Tropical Gastroenterology 2013;34(1):1–4

Editorial

Insulin resistance and "Lipotoxic Liver Diseases"

S K Mahiuddin Ahammed, Abhijit Chowdhury

Department of Hepatology
School of Digestive and
Liver Diseases .
Institute of Post Graduate Medical
Education & Research.
Kolkata -700020, India

Correspondence:
Abhijit Chowdhury
Email:achowdhury2002@yahoo.co.in

An expanded dysfunctional adipose tissue that fails to accommodate, utilise and store as much fat as it should has emerged as the prime mover of the patho physiological sequence that leads to accumulation of fat at ectopic sites – including the liver, in metabolic syndrome and cluster of disorders that include Non alcoholic fatty Liver Disease(NAFLD).[1,2,3] Non alcoholic steato hepatitis (NASH) represent the aggressive subset of NAFLD that can progress to cirrhosis . Insulin is the key driver of metabolic homeostasis, particularly glucose flux across cell membrane – a phenomenon that have connotations for survival and evolution of the organism.[4,5] An impaired sensitivity to insulin action at the adipocyte level is a characteristic biological event in metabolic syndrome.[6,7] The associations of Insulin resistance(IR) with metabolic syndrome is nearly universal – so that the two often have interchangeable pathophysiological inferences, a classical example being type 2 diabetes and the other example is NAFLD/NASH.[8,9,10,11] IR through metabolic syndrome is the template that provide a point of convergence for linked clinical conditions - diabetes, obesity, dyslipidemia, hypertension and NAFLD/NASH. IR needs to be conceptualised not as a fixed cellular event – exerting an all or none effect like many biological processes, rather as a dynamic and regulated physiological response to a host of environmental factors and triggers including inflammation. IR possibly challenges energy homeostasis, nutrient availability and handling and connects metabolism with immune phenomenon. [12] There are different methods for measurement of IR, of which HOMA-IR is the simplest and the most widely used one in clinical and epidemiological studies.[13,14]

Ever since its' initial descriptions, NAFLD has been strongly correlated with obesity; body mass index (BMI) has been the most widely used marker of adiposity in clinical studies.[15,16] Large epidemiological studies on prevalence of fatty liver have also demonstrated this association , while other studies on the impact of BMI on health outcomes have upheld the connection between BMI , socio economic affluence and overall mortality in a population.[17,18,19] BMI has been an independent predictor of fat infiltration in the liver with increasing BMI being associated with increased prevalence of NASH in subjects with NAFLD.[20] Ethnic and racial differences in body composition suggest that Asians(Indians , more specifically): a) Have a lower BMI in general as compared to Caucasians yet , b) Have an increased percentage of body fat as well as a higher proportion of fat in the visceral fat(VF) compartments, c) Are predisposed to metabolic abnormalities and adverse health outcomes at a comparatively lower BMI. The signifcance of these observations is the shift of spotlight on waist circumference as a more meaningful and relevant measure of body composition.[21,22,23] It soon became evident that a subset of non overweight (BMI<25) individuals do have NAFLD along with metabolic syndrome related metabolic dysfunction including diabetes.[24,25,26] This entity, "lean" NAFLD, has subsequently been shown to be a distinct phenotype , described primarily amongst Asians – particularly Indians - although it has been reported from occidental populations subsequently.[27,28] Since fatty liver, NASH and even cirrhosis have been shown to occur with subtle anthropometric markers of obesity and a spectrum of metabolic

dysfunction similar to the classical, more well described obese phenotype – eye brows have been raised as to whether this so called "third world" phenotype is a regional curiosity or a distinct variant with biological plausibility and implications.[29] Insulin resistance (IR) as the critical cellular determinant of metabolic syndrome and NAFLD comes under scrutiny as a logical pathophysiological correlate in studies on pathogenesis of lean NASH .

In this issue of the journal, Bhat et al report a high prevalence (90%) of IR, measured by HOMA –IR, in Indian patients of non obese Indian NAFLD.[30] Non obese patients (BMI<23 – modified Asian Pacific criteria, Waist circumference <90 cm for males and <80 cm for females) constituted 15.3% of 150 consecutive NAFLD patients that were included in the study . More than 80% of the non obese (lean) NAFLD patients had IR and metabolic syndrome, while the grade of IR had a linear correlation with waist circumference, confirming the strong relationship of IR with central adiposity. The current study puts forth further evidence for existence of lean NAFLD as a well defined phenotype and reaffirms the data that have reported in large population based and as well as clinic based studies from India,East Asia and also western populations about the central role of IR in its pathogenesis. IR, therefore, brings pathogenetic homogeneity between obese and non obese NASH and as more evidence evolves about existence of subtle phenotypic differences between them, characterisation of different facets of biology of the variant phenotype becomes increasingly important.Such enquiry, however, needs to address some very pertinent questions before the mist clears and dust settles on lean NASH , which, despite the regional connotations in its initial description , is currently a significant global scientific curiosity .

The first issue concerns the principles of nomenclature within syndromes where clinical dissimilarities exist despite biological similarities. It is relevant to raise the question as to whether it is epistemologically correct to classify subsets within a disease based on observed anthropometric parameters – e.g BMI and waist circumference in NAFLD /NASH.[31] Such attempts are, however, commonplace in the evolution of nomenclature of defined entities in clinical sciences. Non A Non B hepatitis (NANB) hepatitis was the transitional coinage for long periods till Hepatitis C virus was cloned and demonstrated to be the elusive NANB agent. While IR unites the metabolic syndrome cluster and attempts to provide unify genesis , significant divergence exist amongst the constituent phenotypes in terms of strength of the association and biological principles. NAFLD and most importantly NASH, have already got an exclusionary component and fair amount of arbitrariness (amount of alcohol intake) in its current name. It may be argued that adding another prefix that again relies on a probabilistic rather than putative or demonstrated mechanistic association would be adding further confusion and imprecision in understanding the disease.We are yet to have a good biomarker for NASH ,although panels and individual markers (Cytokeratin18) have been shown to be promising.[32] Given the critical role that lipotoxicity and the inflammatory cells play in the pathogenesis of NASH , the nomenclature "Lipotoxic liver disease" holds lot of promise . Standardisation of biomarkers also mandates the need for a well defined criteria for the phenotype being sought. Till a uniformly acceptable pathophysiological and /or etiology based classification emerges – the term "lean NASH" would continue to provide us an opportunity to ponder and refine the matter.

Another crucial issue in defining lean NASH as an entity would be to consider the dynamic nature of fat depots in the body, the fact that currently metabolically obese normal weight (MONW) individuals might in fact be people who were overweight in the past and have lost weight, thereby retaining the propensity of metabolic ill health that obesity incurs. In the same line of evidence, mild weight gain even in the normal weight category (so called non obese) have been shown to alter fat flux in the liver and the reverse happens with weight loss.[33,34] Evidence in the current study that , even within the non obese range , a co-linearity exist between waist circumference and IR and also observations in previous population based studies of a similar association between BMI, metabolic abnormalities and NAFLD, raises the argument that lean NASH by itself is a transitional phenotype on the ascent to obese NAFLD as the environmental factors facilitate .

Variant or alternative phenotypes are biologically intriguing and provide an opportunity for studying pathogenesis, natural history and impact of evolving interventions , including determinants of outcome of the disease through this window. This is even more pertinent in understanding the dynamics of metabolic syndrome cluster of conditions.The homogeneous biological thread knitting together the diversities and sub diversities within seems to be IR. IR involves deviant and deficient insulin signalling in target tissues – most importantly liver, adipocytes and muscle cells. IR has been shown to be

associated with an indolent inflammatory state , termed meta-inflammation , dependent on adipose tissue macrophages (pro-inflammatory M1 versus classically quiescent M2) , T cells of different subsets including T regs infiltrating into the adipose tissue , cytokine and adipokine milieu – all of which are critical in the genesis of Insulin resistance that is peripheral to begin with [35,36] . Liver also participates in IR and accumulates fat as triglycerides. Gut microbiota processes nutrient derived signals, modifies the inflammatory process and can function strategic modulators of the evolution to NASH and less frequently cirrhosis.[37] It is important that each of these components are teased out in scientific studies with well defined lean NASH phenotype to make it a disease warranting specific attention. IR being the physiological event that preserved organisms in peril and now turns pathological during periods of relative abundance and affluence – may hold all clues to the effort .

References

1. Spalding K L, Arner E, Westermark P O, Bernard S, Buchholz B A , Bergmann O et al . Dynamics of fat cell turnover in humans. *Nature*. 2008:**453**;783–7 .
2. Fabbrini E, Sullivan S, Klein S. Obesity and nonalcoholic fatty liver disease: biochemical, metabolic, and clinical implications. *Hepatology*. 2010;**51**:679–89.
3. Marchesini G, Brizi M, Bianchi G, Tomassetti S, Bugianesi E, Lenzi M, et al. Nonalcoholic fatty liver disease: a feature of the metabolic syndrome. *Diabetes*. 2001;**50**:1844–50.
4. Saltiel AR, Kahn CR. Insulin signalling and the regulation of glucose and lipid metabolism. *Nature*. 2001;**414**:799–806.
5. Gökhan S. Hotamisligil. Inflammation and metabolic disorders . *Nature*.2006;**444**:860–7.
6. Korenblat KM, Fabbrini E, Mohammed BS, Klein S. Liver, muscle, and adipose tissue insulin action is directly related to intrahepatic triglyceride content in obese subjects. *Gastroenterology*. 2008;**134**:1369–75.
7. Hwang JH, Stein DT, Barzilai N, Cui MH, Tonelli J, Kishore P, et al. Increased intrahepatic triglyceride is associated with peripheral insulin resistance: in vivo MR imaging and spectroscopy studies. *Am J Physiol Endocrinol Metab*. 2007;**293**:E1663–9.
8. Marchesini G, Brizi M, Morselli-Labate AM, Bianchi G, Bugianesi E, McCullough AJ, et al. Association of nonalcoholic fatty liver disease with insulin resistance. *Am J Med*. 1999;**107**:450–5.
9. Marchesini G, Brizi M, Bianchi G, Tomassetti S, Bugianesi E, Lenzi M, et al. Nonalcoholic fatty liver disease: a feature of the metabolic syndrome. *Diabetes*. 2001;**50**:1844–50
10. Bugianesi E, Gastaldelli A, Vanni E, Gambino R, Cassader M, Baldi S, et al. Insulin resistance in non-diabetic patients with non-alcoholic fatty liver disease: sites and mechanisms. *Diabetologia*. 2005;**48**:634–42
11. Rajala MW, Scherer PE. Minireview: the adipocyte—at the crossroads of energy homeostasis, inflammation, and atherosclerosis. *Endocrinology*. 2003;**144**:3765–73.
12. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from plasma fasting glucose and insulin concentrations in man. *Diabetologia*. 1985;**28**:412–9.
13. Bonora E, Targher G, Alberiche M, Bonadonna RC, Saggiani F, Zenere MB, et al. Homeostasis model assessment closely mirrors the glucose clamp technique in the assessment of insulin sensitivity: studies in subjects with various degrees of glucose tolerance and insulin sensitivity. *Diabetes Care*. 2000;**23**:57–63.
14. Leevy CM. Fatty liver: a study of 270 patients with biopsy proven fatty liver and review of the literature. *Medicine (Baltimore)*. 1962;**41**:249–76
15. National Institutes of Health National Heart, Lung, and Blood Institute. Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults—the evidence report. *Obes Res*. 1998;**6**:51S–210S.
16. Everhart J E , Bambha K M . Fatty Liver: Think Globally. *Hepatology*. 2010;**51**:1491–3.
17. Whitlock G, Lewington S, Sherliker P, Clarke R, Emberson J, Halsey J, et al., Prospective Studies Collaboration. Body-mass index and cause-specific mortality in 900 000 adults: collaborative analyses of 57 prospective studies. *Lancet*. 2009;**373**:1083–96.
18. Dulloo A G , Jacquet J, Solinast G , Montani J-P and Schutz Y . Body composition phenotypes in pathways to obesity and the metabolic syndrome. *International Journal of Obesity*. 2010;34,S4–S17
19. Tilg H, Moschen AR. Insulin resistance, inflammation, and non-alcoholic fatty liver disease. *Trends Endocrinol Metab*. 2008;**19**:371–9
20. Deurenberg P, Van Stewveran W A. Body mass index and percent body fat: A meta analysis among different ethnic groups. *International Journal of Obesity*. 1998;**22**,1164–71.
21. Stommel M and Schoenborn C A . Variations in BMI and Prevalence of Health
22. Risks in Diverse Racial and Ethnic Populations. Obesity .2010;**18**:1821–6.
23. Petersen KF, Dufour S, Feng J, Befroy D, Dziura J,Mann C D. Increased prevalence of insulin resistance and non-alcoholic fatty liver disease in Asian-Indian men. *Proc Natl Acad Sci USA*.2006;**103**:18273–7
24. Park BJ, Kim YJ, Kim DH, Kim W, Jung YJ, Yoon JH, et al. Visceral adipose tissue area is an independent risk factor for hepatic steatosis. *J Gastroenterol Hepatol*. 2008;**23**:900–7
25. Kim H J , Kim H J , Lee K E , Kim D J , Kim S K , Ahn C W , Lim S-K et al . Metabolic Significance of Nonalcoholic Fatty Liver Disease in Nonobese, Nondiabetic Adults. *Arch Intern Med*. 2004;**164**:2169–75.
26. Conus F, Rabasa-Lhoret R , and Pe´ronnet F . Characteristics of metabolically obese normal weight (MONW) subjects. *Appl Physiol Nutr Metab*. 2007;**32**:4–12.
27. Das K, Mukherjee PS, Ghosh A, Ghosh S, Mridha AR, Dhibar T,

et al. Nonobese population in a developing country has a high prevalence of non-alcoholic fatty liver and significant liver disease. *Hepatology*. 2010;**51**:1593–602.

28. Francanzani AL, Valenti L, Bugianesi E, Vanni E, Miele L, Consonni D, et al. Risk of non alcoholic steatohepatitis and fibrosis in patients with non alcoholic fatty liver disease and low visceral adioposity. *J Hepatol*. 2011;**54**:1244–9.
29. Wood N . Non obese Individuals in the developing world are at risk of non alcoholic fatty liver and liver disease . *Nature Reviews in Gastroenterology and Hepatology*. 2010;**7**:357.
30. Bhat G, Sreenivasa Baba C, Pandey A, Neeraj Kumari, Choudhuri G. Insulin resistance and metabolic syndrome in non-obese Indian patients with Nonalcoholic fatty liver disease. *Tropical Gastroenterol*. 2013;
31. Oka R, Miura K, Sakurai M, Nakamura K, Yagi K, Miyamoto S, et al. Comparison of waist circumference with body mass index for predicting abdominal adipose tissue. *Diabetes Res Clin Pract.* 2009;**83**:100–5
32. Machado V Mariana, Cortez- Pinto H. Non-invasive diagnosis of non-alcoholic fatty liver disease. A critical appraisal. *Journal of Hepatol*. 2013;**58**:1007–19.
33. Chang Y, Ryu S, Sung E, Woo H-Y ,Cho S-I, Yoo S-H etal . Weight gain within the normal weight range predict ultrasonographically detected fatty liver in healthy Korean men. *Gut*. 2009;**58**:1419–25.
34. Tanaka S, Honda M, Wu B, Kazumi T. Clinical features of normal weight Japanese patients who have formerly been obese. *Journal of Atherosclerosis and Thrombosis*. 2011;**18**:115–21.
35. Lumeng C N , Saltiel C R . Inflammatory links between obesity and metabolic disease. *Journal of Clinical Investigations*. 2011;**121**:2111–7.
36. Feuerer M , Herrero L , Cipolletta D, Naaz A , Wong J ,Nayer A at al.Lean, but not obese, fat is enriched for a unique population of regulatory T cells that affect metabolic parameters. *Nature*. 2009;**8**:930–40.
37. Tremaroli V, Bäckhed F. Functional interactions between the gut microbiota and host metabolism. *Nature*.2012;**489**:242–9.