Improvement in Liver Stiffness in Pediatric Patients with Hepatitis C Virus after Treatment with Direct Acting Antivirals

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Objectives To assess the degree of liver stiffness using transient elastography in Egyptian children infected with hepatitis C virus (HCV) at baseline and 1 year after achievement of sustained virologic response (SVR) with direct acting antivirals.

Study design This prospective study included children infected with HCV who received treatment with sofosbuvir/ledipasvir and achieved SVR. At baseline and 1 year after achievement of SVR, the extent of hepatic fibrosis was assessed by transient elastography using FibroScan to measure liver stiffness, in addition to noninvasive markers including aspartate aminotransferase/platelet ratio index (APRI) and fibrosis-4 (FIB-4) index.

Results The study included 23 cases that had variable degrees of fibrosis at baseline; their ages ranged between 10 and 18 years. At baseline, 13 patients had F1; 3 patients had F1-F2; 1 patient had F2; 3 patients had F3; 2 had F3-F4; and 2 patients with F4. One year after achievement of SVR, there was a statistically significant improvement in liver stiffness, APRI, and FIB-4 index (P = .03, <.001, .02, respectively). In 13 patients (56.5%), the liver stiffness improved; in 7 patients, it was stationary; and the remaining 3 patients showed mild increase in liver stiffness that was, however, associated with improvement in APRI and FIB-4 index. Comorbid conditions and previous treatment with interferon were not associated with increased liver stiffness 1 year after SVR.

Conclusions Egyptian children infected with HCV genotype 4 achieved significant regression in liver stiffness after treatment with direct acting antivirals. *(J Pediatr 2021;233:126-31)*.

Hepatitis C virus (HCV) treatment with direct-acting antivirals (DAAs) is associated with a high rate of sustained virologic response (SVR); this has changed the natural history of HCV by halting and possibly producing regression of liver fibrosis.[1] Adequate information regarding liver fibrosis staging post-SVR is important to develop follow-up protocols and screening policies for hepatocellular carcinoma.[2]

Noninvasive tools, including liver stiffness measurement and fibrosis-4 (FIB-4) index measurement, have been reported for evaluation of liver fibrosis.[3] Currently, transient elastography (TE) is considered the alternative noninvasive standard method for the evaluation of liver stiffness and widely used for the assessment of liver fibrosis with high degree of accuracy.[3-5]

Aspartate aminotransferase/platelet ratio index (APRI), and FIB-4 index and liver stiffness, as noninvasive measurements of hepatic fibrosis, are found to decrease significantly after SVR, mostly secondary to the inflammation improvement.[6]

Several studies performed on Egyptian adult patients infected with HCV genotype 4 (GT4) and treated with different sofosbuvir (SOF)-based regimens reported a rapid significant regression in hepatic fibrosis, as evaluated by FibroScan, FIB-4, and APRI scores.[7] Similar results were observed in Egyptian patients with HCV GT4 coinfected with HIV.[8]

The aim of the present study was to assess the degree of liver stiffness using TE in Egyptian children and adolescents chronically infected with HCV GT4, 1 year after achievement of SVR with DAAs.

ALT	Alanine aminotransferase	FIB-4	Fibrosis-4
APRI	Aspartate aminotransferase/platelet ratio index	GT4	Genotype 4
		HCV	Hepatitis C virus
AST	Aspartate aminotransferase	LED	Ledipasvir
BMI	Body mass index	SOF	Sofosbuvir
CAP	Controlled attenuation parameter	SVR	Sustained virologic response
DDAs	Direct-acting antivirals	TE	Transient elastography
EOT	End of treatment		

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Methods

This prospective study was conducted at the Pediatric Hepatology Unit, Cairo University Pediatric Hospital, Cairo, Egypt. The study included children chronically infected with HCV GT4, age 12-18 years and/or their body weight was ≥35 kg, who were treated with sofosbuvir/ledipasvir (SOF/LED). An informed consent was obtained from the patients' parents/guardians prior to the study enrollment. The study protocol was approved by Kasr Alainy review board and ethical committee. Patients were excluded if they had concomitant primary liver disease other than HCV.

All patients were subjected to proper history taking including age, sex, comorbid conditions, and previous HCV treatment (interferon/ribavirin). Baseline investigations included complete blood count, liver functions, HCV RNA (was done using quantitative real-time polymerase chain reaction on Applied Biosystems 7500 Real-Time Polymerase Chain Reaction System using kits supplied by Qiagen GmbH [Hoffmann-La Roche AG], which has a lower limit of detection of 15 IU/mL).

Before starting treatment, liver stiffness was assessed using TE by FibroScan device (FibroScan Echosense) performed by 2 fixed operators who had more than 5 years of experience in performing TE. TE was performed with a standard M probe or an XL probe (for obese patients). Measurements were performed, after overnight fasting, through the intercostal spaces, with patient lying in the dorsal decubitus position with the right arm in maximal abduction. Measurement depth was between 25 and 65 mm below the skin surface. Successful measurements were validated using the following criteria: number of shots ≥10, ratio of valid shots to the total number of shots ≥60%, and IQR ≤30% of the median liver stiffness value (IQR/median liver stiffness ≤30%). The results were expressed in kPa. The cut-off values for liver stiffness in kPa in relation to Metavir score, used during this study, were according to de Lédinghen and Vergniol[9] and Castera[10] as follows: F0: 0-5.4 kPa, F1: 5.5-7.1 kPa, F1-F2: 7.2-8.7 kPa, F2: 8.8-9.5 kPa, F3: 9.6-12.5 kPa, F3-F4: 12.6-14.5 kPa, and F4: >14.5 kPa.

Liver steatosis measurements were obtained using controlled attenuation parameter (CAP) values, which were calculated only when liver stiffness measurement was valid for the same signals ensuring that one obtained liver ultrasonic attenuation simultaneously and in the same liver area as liver stiffness measurement. The CAP values were expressed as decibel per meter (dB/m) and were valid if the liver stiffness measurement examination was successfully performed. Liver steatosis grades were assigned as follows: S0 (no steatosis, CAP 0-238 dB/m), S1 (mild steatosis, CAP 238-260 dB/m), S2 (moderate steatosis, CAP 261-290 dB/m), and S3 (severe steatosis, CAP ≥290 dB/m).[11] The operators were blinded to the patients' clinical and laboratory data as well as to the treatment status.

All patients received oral fixed dose combination tablet of SOF/LED (400 mg SOF, 90 mg LED [Harvoni]) once daily for 12 weeks.

To assess treatment efficacy, complete blood count, liver functions and HCV RNA were repeated at week 4, week 8, end of treatment (EOT), and 3 months after treatment discontinuation to assess SVR12. Patients with any degree of liver fibrosis before treatment were followed up after 1 year of treatment. Follow-up investigations included complete blood count, liver functions, HCV RNA, and TE.

APRI and FIB-4 index were calculated for the included patients at baseline, week 4, week 8, EOT, SVR12, and 1 year after achievement of SVR. APRI was calculated using the proposed formula: APRI = [(aspartate aminotransferase, AST level/upper limit of normal)/platelet count (10^9/L)] × 100. FIB-4 index was obtained based on 4 factors including age, AST, alanine aminotransferase (ALT), and platelet count using the following formula: FIB-4 = [age × AST/platelet count (10^9/L) × $\sqrt{}$ALT].[12,13] The upper limit of normal for both ALT and AST used in the study was 40 and 50 IU/L, respectively. Body mass index (BMI) was calculated for all patients at baseline and 1 year after SVR and was correlated to the degree of liver stiffness and hepatic steatosis.

Statistical Analyses

Data were collected and tabulated. SPSS program v 21 was used for data analysis. Mean and SD or median and IQR were estimates of quantitative data including age, laboratory parameters, and fibrosis scores, and frequency and percentage were estimates of qualitative data as sex, comorbidities, and degree of hepatic fibrosis. Differences in biochemical characteristics were tested by the Student paired and unpaired *t* test, Mann-Whitney U test, or Wilcoxon test for quantitative data and by χ^2 test for qualitative data. A 2-sided *P* value of <.05 was considered statistically significant.

Results

Seventy-eight children and adolescents infected with HCV GT4 were treated by SOF/LED. All achieved SVR. At base line 30 (48.5%) had variable degrees of liver fibrosis by TE; 24 completed 1 year of follow-up after achievement of SVR and performed the follow-up investigations. After excluding 1 patient with associated autoimmune hepatitis, 23 patients were included in the study. Their ages ranged between 10 and 18 years (mean ± SD: 14 ± 2 years). Four patients were ≤12 years of age, but their body weight exceeded 35 kg. Fifteen cases were male patients (65.2%). Thirteen patients were treatment-naïve and 10 (43.5%) were treatment-experienced. Ten patients (43.5%) had history of comorbid conditions other than HCV; 5 out of these patients had more than 1 comorbidity. Three patients had congenital heart diseases, 3 had systemic lupus erythematosus, 2 lupus nephritis, 2 familial Mediterranean fever, 2 treated lymphoma, and 1 of each of the following: idiopathic thrombocytopenic purpura, inflammatory bowel disease, diabetes mellitus, Down syndrome, hydrocephalus, and steroid resistant nephrotic syndrome.

At baseline, liver stiffness by TE showed that most of the patients had mild degrees of liver fibrosis (**Table I**). The

mean ± SD of liver stiffness was 8.3 ± 3.8 kPa ranging between 5.5 and 20.5 kPa. APRI at baseline ranged between 0.19 and 2.18 (median [IQR]: 0.42 [0.42]). FIB-4 index at base line ranged between 0.24 and 1.6 (mean ± SD: 0.6 ± 0.3). There was a statistically significant positive correlation between the baseline liver stiffness and baseline APRI score (P = .004, r = 0.598). On the other hand, baseline FIB-4 did not show a statistically significant correlation with the baseline liver stiffness (P = .5, r = 0.158). The mean BMI of the patients at baseline was 21.34 ± 4.4 kg/m^2 ranging between 15.7 and 29.4. There was no correlation between liver stiffness and BMI at baseline (r = −0.236; P = .51).

At EOT, there was a statistically significant improvement in both APRI and FIB-4 index in comparison with baseline levels.

One-year after therapy with oral DAAs, all patients were HCV RNA negative. There was a statistically significant improvement in liver stiffness, APRI and FIB-4 index (P = .03, <.001, .02, respectively) (**Table II**), with no statistically significant correlation between the liver stiffness and either APRI (P = .572, r = 0.127) or FIB-4 index (P = .455, r = 0.168). **Figure 1** shows the significant improvement in APRI and FIB-4 index throughout the treatment duration and the improvement in liver stiffness 1 year after SVR. Thirteen patients (56.5%) showed improvement in liver stiffness by at least 1 stage of fibrosis, and in 7 patients the fibrosis stage remained the same. In the remaining 3 patients, the degree of fibrosis was mildly increased from F1 to F1-F2 but was associated with improvement in APRI and FIB-4 index (**Table I** and **Figure 2**). There was no association between the change in the degree of hepatic fibrosis and the presence of comorbid diseases (P = .7) or previous history of interferon/ribavirin therapy (**Table III**).

The mean BMI 1 year after SVR was 23.4 ± 5.9 kg/m^2 (range 15.6-34.8). Results of liver steatosis were available for the patients 1 year after SVR. The mean CAP was 218.24 ± 58.15 dB/m ranging between 124 and 321 dB/m. Three patients (13%) had S1, 2 with S2, and 3 with S3. The remaining patients had S0. There was a positive correlation between the BMI and the degree of steatosis by CAP (r = 0.530; P = .02). There was no correlation between liver stiffness and either the BMI (r = 0.000; P = 1.000) or the CAP (−0.236; P = .30).

Table I. Degrees of hepatic fibrosis by TE at baseline and 1 year after SVR in 23 children infected with HCV

Degree of fibrosis	At baseline n (%)	1-y after SVR n (%)
F0	0 (0)	7 (30.4)
F1	13 (56.5)	9 (39.1)
F1-F2	3 (13)	6 (26.1)
F2	1 (4.5)	0
F3	3 (13)	0
F3-F4	1 (4.5)	1 (4.5)
F4	2 (8.7)	0

Table II. Fibrosis markers at baseline and at end of treatment and 1 year after SVR

Fibrosis markers	Baseline	EOT	*P* value
APRI; median (IQR)*	0.42 (0.42)	0.2 (0.19)	.001†
FIB-4; mean ± SD*	0.6 ± 0.3	0.4 ± 0.2	.01†
	Baseline	**1 y after SVR**	
LS in kPa; mean ± SD	8.3 ± 3.8	6.4 ± 2.3	.03†
APRI; median (IQR)*	0.42 (0.42)	0.2 (0.1)	<.001†
FIB-4; median (IQR)*	0.4 (0.3)	0.29 (0.15)	.02†

LS, liver stiffness.
*One patient with idiopathic thrombocytopenic purpura who had pretreatment thrombocytopenia was excluded from the mean and median of APRI and FIB-4 index.
†*P* value is significant.

Discussion

Since their approval for children in 2017,[14] SOF/LED led to a response in children infected with HCV, with SVR rates ranging between 98% and 100%.[15,16] Several studies have assessed the effect of DAAs on fibrosis regression in adult patients with chronic HCV infection.

In HCV infected patients, liver disease progresses over time with increasing fibrosis severity. Advanced liver disease because of HCV infection is uncommon during childhood. Although uncommon, cirrhosis can be seen in infected children and adolescents younger than 18 years.[17] At baseline, approximately one-half of the children infected with HCV in the present study had some degree of hepatic fibrosis as estimated by TE, and 7.7% of the total number of patients had advanced degrees of liver fibrosis (F3, F4). TE is considered a noninvasive, rapid, reliable and reproducible method allowing evaluation of liver fibrosis by measurement of liver stiffness.[18] In an earlier Egyptian study, which included children with HCV, TE was a reliable method for detecting different degrees of hepatic fibrosis in children with HCV compared with liver biopsy.[19]

Liver stiffness and other noninvasive fibrosis markers like APRI and FIB-4 index, have been recommended for longitudinal evaluation of liver fibrosis.[3,12] In the current study, there was a significant progressive improvement in both APRI and FIB-4 index following administration of DAAs in our patients. Similarly, liver stiffness had shown a significant improvement after 1 year of therapy (P = .03). This is in concordance with studies performed on adult patients with chronic HCV infection who reported a significant decline in noninvasive fibrosis markers after treatment with oral DAAs[5,20-23] with similar reports in HCV recurrence after liver transplantation.[24] Similar results were reported from studies on adult patients with the same genotype as the study patients (GT4).[25,26] Mauro et al reported a significant improvement in portal pressure and liver fibrosis, detected by both liver biopsy and TE, in HCV recurrence for post-liver transplant patients.[27] In the current study, 56.5% of the patients showed improvement in liver stiffness. Adult studies reported variable frequencies of improvement; Lledo et al reported improvement in 40% and Lee et al in 86.9%.[22,28]

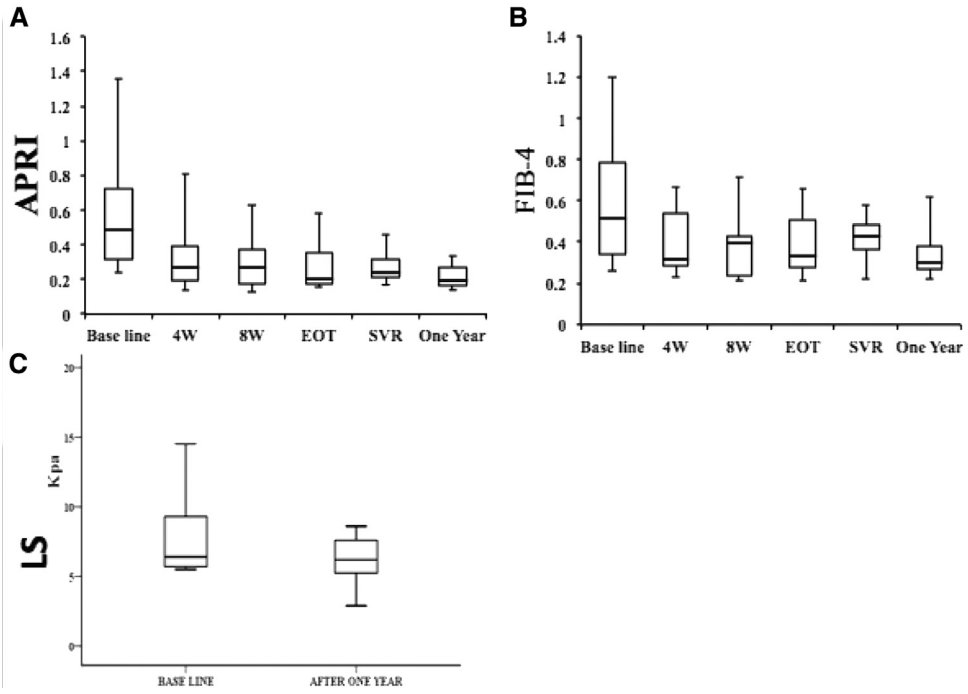

Figure 1. Improvement in hepatic fibrosis markers in children infected with HCV treated with SOF/LED 1 year after SVR. **A,** Shows the progressive decline in the median values of APRI compared with the baseline levels after 4 and 8 weeks of treatment, at EOT, 12 weeks after treatment discontinuation (SVR), and 1 year after SVR. **B,** Shows the progressive decline in the median values of FIB-4 index compared with the baseline levels after 4 and 8 weeks of treatment, at EOT, 12 weeks after treatment discontinuation (SVR), and 1 year after SVR. **C,** Shows the decline in the median values of liver stiffness measurement by TE measured in kPa 1 year after SVR. One patient with idiopathic thrombocytopenic purpura was excluded from the median of APRI and FIB-4 index.

Some studies suggested that the early and rapid decrease in liver stiffness was due to suppression of liver inflammation more than regression of liver fibrosis as demonstrated by a decrease in ALT levels.[29] This could explain why FIB-4 is not useful to grade fibrosis after SVR.[1] Pan et al performed serial liver stiffness measurements after SVR in patients with advanced fibrosis or cirrhosis and demonstrated that in 15 patients, in whom pre- and post-SVR liver biopsy samples were available, liver stiffness improved in most of them at least 1 stage of fibrosis, but 11 patients still had F3-F4 in liver biopsy results.[30] Despite this, a marked reduction in collagen content was observed, thus, demonstrating fibrosis regression. This can be considered one of our study limitations, the lack of pre-treatment and follow-up liver biopsy

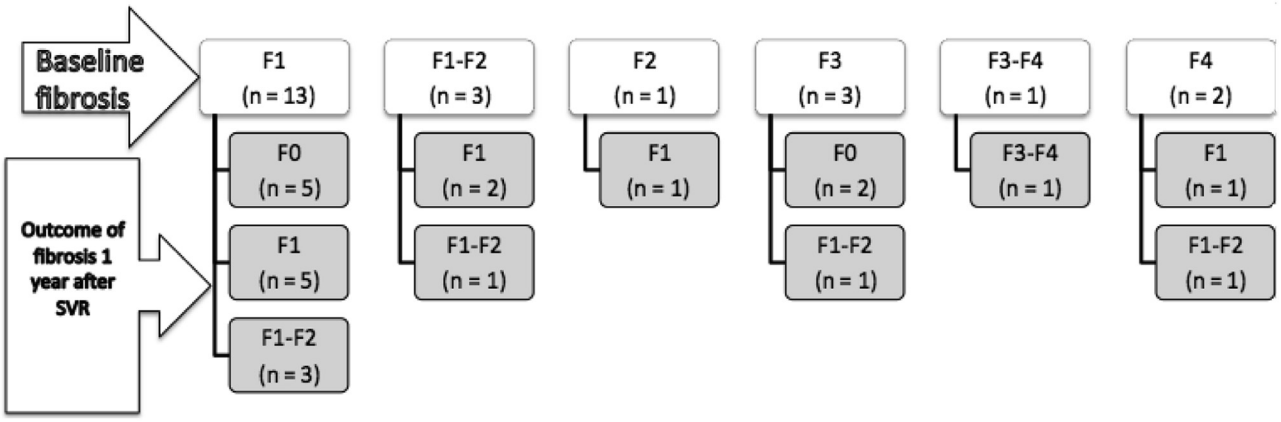

Figure 2. Progression of degrees of hepatic fibrosis by TE at baseline and 1 year after SVR in 23 children infected with HCV.

Table III. Impact of comorbid conditions or previous interferon therapy on the degree of hepatic fibrosis in 23 children infected with HCV treated with SOF/LED 1 year after SVR

Variable	Degree of hepatic fibrosis			*P* value
	Improved	Same	Worse	
Comorbid conditions				
Yes	5 (38.5)	4 (57%)	1 (33.3%)	.7
No	8 (61.5)	3 (43)	2 (66.7%)	
Previous HCV treatment (interferon ribavirin)				
Treatment experienced	5 (38.5%)	4 (57%)	1 (33.3%)	.7
Treatment naive	8 (61.5%)	3 (43%)	2 (66.7%)	

results or magnetic resonance imaging to confirm changes in inflammation, fibrosis and collagen amount.

In our cohort, although the percentage of improvement in the degree of hepatic fibrosis was higher among patients without comorbid conditions, the difference was not statistically significant. In an earlier study from our center in the pre-DAAs era, El-Hawary et al reported that the degree of fibrosis detected by liver biopsy samples in Egyptian children with HCV was not related to the presence of co-morbid conditions.[31]

In the present study, we did not find a correlation between the degree of liver stiffness and steatosis or BMI. Pokorska-Śpiewak et al demonstrated that novel serum biomarkers, as APRI and FIB-4, modified by including the BMI *z* score in their formulas show a better diagnostic performance in detecting significant fibrosis and significant steatosis compared with the standard tests with a better sensitivity and specificity.[32]

In conclusion, Egyptian children infected with HCV GT4 achieved significant regression in the degree of hepatic fibrosis assessed by liver stiffness measurement, after treatment with DAAs. ■

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References

1. Martínez-Campreciós J, Bonis Puig S, Pons Delgado M, Salcedo Allende MT, Mínguez Rosique B, Genescà Ferrer J. Transient elastography in DAA era. Relation between post-SVR LSM and histology. J Viral Hepat 2020;27:453-5.
2. European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. J Hepatol 2018;69:182-236.
3. European Association for Study of Liver. Asociacion Latinoamericana para el Estudio del Higado. EASL-ALEH Clinical Practice Guidelines: Non-invasive tests for evaluation of liver disease severity and prognosis. J Hepatol 2015;63:237-64.
4. D'Ambrosio R, Aghemo A, Fraquelli M, Rumi MG, Donato MF, Paradis V, et al. The diagnostic accuracy of fibroscan for cirrhosis is influenced by liver morphometry in HCV patients with a sustained virological response. J Hepatol 2013;59:251-6.
5. Galal SM, Soror SM, Hussien O, Moustafa EF, Hassany SM. Noninvasive assessment of liver fibrosis in children with chronic hepatitis C: shear wave elastography and APRI versus liver biopsy. Arab J Gastroenterol 2020;21:253-9.
6. Huang R, Rao H, Yang M, Gao Y, Wang J, Jin Q, et al. Noninvasive measurements predict liver fibrosis well in hepatitis C virus patients after direct-acting antiviral therapy. Dig Dis Sci 2020;65:1491-500.
7. Kohla MAS, Fayoumi AE, Akl M, Abdelkareem M, Elsakhawy M, Waheed S, et al. Early fibrosis regression by shear wave elastography after successful direct acting anti-HCV therapy. Clin Exp Med 2020;20:143-8.
8. El-Garem H, AbdAllah M, Omar H, Cordie A, Abdel Alem S, Mohey Eldin Elzahry MA, et al. DAAs therapy associated with improved hepatic fibrosis in HCV-GT4 patients co-infected with HIV. Expert Rev Gastroenterol Hepatol 2019;13:693-8.
9. de Lédinghen V, Vergniol J. Transient elastography (Fibroscan). Gatroenterol Clin Biol 2008;32:58-67.
10. Castera L. Noninvasive methods to assess liver disease in patients with hepatitis B or C. Gastroenterology 2012;142:1293-302.
11. Sasso M, Miette V, Sandrin L, Beaugrand M. The controlled attenuation parameter (CAP): a novel tool for the noninvasive evaluation of steatosis using FibroScan. Clin Res Hepatol Gastroenterol 2012;36:13-20.
12. Wai CT, Greenson JK, Fontana RJ, Kalbfleisch JD, Marrero JA, Conjeevaram HS, et al. A simple noninvasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. Hepatology 2003;38:518-26.
13. Sterling RK, Lissen E, Clumeck N, Sola R, Correa MC, Montaner J, et al. APRICOT Clinical Investigators. Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/HCV coinfection. Hepatology 2006;43:1317-25.
14. FDA News Release. FDA approves two hepatitis C drugs for pediatric patients. FDA. Published April 7, 2017. Accessed June, 2020. https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm551407.htm
15. Balistreri WF, Murray KF, Rosenthal P, Bansal S, Lin CH, Kersey K, et al. The safety and effectiveness of ledipasvir-sofosbuvir in adolescents 12-17 years old with hepatitis C virus genotype 1 infection. Hepatology 2017;66:371-8.
16. El-Karaksy H, Mogahed EA, Abdullatif H, Ghobrial C, El-Raziky MS, El-Koofy N, et al. Sustained viral response in genotype 4 chronic hepatitis C virus-infected children and adolescents treated with Sofosbuvir/Ledipasvir. J Pediatr Gastroenterol Nutr 2018;67:626-30.
17. American Association for the Study of Liver Disease. Updated May, 2018. Accessed June, 2020. https://www.hcvguidelines.org/sites/default/files/full-guidance pdf/HCVGuidance_May_24_2018b.pdf
18. Foucher J, Chanteloup E, Vergniol J, Castéra L, Le Bail B, Adhoute X, et al. Diagnosis of cirrhosis by transient elastography (FibroScan): a prospective study. Gut 2006;55:403-8.
19. Behairy BE, Sira MM, Zalata KR, Salama EE, Abd-Allah MA. Transient elastography compared to liver biopsy and morphometry for predicting fibrosis in pediatric chronic liver disease: does etiology matter? World J Gastroenterol 2016;22:4238-49.
20. Bachofner JA, Valli PV, Kroger A, Bergamin I, Kunzler P, Baserga A, et al. Direct antiviral agent treatment of chronic hepatitis C results in rapid regression of transient elastography and fibrosis markers fibrosis-4 score and aspartate aminotransferase-platelet ratio index. Liver Int 2017;37:369-76.
21. Kobayashi N, Iijima H, Tada T, Kumada T, Yoshida M, Aoki T, et al. Changes in liver stiffness and steatosis among patients with hepatitis C virus infection who received direct-acting antiviral therapy and achieved sustained virological response. Eur J Gastroenterol Hepatol 2018;30:546-51.
22. Lledó GM, Carrasco I, Benítez-Gutiérrez LM, Arias A, Royuela A, Requena S, et al. Regression of liver fibrosis after curing chronic hepatitis C with oral antivirals in patients with and without HIV coinfection. AIDS 2018;32:2347-52.
23. Singh S, Facciorusso A, Loomba R, Falck-Ytter YT. Magnitude and kinetics of decrease in liver stiffness after antiviral therapy in patients with chronic hepatitis C: a systematic review and meta-analysis. Clin Gastroenterol Hepatol 2018;16:27-38.

24. Korda D, Lenard ZM, Gerlei Z, Jakab Z, Haboub-Sandil A, Wagner L, et al. Shear-wave elastography for the assessment of liver fibrosis in liver transplant recipients treated for hepatitis C virus recurrence. Eur J Gastroenterol Hepatol 2018;30:27-32.
25. Tag-Adeen M, Sabra AM, Akazawa Y, Ohnita K, Nakao K. Impact of hepatitis C virus genotype-4 eradication following direct acting antivirals on liver stiffness measurement. Hepat Med 2017;9:45-53.
26. Shiha G, Soliman R, Mikhail N, Ibrahim A, Serwah A, Khattab M. Changes in hepatic fibrosis stages after achieving SVR following direct-acting antiviral treatment: a prospective study. Gastrohep 2020;2:39-48.
27. Mauro E, Crespo G, Montironi C, Londoño M, Hernández-Gea V, Ruiz P, et al. Portal pressure and liver stiffness measurements in the prediction of fibrosis regression after sustained virological response in recurrent hepatitis C. Hepatology 2018;67:1683-94.
28. Lee Y, Hu T, Hung C, Lu S, Chen C, Wang H. The change in liver stiffness, controlled attenuation parameter and fibrosis-4 index for chronic hepatitis C patients with direct-acting antivirals. PLoS One 2019;14:e0214323.
29. Pons M, Santos B, Simón-Talero M. Rapid liver and spleen stiffness improvement in compensated advanced chronic liver disease patients treated with oral antivirals. Ther Adv Gastroenterol 2017;10:619-29.
30. Pan JJ, Bao F, Du E, Skillin C, Frenette CT, Waalen J, et al. Morphometry confirms fibrosis regression from sustained virologic response to direct-acting antivirals for hepatitis C. Hepatol Commun 2018;2:1320-30.
31. El-Hawary M, El-Raziky MS, Esmat G, Soliman H, Abouzied A, El-Raziky M, et al. Assessment of hepatic fibrosis in pediatric cases with hepatitis C virus in Egypt. World J Gastroenterol 2007;13:2846-51.
32. Pokorska-Śpiewak M, Kowalik-Mikołajewska B, Aniszewska M, Pluta M, Marczyńska M. Clinical usefulness of new noninvasive serum biomarkers for the assessment of liver fibrosis and steatosis in children with chronic hepatitis C. Clin Exp Hepatol 2017;3:198-202.

50 Years Ago in *The Journal of Pediatrics*

Progress in Pediatric Diabetes Prediction, Management, and Outcomes

Drash A. Diabetes mellitus in childhood: a review. J Pediatr 1971;78:919-41.

Distinct categories of diabetes, now known as type 1 (T1D) and type 2 diabetes, were first recognized in 1936. Since then, the field has advanced significantly, and in Drash's landmark 1971 review, he summarized the knowledge surrounding pediatric diabetes, treatments available, and expected clinical outcomes. Huge strides have been made in diabetes diagnosis and care since 1971. People with T1D experience decreased vascular complications and lifespans have increased,[1] although the full benefits of current treatment on lifespan remain to be seen.

TrialNet[2] and other studies have exponentially increased our understanding of the etiology and progression of diabetes. At the time of Drash's review, the field accepted prediabetes as a "theoretical category" and the concept of autoimmunity was emerging. We now define stages of T1D based on presence of autoantibodies and glycemia.[3] Antibodies, when combined with clinical and familial factors, generate a genetic risk score, further improving our ability to identify at-risk individuals and screen, a huge advance from even a decade ago. As genetic testing becomes faster and more affordable, the implementation of these techniques will likely grow. Increased recognition of preclinical T1D provides opportunity for new treatments for delaying, and someday preventing, development of clinically symptomatic diabetes.

Another remarkable development is improvement in daily diabetes care. Technology for diabetes now includes continuous glucose monitors to transmit real-time glucose data to patients and caregivers and, combined with insulin pumps, provide closed-loop automated insulin delivery. Glucagon's role in metabolic regulation was not fully understood, but now dual-hormone pumps, containing both insulin and glucagon, are in development for even tighter regulation of blood glucose. Drash, an esteemed figure in pediatric diabetes research and care, thoroughly reviewed the state of diabetes in childhood and provided a foundation for advances in research and care over the past 50 years.

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References

1. Rawshani A, Sattar N, Franzén S, Rawshani A, Hattersley AT, Svensson AM, et al. Excess mortality and cardiovascular disease in young adults with type 1 diabetes in relation to age at onset: a nationwide, register-based cohort study: a nationwide, register-based cohort study. Lancet 2018;392:477-86.
2. Mahon JL, Sosenko JM, Rafkin-Mervis L, Krause-Steinrauf H, Lachin JM, Thompson C, et al. TrialNet Natural History Committee; Type 1 Diabetes TrialNet Study Group. The TrialNet Natural History Study of the Development of Type 1 Diabetes: objectives, design, and initial results. Pediatr Diabetes 2009;10:97-104.
3. DiMeglio LA, Evans-Molina C, Oram RA. Type 1 diabetes. Lancet 2018;391:2449-62.