

The EMRG Consortium: a gate to identify the burden of metabolic (dysfunction)-associated fatty liver disease in Egypt

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Introduction

As a matter of definition, a Consortium is a network of individual investigators, research groups, or centers with a shared interest in a specific research area with an organizational structure that facilitates the development of shared research projects and fosters the acquisition of financial resources to support the activity of the consortium.

With increasing incidence and a prevalence of >25% among adults worldwide, metabolic (dysfunction)-associated fatty liver disease (MAFLD) represents a major public health issue.¹⁻³ MAFLD is intimately linked to other metabolic disorders and progresses to end-stage liver disease and hepatocellular carcinoma, and it increases the risk for cardiovascular disease, diabetes, cancers, and mortality.⁴⁻⁶ Our limited understanding of the magnitude of MAFLD problem in Egypt, level of disease awareness, and the cost burden is a major barrier to the development of action plans and health policies to tackle the growing disease burden. In addition, there is a lack of understanding of the unique characteristics of the pathophysiology and the mechanisms influencing disease progression in Egyptian patients. A better understanding of the genetic basis, metabolic, and microbiota profiles of MAFLD in our cohorts may provide important insights in guiding personalized approaches to the management of the disease.

Notably, while Egypt has very effective action plans for viral hepatitis and is one of the few countries on track to meet World Health Organization (WHO) recommendations for elimination of hepatitis C⁷ and has allocated tremendous resources toward this goal, similar policies

or programs to control the growing burden of MAFLD are virtually non-existent. In addition, research outputs related to MAFLD have been disproportionately low (in both quantity and depth of analysis).⁸

Why was the EMRG consortium set up?

This intuition, along with the recent redefinition of fatty liver disease provides a simple set of diagnostic criteria that can be easily applied in high- and low-resource health systems, led Dr Yasser Fouad and colleagues to initiate the Egyptian MAFLD research group (EMRG) Consortium (Table 1). The EMRG has been formed to bring together Egyptian clinicians and experts from different academic centers and regions of Egypt to discuss, collaborate, and extend bridges of collaboration with other international experts using a unified vision, with the aim to actively contribute to the field of MAFLD and to establish multidisciplinary Egyptian-based research networks to address important issues on the epidemiology, pathophysiology, diagnosis, and treatment in MAFLD. Due to multisystem nature of the disease and the requirement of a multidisciplinary model of care for optimal management of our patients, the EMRG is in the process of including members from other specialties, apart from Hepatology.

The consortium's key goals are to conduct studies that are needed to provide the necessary information to develop health policy plans to improve the management of MAFLD and patient's quality of life, with the aim to increase the fraction of MAFLD cases detected at an early stage by increasing disease awareness and better stratify patients at risk of developing liver-related

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complications by implementing an efficient and cost-effective referral pathway. The ultimate expected impact is to halt the progression of the growing burden of MAFLD, to decrease the complications of the disease, to reduce the need for liver transplantation, and to improve the cost-effectiveness of management.

Within this initiative, we are investing our effort also in communication and dissemination of project progresses to patients, common people, and policymakers for increasing awareness about MAFLD in so that preventive measures can be established to decrease the burden of cirrhosis and to reduce social stigmatization of patients with liver diseases. In the next stage, the consortium will invite patient's representative to join its initiative to bring the patient's perspective, which is crucial in the era of patient-centered models of care.

What is the EMRG vision?

The consortium vision is divided into three integrated phases:

Phase I: Aims to bring robust and comprehensive information on the prevalence and incidence of MAFLD among general population, tertiary care centers, and special subgroups, such as diabetes, thyroid disorders, chronic kidney disease, and bariatric surgery. This would include estimation of the cost burden of the disease and projection of the future impact of it on cirrhosis and hepatocellular carcinoma. In addition, we aim to determine the level of disease awareness among patients and general practitioners and other specialist physicians. This type of information would be crucial to inform the decision of health policymakers and aid to develop action plans to combat the growing burden of the disease.

Phase II: The EMRG is establishing the Egyptian MAFLD Registry, as a national, prospectively recruited observational cohort study with clinical, biochemical, histological information using the online platform REDCap that aims to establish a large, well phenotype patient cohort and linked bioresource. The cohort would enable exploring the genomic, metabolomics, and microbiota profile of the Egyptian patients. In addition, it would allow for identifying and robustly validating biomarkers and their optimal cut-off that diagnose, risk stratify, and monitor MAFLD progression and liver fibrosis stage in our patients.

This registry would represent the basis of multiple ongoing collaborative projects. To this end, we are establishing the required infrastructure, data management and monitoring plans, and the standard operating procedures to ensure the timely and systematic collection of high-quality data and samples.

Phase III: In spite of its large population, having one of the highest prevalence of MAFLD worldwide^{3,9} and multiple preferential advantages for recruitment in our Middle East North Africa (MENA) region, the region has not been considered in most fatty liver disease clinical trials. The MENA region and particularly Egypt has shown great capacity for drug development in the era of hepatitis C trials. Therefore, we aim to establish infrastructure and build networks that facilitate the undertaking of clinical trials for MAFLD in Egypt, a pivotal step to ascertain the efficacy and safety of the investigational drugs in our patients.

What has it found? Key findings and publications

Since the establishment in 2020, the EMRG has contributed to determining the burden of MAFLD in Egypt and the international and regional consensus for the redefinition of fatty liver disease from non-alcoholic fatty liver disease (NAFLD) to MAFLD. In a recent study, we retrospectively analyzed the data of 2097 patients who were referred to three Egyptian Tertiary Care Centers for the possibility of liver disease, and we demonstrated that generally, around 45% of these patients was found to have MAFLD. This work is pointing that the number of patients with MAFLD being referred to tertiary care has increased reflecting the shift from infectious diseases to MAFLD among patients with chronic liver diseases in Egypt. Similarly, in another study of >10,000 patients, we found that MAFLD is highly prevalent among patients with chronic hepatitis C (56.3%) and those with MAFLD and hepatitis C virus (HCV) were more likely to have significant fibrosis compared with patients with HCV only. Worryingly, in another study of 1538 consecutive HCC patients in the duration between 2010 and 2020, 14% of them were due to MAFLD. Notably, from 2010–2015 to 2016–2020, the prevalence of MAFLD–HCC has increased more the double (8–19%, respectively, $p=0.0001$), while HCV–HCC decreased (from 90% to 79%, $p=0.0001$). These findings are suggesting that with the decline of hepatitis C,

Table 1. The consortium members and action plan.

<p>Places and hospitals</p> <p>Ain Shams University Assuit University Benha University Beni-Suef University Cairo university Fayoum University Mahalah Teaching Hospital Minia University National Research Center NHTMRI, Cairo South Valley University</p>	<p>(Senior researcher names)</p> <p>(Nadia Abdelaaty, Sayed Mohamed) (Doaa Abdeltawab, Ahmed Shawkat) (Ebada Saeed) (Dina Attia, Shaymaa Nafady, Asmaa Salama) (Shereen AbdelAlem, Yasmine Gaber) (Ahmed Gomaa, Manar Sayed, Eman Fares) (Yousry Aboamer) (Yasser Fouad, Inas Kamal) (Mohammed AbdAllah) (Mai Mehrez) (Shamardan Bazeed)</p>
<p>Action plan:</p> <p>Phase I: Epidemiological studies and evaluation of magnitude of the problem of MAFLD and its extrahepatic associations in addition to increasing awareness among specialists and general practitioners.</p> <p>Phase II: The EMRG is establishing the Egyptian MAFLD Registry. Then, the genomic, metabolomics, and microbiota profile of the Egyptian patients will be studied. In addition, it would allow for identifying and robustly validate biomarkers and their optimal cut-off that diagnose, risk stratify, and monitor MAFLD progression and liver fibrosis stage in our patients.</p> <p>Phase III: Establishing infrastructure and build networks that facilitates the undertaking of clinical trials for MAFLD in Egypt, a pivotal step to ascertain the efficacy and safety of the investigational drugs in our patients.</p>	
<p>Funds</p> <p>Currently: locally supported by the centers Future: applying for governmental funds</p>	
<p>EMRG, Egyptian MAFLD research group; MAFLD, metabolic (dysfunction) associated fatty liver disease.</p>	

MAFLD is becoming a major cause of HCC in Egypt.¹⁰

To determine the level of disease awareness among patients and physicians, in two recent studies, we found a substantially low level of awareness of the disease nature and severity among both patients and physicians.^{11,12} In addition, in this study, >80% of patients indicated that they would not be concerned at all if they are diagnosed with NAFLD and would not undertake any actions. For comparison, >90% of these patients indicated that they would be very concerned if they were diagnosed with either hepatitis C or diabetes.¹¹ Moreover, >95% of patients will decline liver biopsy to assess for NASH if they have been asked to do, as they believe the disease is not serious.¹⁰ More than 90% of physicians indicated that the acceptance rate for liver biopsy is substantially lower in patients with NAFLD when compared with that in patients with hepatitis C.¹²

Collectively, this alarming increase in the prevalence of MAFLD accompanied with this substantial low awareness and trivialization of the disease suggests that strategies to increase awareness and

education on MAFLD and combat this growing burden are urgently needed.

In 2020, a landmark initiative of an international expert consensus panel led by Esalm *et al.* put forth a proposal for the redefinition of adult fatty liver disease associated with metabolic dysregulation. This included an update of the ‘negative’ term NAFLD to the term MAFLD and the introduction of a simplified and easily applicable set of ‘positive criteria’ for diagnosis.^{13,14} We have been part of this international effort. In addition, we have been subsequently involved in leading efforts for developing the Middle East and North Africa and sub-Saharan Africa consensus.^{9,15} We also led the statement of nurse and allied health perspective on this redefinition and provided seminal viewpoints on this aspect.¹⁶ Furthermore, Fouad *et al.* demonstrated the validity and applicability of these criteria and provided evidence that patients with concurrent MAFLD and chronic hepatitis C have a more severe liver injury than those with either disease alone.¹⁷ More recently, we led the effort of a wide panel of an international key opinion leader to develop recommendations for the integration of MAFLD as a part of the global hepatitis C elimination effort, an aspect

of special importance in Egypt. This work would allow or identify coexisting MAFLD in patients with chronic hepatitis or those who cleared the virus, which is pivotal for the delivery of holistic care. Collectively, our work has received significant worldwide attention.^{1,9,15,16,18–24}

Future directions and areas of gaps

Despite that EMRG had made a progress in the MAFLD research field, we identify various gaps in our current knowledge, and we suggest the following aspects as research prioritizes in Egypt.

Although we have also undertaken studies that provided robust evidence for the validity of adopting the criteria for improving clinical practice,¹⁷ further studies would be needed to validate the MAFLD diagnostic criteria in other population-based cohorts and to estimate the cost-effectiveness of adopting these criteria. Future studies in Egyptian cohorts of patients with MAFLD also would be required to validate the performance and determine the optimal cut-offs of noninvasive diagnostic tests for identifying at high-risk patients of MAFLD and the specific cut-off values for lipid and waist circumference. These studies would allow for the developing of Egyptian guidelines for the management of MAFLD. Finally, characterizing the genetics, metabolomics, and microbiota profile of Egyptian patients and enhancing their consideration of the ongoing clinical trials would be required.

In conclusion, though it is not well recognized yet, the emerging evidence suggests that the burden of MAFLD in Egypt is substantial, but the disease awareness is very low, which is alarming that immediate action plans and health policies are required to combat this growing burden. This would require an integration of efforts between all stakeholders, and in the core of this is accelerating the research on this disease in Egypt to inform these stakeholders. For these purposes, the EMRG was established in 2020 to maximize research efficiency for MAFLD and to share comparable epidemiological and clinical data, and biological samples across studies. In a short time, the EMRG has the demonstrable capacity to support research and biomarker development at scale and pace. Finally, while the purpose of this editorial is to introduce the EMRG Consortium to the hepatology community, we acknowledge the important work by other groups

and consortia in the field, thank our colleagues for the productive collaborations, scientific exchange, and fruitful discussions, and call other colleagues for further collaboration.

Author contributions

YF, AG, and DA designed the study and wrote the manuscript. All authors revised the manuscript.

Conflict of interest statement

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