

Nonalcoholic fatty liver disease in developing countries

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TO THE EDITOR

Nonalcoholic fatty liver disease (NAFLD) is an increasingly known medical entity with high prevalence, about 10 to 24 percent in general population and up to 74% in obese population^[1]. The prevalence of the disease is expected to increase worldwide, as we are encountering the global obesity epidemic and the trend in developing countries toward the Western lifestyles. However, it looks that there are some differences between the demographic and epidemiologic features of NAFLD in developing and developed countries.

Some studies conducted in developing countries^[5] have shown somewhat different epidemiologic and demographic characteristics for NAFLD. For example, while NAFLD and nonalcoholic steatohepatitis (NASH) were primarily thought to be more common in women than in men, many studies conducted in developing countries demonstrated either a male predominance^[2-5] or no difference in gender distribution. Such a result was observed only in a few studies in developed countries^[6]. Similarly, although a higher prevalence of diabetes mellitus was reported in patients with NAFLD and NASH, the prevalence of diabetes in several studies carried out in developing countries has been lower than what was primarily explained^[2-4].

The reaction of the scientific community to such anomalies has been limited to a more conservative explanation of the demographic and epidemiologic characteristics of NAFLD and NASH. Nowadays, most review articles do not highlight the effect of gender on the disease and do not place much emphasis on diabetes mellitus, although insulin resistance is known to be a very important risk factor of the disease. In other words, we have ignored the possibility that these

differences might indicate more systematic and fundamental differences in these populations and detecting the source of these differences might shed light on some important pathophysiologic aspects of the disease.

We are currently at a very crucial phase of understanding NAFLD and NASH, which is called the maturation of the *paradigm*. Based on Thomas Kuhn's ideas^[7], the sciences mostly work within a single framework, *scientific paradigm* or *disciplinary matrix*, driven by exemplars of past scientific achievements. This disciplinary matrix, paradigm, is a set of theories, beliefs, and principles that can solve current problems and gives rise to subsequent research questions. Our knowledge of NAFLD, as an increasingly known medical entity, has been rapidly increased in the last decade and it seems that the scientific community is currently forming a paradigm for the disease-based on the knowledge we have achieved so far. At this crucial phase, we have to ascertain that no considerable piece of evidence is neglected.

As explained below, the discrepancy between the epidemiologic and demographic characteristics of the disease might be due to different factors. But even if there is a small probability that such differences are indicators of more fundamental issues, it is worth to evaluate that possibility now, rather than paying more cost later to change the paradigm.

Possible sources of discrepancy

Different factors, such as cultural and socioeconomic characteristics, dietary habits, and genetic factors, can give rise to such a discrepancy between patients and/or studies in developing and developed countries.

Provided the indisputable role of cultural factors on alcohol consumption, these factors might explain some degrees of the differences between the characteristic of NAFLD in these two societies. Alcohol consumption is the most important factor to be ruled out in order to diagnose NAFLD. The pattern of alcohol consumption in some developing countries is different from developed countries. In fact, in many Muslim countries^[3,5], the alcohol consumption rate is extremely low.

In addition to alcohol consumption habits, other cultural differences might also play a role in this discrepancy. For example, pointing at some cultural differences between these two populations, some of our colleagues in the US have questioned if in developing countries men are more likely to ask for medical services than women. In other words, it might be postulated that these differences are caused by a bias that is introduced into these studies because of cultural differences. One clinic-based study has tested this hypothesis by looking at gender distribution in other cases referred to that clinic and it was shown that there is a female predominance in other hepatic diseases^[4]. However, this hypothesis should

be more precisely tested in community-based studies in developing countries.

The other important factors that might explain this discrepancy are socioeconomic factors. Studies conducted in both developing and developed countries should take this factor into account. For example, access to health care might play a crucial role in the patterns of NAFLD and NASH in these two societies. Inappropriate distribution of health care system in developing countries can distort the distribution of risk factors such as diabetes as well as diagnosis and control of such factors.

Dietary habits are the other important differences between developing and developed countries. These differences are not limited to the difference in high-calorie high-fat diets and their role in metabolic syndrome, obesity, and other risk factors of NAFLD. Diet is highly interrelated with cultural and socioeconomic factors, but we have discussed it separately to emphasize on its importance. Further inspection of the dietary habits in developing countries should be considered only if studies approve that food has an important effect on key determinants of the discrepancy between two populations after controlling for cultural and socioeconomic factors.

The other important factors that might explain such differences are genetic factors. In fact, in my personal communication with many colleagues in different countries, genetic factors were the first suggestions. Our knowledge about genetic characteristics of NAFLD and NASH is very limited and genetic differences have this potential to cause this discrepancy. However, developing countries do not have a homogeneous population and probably genetic differences between different developing countries is as much as, if not more than, the differences between developing and developed countries. Further studies on genetic factors might provide some clues about the validity of this hypothesis.

What mentioned above are only some hypotheses that might be responsible for some part of the differences between results of studies on demographic and epidemiologic characteristics of NAFLD and NASH. There might be many other hypotheses that are not mentioned here. However, it is very important to notice that this discrepancy might be not more than only random or systematic errors in different studies. Many studies published in both developing and developed countries, particularly the former, are conducted on small samples and mainly on cases referred to hospitals or clinics. Difference in quality of studies is an important factor that if true can result in factitious difference in published articles.

Recommendations

In summary, there is a discrepancy in epidemiologic and demographic characteristics of NAFLD and NASH between studies conducted in developing and developed countries. This discrepancy in publications may, or may not,

provide a clue to some differences between the pathophysiology of the disease in these two populations. Therefore, it is worth for scientific community to evaluate the possibility of such a difference at this time rather than attempting to change the paradigm later. If this difference does exist, it provides many clues for further investigation on NAFLD and NASH. For example, while insulin resistance is known to be one of the most important factors in pathophysiology of NAFLD and NASH, low prevalence of diabetes in some populations might indicate the presence of a competing causal factor, yet to be defined. Below are some recommendations for future studies on NAFLD and NASH in order to define whether such a difference does exist and if yes, which factors can explain this discrepancy.

(1). Large community-based studies are strongly required in developing countries. As mentioned above, this discrepancy might be only due to the quality of studies, particularly in developing countries. Large community-based studies with appropriate design can shed light on whether there is a difference between these two populations. (2). Epidemiologic studies in both developed and developing countries should put more emphasis on the factors that have different distributions in these two populations and particularly on socioeconomic factors. Socioeconomic factors are the most consistent difference between these two populations. Therefore, the effect of these factors-regardless of their effect through other variables such as diet, obesity, *etc.*-should be evaluated in studies conducted in both developing and developed countries. (3). More studies are needed on genetic aspects of NAFLD and NASH in developing countries and verification of the results of the research conducted by our colleagues in developed countries.

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