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Editorials

Genomic medicine in hepatology: Towards personalized medicine in obesity and chronic liver disease

Genomic Medicine emerged after the unraveling of the DNA blueprint of the human genome representing a paradigm shift in the "one-size-fits-all" medical model. Paving the road of Genomic Medicine achieved by the development of the molecular biology-omic technologies known as: genomics, epigenomics, metagenomics, transcriptomics, proteomics, and metabolomics has provided substantial omic data (Big Data) of the human population. Creating multi-omic diagnostic tools to discriminate between low-risk and high-risk profiles while including their association with environmental factors is the next goal towards building molecular-clinical algorithms for Personalized Medicine approaches. Making medical decisions to tailor clinical care based on the patient's omic-environmental background aims to prevent and treat diseases at early stages, thus reshaping the practice of Medicine [1].

Currently, Genomic Medicine in Hepatology is also submerged in the challenge to shift from the current therapeutic paradigm focusing on the management of complications in advanced stages towards the early detection of liver damage [2]. This action will require defining the set of genetic and environmental etiological factors specific to each population or region involved in the onset and progression of chronic liver disease. In this sense, the Latin American (LA) population has a particular genome characterized by the admixture of African, European, and Amerindian ancestries, which makes this population unique. High rates of obesity and sedentary lifestyle, as well as the consumption of a hepatopathogenic diet have also been described in LA countries, which synergistically contributes to liver damage. The characterization of these factors will allow identifying early markers of disease onset and progression as well as implementing personalized-medicine strategies for the precise management of chronic liver disease. This knowledge also contributes to the understanding of the molecular processes involved in liver disease and the discovery of novel therapeutic targets.

The special issue on "Genomic Medicine in Obesity and Chronic Liver Damage" aimed to provide knowledge regarding the genetic, metabolic or environmental aspects involved in liver diseases and to gain insight on how they can be avoided based on these points. In fact, chronic liver diseases, caused by viral hepatitis (with exception of hepatitis C), alcohol consumption, obesity-related non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) are etiologies that can not be solely treated or cured with pharmacological regimens to date. Thus, a personalized-medicine approach embracing both the genetic susceptibility and lifestyle factors such as nutrition, physical activity and mental health could be an option for patients, mainly at early stages of diagnosis [3, 4]. With this in mind, the issue offers the hepatologists' community with further insight about the ongoing research in the region of LA and abroad.

Beginning with D. Compean's Opinions, his analytical reflection about the implications in redefining NAFLD as the metabolic-associated fatty liver disease (MAFLD) highlights the challenge that remains ahead in the field of hepatology worldwide, since reaching a definition consensus is warranted to prevent and treat it properly. As stated by the author, the sooner the better, so that first-line clinicians and hepatologists can work together to avoid obesity-related liver damage [5].

However, the worldwide prevalence of NAFLD is heterogeneous, which can be attributed to genetic, environmental and cultural differences among populations. As shown by Ortega-Rojas Y *et al.*, their epidemiological systematic review came to the conclusion that the overall prevalence of NAFLD in LA is close to 24%, whose rates notably increase in high-risk groups such as postmenopausal women (38%) and patients with type 2 diabetes mellitus (73%) or obesity (80%) [6]. These high alarming numbers are consistent with studies that have documented the presence of NAFLD/NASH in young-aged obese population of México [7] and sets the stage for conducting further research to seek population-based diagnostic markers at earlier stages of disease [8].

Finding strategies to prevent NAFLD/NASH depend upon experimental research reproducing aspects of human NASH as presented by Vargas-Pozada EE *et al.* In this study, the pathological mechanisms based on the molecular and cellular activation of the nucleotide-binding domain, leucine-rich-containing family, pyrin domain-containing-3 (NLRP3) inflammasome were elucidated in a mice model revealing the effect of a hepatopathogenic diet exacerbated by low doses of CCl_4. The findings suggest that the NLRP3 inflammasome may be considered as a potential therapeutic target [9].

On the other hand, the complexity of the task to find the proper diagnostic marker is exposed by the genetic heterogeneity of the human population, in contrast to experimental models. The Brazilian study by Cavalcante LN *et al.*, shows that the analysis of genetic variants and interactions with the environment may help to understand the physiopatological processes involved in NAFLD and its evolution to NASH, opening the possibility of tailored genomic medicine interventions. In this regard, the *PNPLA3* G allele has been associated with worse NAFLD evolution in Hispanics and Caucasians, whereas populations with higher degree of African ancestry carry a lower frequency of this risk allele, suggesting a possible NAFLD ancestry-related protective factor gained by the African lineage [10]. This finding underscores the value of personalized-medicine strategies in genetically admixed populations, including LA.

In addition, Torres-Reyes A *et al.* revealed by means of Whole Exome-Sequencing techniques the presence of polymorphisms related to the Olfactory Receptor gene pathways in Mexican patients

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presenting extreme obesity with progression for NASH. These pathogenic variants were located at *HSD17B4*, *OR1I1*, *OR5R1*, and *ADGRV1* genes affecting odor sensory perception and detection of related chemical stimuli, which could represent new potential therapeutic targets in obesity care [11].

In addition to genetics, metabolic and weight parameters can be also used as early markers of chronic liver disease. In this context, epidemiological data registered in the Korea National Health and Nutrition Examination Survey was analyzed by Hyukjin M *et al.* who demonstrated that the metabolically-unhealthy obesity phenotype was associated with a higher prevalence of laboratory liver cirrhosis, where blood glucose abnormalities play a mediation role [12]. Likewise, Dongna Z *et al.* analyzed data from the Kailuan Study, an ongoing prospective community-based cohort, to provide accessible clinical markers among the Chinese [13]. In this case, the effect of abdominal obesity and chronic inflammation (hs-crp) for risk of NAFLD was evaluated by considering the waist circumference/height index due to the smaller skeleton size but relatively thicker abdominal fat of the study population. Thus, in both studies, the evaluation of the metabolic status in obesity was tailored based on the phenotypic features of the population, which may be a useful tool for the establishment of preventive strategies of liver damage in these specific populations.

Yet, further efforts to provide clinicians with validated diagnostic tools are an opportunity for further research related to the early diagnosis of NAFLD/NASH in different regions of the world. As documented by Contreras D *et al.* their systematic review and meta-analysis regarding the diagnostic efficacy of the conventional blood markers and non-invasive scores to stage liver damage showed that the most validated scores are the fatty liver index (FLI) for NAFLD and AST to platelet ratio index for NASH. Interestingly, the target populations of these studies are mainly from China, United States and Japan, thus revealing that clinicians in other regions may prefer using alternative diagnostic scores or imaging techniques. However, more importantly, this situation implies that LA hepatologists are in need of establishing their own set of validated diagnostic markers for NAFLD/NASH based on the characteristics of the LA population while testing at early stages of disease [14].

On the other hand, advanced liver diseases are mostly treated by a canonical medical-pharmacological approach, however obesity and its associated comorbidities are preventable at early stages by promoting changes in lifestyle factors involving nutrition and exercise as main actions to follow. Under the umbrella of Genomic Medicine, personalized nutrition or genome-based nutritional strategies are governed by the principle that the genetic inheritance should be aligned with the proper nutrients. Thus, Rivera-Iñiguez I *et al.* provide a short review regarding several metabolic pathways that are influenced by nutrients to prevent NAFLD and NASH. Adopting these strategies will be the next challenge based on the genetic and food cultural background of the study population [15].

No one can truly disagree that weight loss is a critical cornerstone target in the treatment of NAFLD due to its relevant histological and metabolic improvements. Current strategies for weight reduction in NAFLD range from lifestyle modifications (such as diet and physical exercise) as first line therapies to alternative methods such as endoscopic/bariatric surgery, especially in extreme obesity cases. Unfortunately, numerous reports point out the difficulties that patients have for maintaining weight loss. Although to date no pharmacological treatment has been approved for the NAFLD spectrum, Compean D *et al*, present an overview of the advantages of the new antidiabetic drugs (i.e., GLP-1 Ra, SGLT2 and DPP-4) inducing weight loss as well as glycemic control, opening the door to synergic complementary treatments in this disease [16].

Furthermore, in the case of viral-induced liver diseases, patients who are infected specifically with the hepatitis B virus need to be given the best options that science can offer. To date, a total molecular cure against the HBV cccDNA has not been achieved despite the advancements in antiviral drug therapy, opening the possibility that nutrition-based adjuvant regimens can aid to improve liver health. Jose-Abrego A *et al.* present an overview describing recent studies that highlight the hepatoprotective role of several nutrients and foods in HBV infection through affecting key viral processes involved in virus cycle, gene expression, inflammation features, and oxidative status. Thus, micronutrients (vitamin E, selenium), plant-derived bioactive compounds (resveratrol, luteolin-7-O-glucoside, curcumin, epigallocatechin-3-gallate, chlorogenic acid) and food derivatives (moringa extracts) could represent an coadjuvant treatment strategy for patients infected with hepatitis B. Of note, many natural sources of these nutritional agents are found in foods endemic to LA countries, emphasizing the opportunity to regionalize these recommendations [17].

While obesity is currently a global health problem, malnutrition is a common clinical feature in patients with alcoholic liver disease, often needing effective nutritional support in order to improve prognosis. For this purpose, Zhao J *et al.* present a comparative study in Chinese patients testing the effects of different nutritional interventions on energy metabolism indexes and serum amino acid levels in which a late evening snack and oral amino acid capsules were the most recommended long-term nutritional interventions due to significant improvements in key parameters such as isoleucine concentrations and respiratory quotient [18].

Finally, the implications of body mass index and liver disease is underscored in the study by Villalobos-Bello V *et al.* describing the health conditions of women presenting intrahepatic cholestasis of pregnancy and the maturation of the placenta. These cases reveal the importance of establishing awareness by training both gynecobstetrians and hepatologists to detect as early as possible the appearance of clinical signs and symptoms in women at risk during reproductive ages and provide the needed care [19].

In summary, chronic liver diseases are and will continue to be a challenge for health professionals and public health authorities to convey the message that obesity is an emerging silent risk factor. As shown in this issue, ongoing worldwide research is at different stages of advancements: analyzing epidemiological data, performing basic studies, rethinking treatment regimens and searching for appropriate metabolic and genomic markers. In the context of Genomic Medicine, pathing the way towards a personalized-medicine and personalized-nutrition approach is a task requiring a regional and global teamwork effort to provide the knowledge that is needed to prevent chronic liver damage, mainly at early stages. It is our hope that the readers of AoH find these works useful in their clinical practice.

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