

Non-Obese South Asians with Diabetes: A Pathophysiological Conundrum

Misra A^{*1,2,3} and Anoop S^{1,2}

¹Centre of Nutrition & Metabolic Research (C-NET), National Diabetes, Obesity and Cholesterol Foundation (N-DOC), India

²Diabetes Foundation (India), India

³Fortis C-DOC Centre of Excellence for Diabetes, Metabolic Diseases and Endocrinology, India

***Corresponding author:** Anoop Misra, Chairman, Fortis C-DOC, Centre of Excellence for Diabetes, Metabolic Diseases and Endocrinology, B-16, Chirag Enclave, New Delhi-110048, India, Tel: +91-11-4277-6222 (Ext: 5030); E-mail: anoopmisra@gmail.com

Editorial

Volume 1 Issue 2

Received Date: August 26, 2016

Published Date: September 06, 2016

DOI: 10.23880/doi-16000124

Editorial

Type 2 diabetes mellitus (T2DM) is one of the leading causes of mortality and mortality in developing countries. Globally, a rising trend in type 2 diabetes, usually related to obesity, is being witnessed in young adults, including South Asians [1]. In South East Asia, nearly 1.2 million deaths were attributed to T2DM. The number of people (aged 20-79 years) with diabetes in this region is estimated to increase to 1.31 billion by 2040. With prevalence rate of 8.7% the pandemic of T2DM continues to rise in India [2]. Interestingly, nearly one third of urban Asian Indians with T2DM are non-obese [body mass index (BMI) <25 kg/m²] [3]. Importantly, a higher prevalence of pre-diabetes and a more rapid progression from pre-diabetes to diabetes has been reported in South Asians, presumably caused due to premature beta cell exhaustion, as compared to White Caucasians [4].

South Asians have excess body fat and low lean mass from early life, though body weight may be in normal range ("high body fat-normal weight/BMI-low lean mass") phenotype [5]. Specifically, as compared to White Caucasians, Asian Indians typically have increased subcutaneous abdominal adipose tissue (SCAT) and intra-abdominal adipose tissue (IAAT) [6]. Further, in addition to low muscle mass [7], extra deposition of fat in skeletal muscles (intra-myocellular triglycerides) has been shown in Asian Indians [8]. Finally, larger subcutaneous adipocytes, likely to be more insulin resistant, are seen in

South Asians as compared to white Caucasians [9]. In an obese person with body composition as mentioned above, insulin resistance leads to dysmetabolic state, resulting in diabetes.

In non-obese persons the pathophysiology for the development of diabetes is unclear. Interestingly, even 'non-obese' persons (BMI<25kg/m²) may have dysmetabolic state due to their body composition. Such person's often termed as 'metabolically obese normal weight' (similar phenotype as of Asian Indians), actually have higher proportion of body fat, located primarily at truncal-abdominal depots (truncal subcutaneous, pericardiac and intra-abdominal depots and the liver). Our observations on young non-obese Asian Indians with type 2 diabetes shows increased total abdominal fat (19.4%), total intra-abdominal fat (49.7%), intra-peritoneal fat (47.7%) and retroperitoneal fat (70.7%) as compared to BMI matched non-diabetic controls [10].

In such 'non obese' persons, excess accumulation of hepatic fat assumes importance. A strong relationship exists between hepatic steatosis and insulin resistance [11]. We have previously shown that non-obese, non-diabetic Asian Indians with Non-Alcoholic fatty liver (NAFLD) have deranged gluconeogenesis, as investigated using proton magnetic resonance spectroscopy [12]. Remarkably, Asian Indians have more than two fold

excess hepatic triglyceride content and lower insulin sensitivity as compared to Caucasian men [13]. Further, in a detailed MRI study, in non-obese Asian Indians with T2DM, we recently reported increased liver span (a surrogate marker of hepatic fat), correlated with increased intra-abdominal fat volume as compared to non-obese controls [10]. Overall, presence of NAFLD in a non-obese patient has important implications for development of type 2 diabetes.

A less investigated area is ectopic fat deposition in the pancreas ("fatty pancreas") and its association with insulin resistance, insulin secretion and diabetes. Three out of five MRI-based studies on pancreas, including ours [10] have reported increased pancreatic volume in patients with type 2 diabetes as compared to controls [14-16]. Specifically, we reported 26% higher pancreatic volume (a surrogate marker of fat deposition in pancreas) in young, non-obese, Asian Indians with type 2 diabetes as compared to BMI-matched non-diabetic controls. Further, increased pancreatic volume correlated with intra-abdominal fat and liver span in these patients [10].

Increased abdominal adiposity and large adipocyte size [9] in Asian Indians lead to increased release of non-esterified free fatty acids (NEFAs) as compared to Whites [17]. Importantly, NEFAs overload in islet cells of the pancreas leads to impaired beta cell response to hyperglycemia. Prolonged hyperglycemia and lipotoxicity may result in fatty deposit, fibrosis, and deranged functions of pancreatic islet cells; effects similar to steatonecrosis in the liver. It is noteworthy that fat infiltration in the pancreas may impair beta cell response to hyperglycemia [18]. Notably, Asian Indians with impaired glucose tolerance may have declining beta cell function, irrespective of age, adiposity, insulin sensitivity, or family history of diabetes [19,20], and infiltration of fatty tissue in pancreas could further contribute to it, or worsen it. This phenomenon has important clinical implications especially in the clinical management of diabetes in non-obese Asian Indians where both insulin resistance and insulin secretory defect should be kept in relationship at "fatty pancreas" with diabetes consideration while formulating management strategy.

No doubt there are other, most notably genetic factors, to consider. For instance, the association of the *TCFL 2* variants has been implicated in WNT signaling, secretion and pancreatic development [21] and many other need further research and consideration in pathogenesis of diabetes in non-obese Asian Indians with diabetes.

References

1. Chen L, Magliano DJ, Zimmet PZ (2011) The worldwide epidemiology of type 2 diabetes mellitus - present and future perspectives. *Nat Rev Endocrinol* 8: 228-236.
2. (2015) World Diabetes Atlas.
3. Vikram NK, Misra A, Pandey RM, Dudeja V, Sinha S, et al. (2003) Anthropometry and body composition in northern Asian Indian patients with type 2 diabetes: receiver operating characteristics (ROC) curve analysis of body mass index with percentage body fat as standard. *Diabetes Nutr Metab* 16(1): 32-40.
4. Sattar N, Gill JM (2015) Type 2 diabetes in migrant south Asians: mechanisms, mitigation, and management. *Lancet Diabetes Endocrinol* 3(12): 1004-1016.
5. Misra A (2003) Impact of ethnicity on body fat patterning in Asian Indians and Blacks: Relationship with insulin resistance. *Nutrition* 19: 815-816.
6. Misra A, Khurana L (2008) Obesity and the metabolic syndrome in developing countries. *J Clin Endocrinol Metab* 93(S11): S9-S30.
7. Bhatt SP, Nigam P, Misra A, Guleria R, Luthra K, et al. (2012) Association of the Myostatin gene with obesity, abdominal obesity and low lean body mass and in non-diabetic Asian Indians in north India. *PLoS One* 7(8): e40977.
8. Misra A, Sinha S, Kumar M, Jagannathan NR, Pandey RM (2003) Proton magnetic resonance spectroscopy study of soleus muscle in non-obese healthy and type 2 diabetic Asian Northern Indian males: high intra myocellular lipid content correlates with excess body fat and abdominal obesity. *Diabet Med* 20(5): 361-367.
9. Chandalia M, Lin P, Seenivasan T, Livingston, EH, Snell PG, et al. (2007) Insulin resistance and body fat distribution in South Asian men compared to Caucasian Men. *PLoS One* 2(8): e812.
10. Misra A, Anoop S, Gulati S, Mani K, Bhatt SP, et al. (2015) Body fat patterning, Hepatic fat and Pancreatic Volume of non-obese Asian Indians with Type 2 Diabetes in North India: A case-control Study. *PLoS One* 10(10): e0140447.

11. Misra A, Vikram (2003) Clinical and pathophysiological consequences of abdominal adiposity and abdominal adipose tissue depots. *Nutrition* 19(5): 457-466.
12. Dixon JB, Bhathal PS, OBrien PE (2001) Nonalcoholic fatty liver disease: predictors of nonalcoholic steatohepatitis and liver fibrosis in the severely obese. *Gastroenterol* 121(1): 91-100.
13. Petersen KF, Dufour S, Feng J, Befroy D, Dziura J, et al. (2006) Increased prevalence of insulin resistance and non- alcoholic fatty liver disease in Asian-Indian men. *Proc Natl Acad Sci* 103(48): 18273 -18277.
14. Burute N, Nisenbaum R, Jenkins DJ, Mirrahimi A, Anthwal S, et al. (2014) Pancreas volume measurement in patients with Type 2 diabetes using magnetic resonance based planimetry. *Pancreatol* 14(4): 268-274.
15. Lim S, Bae JH, Chun EJ, Kim SY, Kim KM, et al. (2014) Differences in pancreatic volume, fat content and fat density measured by multidetector-row computed tomography according to the duration of diabetes. *Acta Diabetol* 51(5): 739-748.
16. Saisho Y, Butler AE, Meier JJ, Monchamp T, Auerbach AM, et al. (2007) Pancreas volumes in humans from birth to age one hundred taking into account sex, obesity, and presence of type-2 diabetes. *Clin Anat* 20(8): 933-942.
17. Abate N, Garg A, Peshock RM, Gundersen JS, Grundy SM (1995) Relationships of generalized and regional adiposity to insulin sensitivity in men. *J Clin Invest* 96(1): 88-98.
18. Kim JW, Yoon KH (2011) Glucolipotoxicity in Pancreatic β -Cells. *Diabetes Metab J* 35(5): 444-450.
19. Staimez LR, Weber MB, Ranjani H, Ali MK, Echouffo-Tcheugui JB, et al (2013) Evidence of reduced β -cell function in Asian Indians with mild dysglycemia. *Diabetes Care* 36(9): 2772-2778.
20. Mohan V, Amutha A, Ranjani H, Unnikrishnan R, Datta M, et al. (2013) Associations of β cell function and insulin resistance with youth-onset type 2diabetes and prediabetes among Asian Indians. *Diabetes Technol Ther* 15(4): 315-322.
21. Smith U (2007) TCF7L2 and type 2 diabetes-we WNT to know. *Diabetologia* 50(1): 5-7.

