.045
Other: American Indian/Native Alaskan – Other: Other	0.942	0.047
Female - Male	0.113	0.005

In the assessment of imaging-based hepatic steatosis, evidence of fatty liver was identified in 112 out of 1075 patients using abdominal imaging studies. Specifically, 62 cases were detected via abdominal ultrasound, 5 via MRI, and 45 via CT scan.

Discussion

The revised acronym "metabolic dysfunction-associated steatotic liver disease" was recommended by an international group of experts from 22 nations in 2020 as a replacement for NAFLD. This phrase highlights the close connection between T2DM and MASLD. Not only do MASLD and T2DM have almost identical risk factors, but they also influence each other's disease development and consequences in a complementary way [20] Therefore, for the prevention and management of both T2DM and MASLD, frequent screening for T2DM in people with MASLD and vice versa, together with dietary and physical activity adjustments, are advised.

An optimal non-invasive method for evaluating hepatic fibrosis would be characterized by its high sensitivity and specificity, and its cost-effectiveness for patients [3]. Additionally, it should apply to all types of chronic liver diseases. In the case of MASLD, this test should also be able to differentiate between a fatty liver and steatohepatitis.

Probably the most common reason for underdiagnosing MASLD is that primary care physicians and diabetes specialists only depend on normal liver enzymes to rule out the condition. AST and ALT in our study were within normal ranges, even though a high % of participants had MASLD suspicions.

To date, none of the presently existing tests fulfill these requirements, thus, it is important to evaluate the effectiveness of any marker by considering both the specific clinical query at hand and how well the marker performs within that clinical context [4].

A meta-analysis that was published in 2019 concluded that, among 80 studies from 20 countries, there were 49,419 individuals with T2DM (mean age 58.5 years, mean body mass index 27.9 kg/m2, and males 52.9%). The global prevalence of MASLD among patients with T2DM was 55.5% (95% CI 47.3–63.7) [21].

The dependability of non-invasive biomarkers like FIB-4, NFS, and APRI extends beyond the general populace to include various special groups, such as those with co-morbid conditions, diverse ethnic backgrounds, and unique physiological states [22]. Research has shown that these biomarkers maintain their diagnostic accuracy in populations with diabetes, obesity, and chronic kidney disease, underscoring their versatility and utility across diverse clinical environments [22, 23]. Specifically, studies have demonstrated the consistent performance of FIB-4 and APRI in evaluating liver fibrosis among HIV-infected patients, showcasing their robustness even within immunocompromised populations [24]. Moreover, the use of these biomarkers in pediatric patients and pregnant women has offered significant non-invasive methods for monitoring liver health, further validating their incorporation into everyday clinical practice [25, 26]. These findings highlight the extensive applicability and reliability of non-invasive biomarkers across various clinical scenarios, reinforcing their integral role in comprehensive patient care.

In our study, we concluded that potentially advanced' fibrosis is found in 1–4% of T2DM patients using APRI or FIB-4 respectively. However, using NFS, the number of patients with possible F3/F4 is 28%. This may raise a concern of the internal validity of the NFS; which may be associated with more False positive results. This conclusion is consistent with recent literature. In 2023, when Kjaergaard et al. conducted a large clinical trial including 3,378 participants (1,973 general population, 953 at risk of alcohol live disease, 452 at risk of MASLD), with a median age of 57 years to screen the population for liver disease. They calculated the false positive rates in FIB-4, NFS, and other NITs, the FP rate was 35% and 45% in FIB-4 and NFS respectively [27].

Based on this significant variability in fibrosis percentages among different scores, the need for further validation of the scoring systems in diabetic patients with elastography or liver biopsy is warranted. However, it is not negligible that T2DM patients face the risk of MASLD with its different degrees, as our research showed.

Further stratified analysis revealed that the majority of MASLD cases were females ($n = 675$, 62.7%) which is contrary to the demographic analysis done in the meta-analysis published in 2017 where the pooled prevalence of MASLD in both male and female T2DM patients was 60.11% (95% CI: 53.63–66.41%) and 59.35% (95% CI: 53.28–65.28%), respectively [28].

Based on what Shah et al. concluded in their study, NFS outperforms seven other non-invasive markers of fibrosis in patients with MASLD [29], we did consider it in our study and the findings of fibrosis using NFS classification were significantly associated with the age group (< 65 Vs >-65) and ethnicity. According to a recent (National Health and Nutrition Examination Survey [NHANES] 2015-2016 database), individuals with T2DM had significant rates of hepatic steatosis and fibrosis with ethnic variations [30]. In a similar vein, certain ethnicities in our study showed a strong correlation between T2DM status and NFS and MASLD classification, whereas other ethnicities showed no such correlation—among Hispanic/Latino, for example.

The regression model we ran for the NFS scoring system showed insignificant results for race, gender, and uncontrolled DM indicated by A1C ≥ 10.0. Thus, we conclude that these variables are not to be considered when looking at MASLD risk for T2DM patients using the NFS scoring system.

We plan to use our results to guide us in the next step of our project, which will provide a free fibro scan screening using vibration-controlled transient elastography (VCTE) and linkage to care in our hepatology clinics.

Limitations

Being a retrospective study, there is more susceptibility to biases and confounding factors than prospective designs. The results of this single-centered study are limited in their applicability to other groups and contexts.

The accuracy of the MASLD risk assessment may be compromised in individuals who lack laboratory measurements, which are required to calculate the various scores employed.

Individuals with other stages of hepatic fibrosis or other liver disorders may be unable to benefit from the study's findings, which were designed to identify people with a higher risk of F3/F4 fibrosis.

Our study design limits the applicability of findings for diabetic patients, controlled on medication, with A1C < 6.5. MASLD with significant fibrosis can be seen in patients with controlled T2D with A1C of 5.7 and less than 6.5% or even less than 5.7.

We excluded subjects with prior liver biopsy from the study population because we targeted non-invasive selection and inclusion criteria. Moreover, Patients with a history of significant alcohol consumption (> 14 standard drinks/week in men, > 7 standard drinks/week in women) were excluded from our cohort. Thus, those cases will meet the diagnosis of Alcoholic liver disease (ALD). However, there is a more updated definition/classification of steatosis liver diseases made by AASLD that classify it based on the number of grams of alcohol consumed per day/week for males vs. females (< 20–20-50 - >50 g/day for females and < 30–30-60 - >60 g/day for males). will fit into three categories; Pure MASLD vs. Met ALD (a new category, outside pure MASLD, was selected to describe those with MASLD who consume greater amounts of alcohol per week vs. ALD [31].

Conclusion

Endocrinologists, primary care physicians, and gastroenterologists ought to screen for MASLD in diabetic patients. Based on the conclusions drawn from our study conducted at our urban Diabetes Centers, utilizing the fibrosis NITs may predict patients with advanced liver disease in different percentages. The obtained scores can be used to assess clinical progression. Further research is needed to correlate these findings to transient elastography. More screening for hepatitis B and C is needed to successfully rule out infectious causes of liver disease before attributing it to MASLD and other liver-associated metabolic syndromes.

Abbreviations

MASLD	Metabolic dysfunction associated steatotic liver disease
T2DM	Type 2 diabetes mellitus
MFA	Medical Faculty Associates
HbA1c	Hemoglobin A1c
FIB-4	Fibrosis-4 Index
NFS	NAFLD Fibrosis Score
APRI	AST to Platelet Ratio Index
CDC	Centers for Disease Control and Prevention
ANOVA	Analysis of variance
ALT and AST	Alanine transaminase and aspartate transaminase
IFG	Impaired fasting glucose
BMI	Body mass index
CI	Confidence interval
SD	Standard deviation
HIV	Human Immunodeficiency virus
AASLD	American Association for the Study of Liver Disease

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Author contributions

AE, FM, VM, SP and SD contributed to the study design, data collection and manuscript writing. JP, FM, AE and AA contributed the data analysis. AA, ZV, SG, LJ and DE contributed to the analysis review and manuscript review and editing.

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Data availability

The datasets analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

The study got approved by the George Washington Institute of Review Board with a study exempt # NCR224560.

Consent for publication

Given the study's retrospective nature, the GW IRB approved a full HIPPA waiver form. Thus, there was no need for consent from the study subject to participate or permission to publish. We have used password-encrypted data sheets from the GW EMR systems. Only the study personnel had access to the data.

Competing interests

The authors declare no competing interests.

Author details

[1]The George Washington University, Washington, DC, USA
[2]Department of Medicine, The George Washington University Hospital, Washington, DC, USA
[3]Department of Surgery, The George Washington Transplant Institute, The George Washington University Hospital, Washington, DC, USA
[4]Department of Endocrinology, The George Washington University Medical Faculty Associates, Washington, DC, USA

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