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## Editorials

# Negative impact of COVID-19 pandemic on the lifestyle and management of patients with homozygous familial hypercholesterolemia



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The sudden outbreak of coronavirus disease 2019 (COVID-19) caused unprecedented pressure on the community and the national health systems.<sup>1,2</sup> The irreplaceable prioritization of the treatment of COVID-19 has diverted all resources to the care of this enormously increasing patient population.<sup>1,2</sup> However, the pandemic also had a negative impact on noninfected patients with chronic and rare diseases.<sup>1</sup> Severe restriction of daily life, including lockdown, to prevent the spread of the COVID-19, affected the management and access to treatments of patients with these disorders.

Homozygous familial hypercholesterolemia (HoFH) is a rare chronic genetic disease with very high low-density lipoprotein cholesterol (LDL-C) levels leading to early atherosclerosis.<sup>2,3</sup> Aggressively reducing LDL-C levels is crucial for the survival of patients with HoFH by delaying the progression of atherosclerosis and decreasing the incidence of major cardiovascular (CV) events.<sup>2,3</sup> Regular LDL apheresis (LA), in combination with standard lipid-lowering therapy (LLT), is the most effective means of lowering LDL-C. In addition, preventive lifestyle interventions including cessation of smoking, exercise, and a heart-healthy diet are fundamental for these patients.<sup>2–4</sup> Moreover, because of their lifelong risk of CV disease, at every age, patients with HoFH may have an increased risk of experiencing a severe course of COVID-19 and may be augmented with the presence of atherosclerotic CV disease.<sup>2</sup> In vitro studies report a possible link via ACE2

receptors leading to increased corona-viral entry to host cells in case of high cholesterol levels.<sup>5</sup> Previous viral epidemics have shown that CV events significantly increase during these times in association with high LDL-C levels.<sup>6</sup> Therefore, in all aspects, it is vital to continue the treatment of these patients and keep LDL levels low during the pandemic period.<sup>2</sup>

We recently conducted a survey to investigate the effect of the COVID-19 outbreak and the ensuing quarantine measures on the heart-healthy lifestyle, anxiety level, and management of patients with HoFH. Inclusion criteria included age  $\geq 18$  years and being under regular follow-up with the diagnosis of HoFH<sup>3</sup> at the Lipid Outpatient Clinic of Ege University Medical School Cardiology Department. Data were collected by phone contacts, and participants were requested to reply an 18-item questionnaire constructed to understand the impact of COVID-19 pandemic on management, healthy lifestyle habits, and anxiety levels. Participants were requested to rate their anxiety level during this pandemic, between 1 and 10 (1 represented the lowest score). **Table 1** displays the questions and results of the survey.

Our cross-sectional study included 34 patients with HoFH (mean age:  $42.53 \pm 14.07$  years, 55.9% female, 25 with genetically confirmed diagnosis of HoFH). The median follow-up duration in the center was 6 years. Overall, 70.6% of the cases had had documented CV disease (including aortic stenosis). All patients were on maximal doses of statins (rosuvastatin 40 mg or atorvastatin 80 mg daily) combined with ezetimibe. Fourteen (41.2%) patients were on regular weekly therapeutic LA with the clinical diagnosis of HoFH<sup>3</sup> in the center. In addition, 7 patients were on a new-generation LLT [2 patients on lomitapide (20–30 mg/d) as compassionate use and 5 patients on ORION-5<sup>7</sup> trial receiving inclisiran] on top of LA. One patient who had a severe recurrent increase in LDL-C levels after liver transplantation was on evolocumab therapy, and 1 patient was receiving inclisiran without LA, with the ORION-5 protocol. Overall, 9 (26.5%) patients were

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COI statement: M.K. has received honoraria (for lectures and consultancy) from Abbott, Actelion, Astra-Zeneca, Abdi Ibrahim, Aegerion, Bayer Schering, Menarini, Sanofi Genzyme, and Pfizer, and research funding from Aegerion, Amryt Pharma, Amgen, Pfizer, and Sanofi and has participated in clinical trials with Amgen, Bayer Schering, and Sanofi for the last 3 years. O.K.T. and L.H.C. had no conflicts of interest. L.T. has received honoraria/consultancy fees from Merck, Amgen, Astra, Novartis, Abbott, Daiichi Sankyo, Nova Nordisk, Pfizer, Actelion, Servier, Sanofi, Boehringer Ingelheim, Menarini, Kowa, Aegerion, and Abbott.

**Table 1** Study populations' anxiety level, attitude and behavioral changes since the emergence of the outbreak with regard to access to lipid apheresis and use of additional new-generation lipid-lowering agents

Questionnaire items	Replies	All HoFH	Patients lost access to LA session due to COVID-19 pandemic		
			All group	No additional new-generation LLT use	Additional new-generation LLT use
N		34	14	7	7
Any complaint, n (%)	-	3 (8.8)	1 (7.1)	1 (14.3)	0
Use of medicines regularly, n (%)	-	30 (88.2)	12 (85.7)	5 (71.4)	7 (100)
Working during the epidemic, n (%)	a working from home	1 (2.9)	0	0	0
	b working	3 (8.8)	0	0	0
	c no	30 (88.2)	14 (100)	7 (100)	7 (100)
Increase in anxiety, n (%)	-	21 (61.8)	9 (64.3)	6 (85.7)	3 (42.9)
Anxiety level, * mean $\pm$ SD (minimum–maximum)	-	4.79 $\pm$ 2.57 (0-9)	4.93 $\pm$ 2.26 (2-8)	5.14 $\pm$ 2.12 (2-8)	4.71 $\pm$ 2.56 (2-8)
Sleep, n (%)	a sleeping less	6 (17.6)	3 (21.4)	2 (28.6)	1 (14.3)
	b sleeping more	6 (17.6)	2 (14.3)	1 (14.3)	1 (14.3)
	c no change	22 (64.7)	9 (64.3)	4 (57.1)	5 (71.4)
Appetite, n (%)	a eating less	5 (14.7)	4 (28.6)	3 (42.9)	1 (14.3)
	b eating more	8 (23.5)	1 (7.1)	0	1 (14.3)
	c no change	21 (61.8)	9 (64.3)	4 (57.1)	5 (71.4)
Dietary compliance, n (%)	a better	20 (58.8)	9 (64.3)	5 (71.4)	4 (57.1)
	b worse	5 (14.7)	0	0	0
	c no change	9 (26.5)	5 (35.7)	2 (14.3)	3 (42.9)
Exercise habits, n (%)	a better	8 (23.5)	4 (28.6)	2 (28.6)	2 (28.6)
	b worse	17 (50)	7 (50)	3 (42.9)	4 (57.1)
	c no change	9 (26.5)	3 (21.4)	2 (66.7)	1 (14.3)
Smoking, n (%)	a nonuser	27 (79.4)	12 (85.7)	6 (85.7)	6 (85.7)
	b more	1 (2.9)	0	0	0
	c less	4 (11.8)	2 (14.3)	1 (14.3)	1 (14.3)
	d no change	2 (5.9)	0	0	0
Thought of increased vulnerability within the course of COVID-19 due to underlying FH, n (%)	a yes	27 (79.4)	11 (78.6)	7 (100)	4 (57.1)
	b no	5 (14.7)	2 (14.3)	0	2 (28.6)
	c do not know	2 (5.9)	1 (7.1)	0	1 (14.3)
Have admitted to a hospital during the pandemic? n (%)	-	9 (26.5)	3 (21.4)	0	3 (42.9)
Would admit to a hospital due to a complaint, n (%)	-	9 (26.5)	2 (14.3)	0	2 (14.3)

FH, familial hypercholesterolemia; LA, LDL apheresis; LLT, lipid-lowering therapy; SD, standard deviation.

\*The anxiety level for all samples has a skewed distribution; the median level is 5.

receiving new-generation LLT. Based on the findings of the survey, we can summarize the impact of the COVID-19 outbreak under 5 headings.

## Impact of COVID-19 pandemic on heart-healthy behavioral changes

Overall, half of the patients with HoFH reported a disruption at least in one or more components of the healthy life behaviors since the emergence of the outbreak. Change in sleep or appetite was observed in more than one-third of the patients. Patients reported that 35.3% experienced a change in sleep duration, 38.2% experienced a change in appetite, and almost 60% of the population was trying to be more compliant with a healthy diet during the outbreak. However, dietary compliance was decreased in 15%. Physical activity was reduced in 50%, and 23.5% reported an increased level of exercise.

## Increase in anxiety

Almost 62% of the patients reported an increase in their anxiety level during the outbreak. The median anxiety level was 5 (min = 0, max = 9). The anxiety level was not associated with age, gender, history of CV disease, or duration of the disease. Having a previous psychiatric diagnosis or psychotropic drug use (almost 20%) did not have any impact on lifestyle measure changes, anxiety level and was not associated with age.

## Awareness of increased vulnerability to COVID-19 due to HoFH

Almost 80% of the study population perceived themselves more vulnerable to COVID-19 and its complications due to their underlying HoFH. Patients who claimed that HoFH would not lead to a worse prognosis reported lower anxiety level than the patients who perceived themselves vulnerable ( $P = .016$ ,  $z = -2.399$ , medians: 2 vs 5) and the ones who were unsure about it ( $P = .044$ ,  $z = -2.010$ ; medians: 2 vs 7.5).

None of the study population had a diagnosis of COVID-19 or the complaints associated with COVID-19. As these patients were on regular follow-up of median 6 years in a tertiary center, probably their awareness was higher than the general population with HoFH. Therefore, the personal protection against contracting the coronavirus was probably effective.

## Avoidance of seeking medical care

Most of the study population (73.5%) reported that they would not go to a hospital even if they had a severe complaint during the COVID-19 outbreak. The picture was

the same for those with a history of CV disease; 67% reported that they would avoid going to a hospital even if they had a complaint like a chest pain, which might be a sign of a fatal heart attack. Avoidance of seeking medical care was not associated with the anxiety level, the duration of follow-up in the center, and age. This striking finding of avoidance of seeking medical care in patients with HoFH was completely due to fear of contracting the coronavirus in health care services. This observation is extremely important as the study population constituted of patients with very high health literacy and highly aware patients of their own CV risk. The fear that these patients declared might be the underlying cause of the reduced and late number of admissions of acute coronary syndromes, reported during the COVID-19 breakout.<sup>8</sup>

## Management of HoFH and access to LA during the pandemic

We observed that most of our patients were using their conventional LLT regularly during the pandemic period; only 4 (11.8%) patients could not receive CV medications regularly; 3 because of lack of social security and 1 because of forgetfulness. With the initiation of the pandemic, to avoid unnecessary visits to hospitals, the Ministry of Health enabled patients to access drugs for chronic diseases from pharmacies without new prescriptions for 6 months. This action was a very effective precaution to avoid interruption of pharmacotherapy in the management of chronic diseases during the pandemic.

However, access to LA, which is a lifesaving therapy for patients with HoFH was significantly restricted during the pandemic. All the patients with HoFH ( $n = 14$ ) on regular LA had no access to LA treatment since the emergence of the COVID-19 outbreak. The institutional apheresis center had to postpone the LA sessions as the center was occupied with COVID-19 patients. Among those 14 patients, 7 were already on additional new-generation LLT. Further evaluation of these patients who could not get access to LA during the pandemic also revealed that patients receiving additional new-generation LLT had a lower anxiety level than nonusers (85.7% vs 42.9%) (Table 1). Nonusers were sleeping less, eating less, and trying to be more compliant with a healthy diet than users probably reflecting both a high-risk perception and/or anxiety due to no access to an effective LLT modality.

Synchronously, we sent e-mails to other apheresis centers in the country ( $n = 22$ ) to ask the accessibility of LA during the pandemic period. Of note, we have been collaborating with these centers for a nationwide registry provided insight into the real-life management of patients with HoFH undergoing LA in Turkey.<sup>3</sup> Information received from other centers revealed that LA was accessible in 61% of the centers. However, most of the patients (75%) were not attending their LA sessions with the fear of getting infected.

The hindered LA therapy in patients with HoFH leads to a significant increase in LDL-C levels. Even in non-FH patients, high visit-to-visit variability in LDL-C levels is an independent predictor of adverse CV events.<sup>9</sup> Therefore, keeping LDL-C levels on target is extremely important in the management of these patients with HoFH. The present study illuminated the importance of easily accessible LLT during a pandemic or any other disaster. Although LA is the most effective way of lowering LDL-C in patients with HoFH, it is a hospital-based chronic treatment procedure. Therefore, effective pharmacotherapies are needed to avoid the dependence of these patients on the hospitals.

### How to overcome the negative impacts of pandemic on patients with HoFH?

Gradual quarantine measures, economic concerns, emotional load, and the fear of contracting the coronavirus are probably the explanation of the increased anxiety and disruption of heart-healthy lifestyle changes observed in our patients. The observed 50% decrease in compliance to at least one or more components of these healthy life behaviors denotes the need for increased follow-up and education. The current COVID-19 crisis with social distancing, lockdown, and telecommuting markedly decreased levels of physical activity.<sup>4</sup> Staying at home with a sedentary lifestyle and enormously increased screen time decreased energy consumption meanwhile increasing the difficulty to access fresh fruit and vegetables hampering most of heart-healthy eating habits.<sup>4</sup>

All our findings denote the importance of being in contact with the patients and providing the necessary information, as optimum anxiety and high perceived risk were correlated with taking some preventive measures; meanwhile, uncertainty of the risk and disbelief in media reports were associated with low adherence to the recommendations, in previous outbreaks.<sup>10</sup> Telemedicine should be in place for remote monitoring of these high-CV-risk patients to optimize risk factor control, physical activity levels, and assess diet while isolated.<sup>4</sup> Telemedicine will not only help the follow-up of these patients, but also will increase the adherence to CV medications. In addition, national scientific societies and more importantly patient organizations may play a key role in supporting patients by providing reliable, accurate information and advice in this time of greatest need.<sup>2</sup> Increasing public awareness with the help of social media is of prime importance in overcoming the patients' fear of contracting the coronavirus leading to medical care avoidance even in the presence of severe CV symptoms. In Europe, a new campaign organized by the patient organizations FH Europe, Global Heart Hub and supported by the European Atherosclerosis Society encouraging patients to seek medical help has started. This campaign is called 'When your heart says so, #JustGo' and has been reached by 80,000,000 people on the social media in 18 counties.

Measures should be taken to ensure to continue pharmacotherapy and LA. Hospital-based therapies can be disrupted during a pandemic. Access to new LLT with easier administration than LA such as lomitapide (oral therapy) or those that can be less frequently administered such as an ANGPTL3-inhibitor, evinacumab (require hospital based IV administration) or inclisiran (if approved) could be useful during the outbreak and lockdown times.

### Conclusion

Patients with HoFH like other rare diseases require regular and sustained medical care even in the pandemic era.<sup>2</sup> However, the results of this descriptive survey revealed that management of patients with HoFH with regard to heart-healthy lifestyle and access to LA has significantly deteriorated during the pandemic in a tertiary lipid center. More rigorous follow-up and education of these patients with telemedicine, better measures such as establishing COVID-free hospitals to make sure these patients have access to apheresis, or effective medications are necessary especially if prolongation or recurrence of pandemic is expected.

### Acknowledgments

The study protocol was approved by both the Institutional Review Board (20-5T 49) and the Ministry of Health COVID-19 Scientific Research Oversight Committee.

We cordially thank Prof Dr Serdar Payzin, MD for preparing the graphical abstract.

Authors' contributions: All authors made substantial contributions to all the following: (1) the conception and design of the study, or acquisition of data, or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, (3) final approval of the version to be submitted.

Meral Kayikcioglu, MD\*

*Ege University Medical Faculty, Department of Cardiology  
İzmir, Turkey*

\*Corresponding author. Ege University Medical Faculty,  
Department of Cardiology, 35100 Izmir, Turkey.  
E-mail address: [meral.kayikcioglu@gmail.com](mailto:meral.kayikcioglu@gmail.com)

Lale Tokgozoglu, MD

*Hacettepe University Medical Faculty  
Department of Cardiology  
Ankara, Turkey*

Ozlem Kuman Tuncel, MD

Sebnem Pirildar, MD  
*Ege University Medical Faculty  
Department of Psychiatry  
İzmir, Turkey*

Levent Can, MD  
Ege University Medical Faculty  
Department of Cardiology  
İzmir, Turkey

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