Editorial

Can metabolomic signature foster precision medicine approaches in nonalcoholic fatty liver disease arena?

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Abnormal chemical reactions disrupting physiological bio-transformations in human body set the stage for the development of metabolic disorders (1). Clinically and epidemiologically, the metabolic syndrome is the most demanding among metabolic disorders in as much as it is globally common and exacts a major toll in terms of healthcare expenditures. The metabolic syndrome defines a cluster of self-perpetuating and self-aggregating conditions comprising visceral obesity, impaired glucose tolerance/type 2 diabetes, arterial hypertension and atherogenic dyslipidemia (2). In many cases, it is the expansion of visceral adipose tissue that triggers the full-blown metabolic syndrome. In this setting, lipotoxicity defines spillover of accumulated inert fat from visceral adipose tissue to non-adipose tissues (e.g., the liver, muscle, and pancreas) eventually resulting—in predisposed individuals—in either functional or anatomical damage of these target organs (1).

An impressively consistent line of research has identified the intrahepatic accumulation of fat [i.e., steatosis, of which the most common cause in nonalcoholic fatty liver disease (NAFLD)] as a fundamental intermediate step in the complex process eventually leading, via insulin resistance, to incident type 2 diabetes; incident metabolic syndrome; as well as to metabolic damage of target organs (3). The spectrum of this target organs damage is phenotypically diverse and spans from cardiovascular morbidity and mortality to cirrhosis and end-stage liver failure, recurrent and *de novo* NAFLD following liver transplantation, chronic kidney disease, and hepatic and extra-hepatic cancers.

Therefore, far from being a clinically monotonous and predictable condition, NAFLD exhibits a remarkable pathogenic and clinical heterogeneity, with some individuals following a benign and indolent course and others developing type 2 diabetes or any the above-mentioned target organ damage phenotypes. For the clinician, NAFLD will probably remain an enigma until a consistent precision medicine approach is adopted (4-6). One of the proposed classification systems is the so called "LDE" an initialism for liver, determinants, and extrahepatic features (7-9). However, the LDE system is a descriptive clinical classification and does not involve any specific metabolomic approaches. Together with diabetes, obesity is a major determinant of NAFLD and of the recently coined and extensively endorsed metabolic-associated fatty liver disease.

Measures defining obesity vary as a function of ethnicity given that the threshold of accumulated body fat required before metabolic complications appear is not uniform across different populations (10). For example, Asians tend to be more sensitive to such metabolic complication at lower levels of overall obesity. Conversely, for any given BMI, compared to Caucasians, black people tend to have lower body fat and higher lean muscle mass accounting for a lower risk of obesity-related metabolic diseases.

Irrespective of ethnicity, the (fatty) liver also plays a role in determining the development of these metabolic complications of obesity, such that the presence of NAFLD is associated with a worse metabolic profile (11). The pathomechanisms underlying this association include the liver being overwhelmed by fatty acids via portal route, which will lead to NAFLD and insulin resistance (12,13).

With this backset, Pang *et al.* utilized data from the prospective China Kadoorie Biobank database, which is

finalized to assessing the associations of adiposity with metabolic biomarkers; circulating metabolites with incident NAFLD; and the predictive role of metabolomics in identifying incident NAFLD cases (14).

For their case sub cohort study, Pang *et al.* evaluated a random sample of 192 cases of NAFLD (the diagnosis was based on medical records and as many as 93% of cases were submitted to either ultrasound or computed tomography imaging studies of the liver) out of a total of approximately 1,000 accumulated cases; and a sub cohort of 192 randomly sampled participants with genotyping data available (15).

Mendelian Randomization (MR) analysis showed consistent associations between some BMI-associated metabolomic biomarkers with the risk of incident NAFLD risk, suggesting that these may virtually mediate the nexus between adiposity and NAFLD (15). Some qualifying technical aspects of this study deserve comment: MR and metabolomic signature.

A key aim in epidemiological sciences is assessing the cause-and effect relationship linking certain measures of exposures (for example clinical phenotypes; biomarkers; and different risk factors) with meaningful health and disease sequels (for example overall survival; disease free survival; organ transplantation; major cardiovascular events and others) (16). While deemed to be the best means of establishing the causal relation between exposure and outcome (17) randomized controlled trials are expensive, time-consuming, incur in rates of failure exceeding 50% and are neither ethical nor invariably diagnostic under all circumstances, in which case information regarding causality may be best obtained from observational epidemiological studies (18). In its turn, direct inference of causality in epidemiological studies may reveal problematic owing to the risk of differentiating *direct causation* (variable A causes variable B) from *reverse causation* (variable B causes variable A) (16). Additionally, interpretative issues may result from a *confounding factor*, namely a shared common cause which affects both variables at the same time (e.g., variable C causes both A and B) or, finally, owing to the outcome resulting from a combination of both causal and confounding effects (16).

MR has been gaining increasing popularity to overcome the above difficulties in conducting and interpreting epidemiological studies (16). Aimed at making causal inferences regarding the outcomes of the modifiable exposure, MR exploits germline genetic variants as proxy variables for environmentally modifiable exposures (19).

Additionally, in the study by Pang *et al.* (15) the Metabolon platform was used to ascertain the concentrations of 1,208 metabolites in baseline blood samples. Based on chemical structure, these metabolites were grouped into eight classes (amino acids, carbohydrates, cofactors and vitamins, energy metabolites, lipids, nucleotide metabolites, peptides, and xenobiotics) which were further classified into 9 super-pathways and 105 sub-pathways. Considered together, MR, metabolic analysis and robust epidemiological bases represent definite points of strength of this study (15).

Some methodological limitations and the contribution of this study (15) to promoting our understanding of the pathomechanisms involved in adiposity associated NAFLD must not be neglected and have recently been discussed elsewhere (20). Having said that, it should be underlined that, once replicated across different ethnicities, the findings from this study might potentially be utilized in clinical practice soon. It could indeed be envisaged to build a "metabolomic identity card" describing homogenous patient populations to be submitted to therapeutic trails and personalized follow-up schedules. This would render immediately available those precision medicine approaches that are eagerly awaited in NAFLD arena to overcome the limitations in our present therapeutic armamentarium (5-7,20).

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