Sweeping 'Metabolic Dysfunction' off the Front Foot – Deceived by the "Wrong 'un": Implications of Dysmetabolism Analysis in Healthy Subjects

The recent proposal to rename non-alcoholic fatty liver disease (NAFLD) to metabolic (dysfunction)-associated fatty liver disease (MAFLD) has opened a Pandora's box of questions as to what exactly is metabolic dysfunction.[1] MAFLD is defined as the presence of hepatic steatosis with at least two metabolic risk abnormalities in non-overweight/obese individuals.[1] Cirrhosis and hepatocellular carcinoma (HCC) patients are also being labeled as 'non-alcoholic steatohepatitis (NASH)-related' based on the presence of these metabolic risk factors.[2] Fatty liver disease has been shown to be the single most important indicator of metabolic syndrome.[3] Therefore, we decided to evaluate the criterion for metabolic dysfunction in healthy individuals without fatty liver to precisely check how the above criterion applied to a healthy population.

Clinical and biochemical parameters of 171 healthy individuals without fatty liver obtained from the database of Kalinga Gastroenterology Foundation (KGF) were analyzed. A total of 94.2% of the subjects and all females were teetotallers. The mean body mass index (BMI) of the cohort was 21.61 ± 3.23 kg/m^2. The mean high-density lipoprotein (HDL) and triglyceride (TG) levels were 45.34 ± 8.55 mg/dL and 130.98 ± 58.29 mg/dL, respectively. However, the mean HDL level of females was 46.14 ± 8.91 mg/dL which is below the normal cut-off for females. A total of 33.9% individuals (45.6% of females and 28.07% of males) satisfied two of the seven parameters enumerated in the MAFLD criterion for metabolic dysfunction. Only 8.8% of individuals satisfied the criterion of the metabolic syndrome as per Adult Treatment Panel III (ATP III) criteria.[4] The results are shown in Table 1.

Table 1 Comparison of Anthropometric and Metabolic parameters between apparently healthy males and females.

Parameter	Males (n = 113)	Females (n = 58)	*P* value
Mean BMI (kg/m^2)	21.24 ± 2.74	22.35 ± 3.96	0.06
Mean Waist circumference (cm)	80.25 ± 9.40	76.16 ± 13.64	0.04
Mean HDL (mg/dL)	44.94 ± 8.37	46.14 ± 8.91	0.39
Dysmetabolism (%)	28.07	45.6	0.02
Metabolic syndrome (%)	6.14	14.03	0.07
Alcohol intake (%)	8.77	0	0.03

**P* value calculated by independent t-test for continuous variables and chi-square test for categorical variables.

There are multiple problems with the dysmetabolism criterion of MAFLD. To begin with, the criterion is based on the premise that the presence of at least two metabolic risk abnormalities along with fatty liver makes it metabolic (dysfunction) associated. This assumption disregards the definition of the metabolic syndrome laid down by ATP III criterion which states that 'the diagnosis of the metabolic syndrome is made when 3 or more of the risk determinants …. are present."[4] The MAFLD criterion further labels individuals as having metabolic dysfunction if the fasting plasma glucose (FPG) is above 100 mg/dL. This is again in contrast to the ATP III criterion where the cut-off is 110 mg/dL. It is also well known that compared with the Western populations, Indians and South Asians have higher TG levels and lower HDL levels.[5]

Our observations seem to have pulled a rabbit out of the hat. The presence of dysmetabolism as per MAFLD criterion in one-third of a healthy cohort is entirely unexpected. Extrapolating this to larger cohorts would render a huge number of seemingly healthy individuals 'dysmetabolic' creating confusion regarding their evaluation and management. If one-third of a 'healthy' cohort can be consigned to the 'unhealthy dungeons of dysmetabolism' based on this criterion, it would be a travesty of scientific logic to stamp the label of 'metabolic dysfunction' as the causative factor on a whole gamut of cirrhosis and HCC patients. Association never means causation and to find an analogy in cricketing parlance, we might risk getting bowled by the leg spinner's surprise wrong 'un in trying to play 'dysmetabolism' off the front foot!

CONFLICTS OF INTEREST

None to disclose.

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Abbreviations: ATP III: Adult Treatment Panel III; BMI: Body mass index; FPG: Fasting plasma glucose; HCC: Hepatocellular carcinoma; HDL: High-density lipoprotein; LFT: Liver function test; MAFLD: Metabolic-associated fatty liver disease; NAFLD: Non-alcoholic fatty liver disease; NASH: Non-alcoholic steatohepatitis; TG: Triglyceride

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