



# Adipocytokines and The Expanding 'Asian Indian Phenotype'

V Mohan, R Deepa

The prevalence of diabetes in India is growing rapidly and recent studies have documented a 72% increase in the prevalence of diabetes in urban areas in the last 15 years.<sup>1</sup> Indeed, the number of subjects with diabetes in India is expected to double from the current figures of about 40 million to nearly 80 million by 2030.<sup>2</sup> Increased ethnic susceptibility to diabetes in Indians was identified decades ago when migrant Indian studies showed higher prevalence rates in diabetes compared to virtually every other ethnic group studied.<sup>3</sup> It was further shown that Indians have evidence of hyperinsulinemia and greater degree of insulin resistance compared to their European counterparts.<sup>4,6</sup> Later studies showed some unique phenotypic features among Indians. While the overall prevalence of obesity was lower, Indians tend to have increased waist circumference compared to other ethnic groups.<sup>7</sup> This was attributed to increased visceral fat.<sup>8</sup> Even more interestingly, these features appear to be present from birth as Indian neonates tend to have increased body fat compared to their white Caucasian counterparts despite lower birth weights.<sup>9</sup> These unique features led to the coining of the term 'Asian Indian Phenotype'.<sup>10</sup>

It has been recently recognized that adipose tissue is not a mere depot for fat storage but is an active endocrine organ. Adipose tissue secretes various adipocytokines which includes adiponectin, leptin and resistin. These cytokines have been linked to metabolic abnormalities such as diabetes, dyslipidemia and insulin resistance all of which predispose to coronary artery disease.<sup>11</sup> Most of these adipocytokines (e.g. resistin, visfatin and TNF- $\alpha$ ) increase the risk for diabetes, while adiponectin is unique because it is known to be protective against diabetes. Adiponectin has many metabolic functions including regulation of energy homeostasis, decreasing plasma glucose, increasing clearance of glucose load, and decreasing insulin resistance.<sup>11</sup> With regard to resistin, there have been contradictory findings with recent studies suggesting it may be important in mice but not in humans.<sup>12</sup> Leptin plays a key role in the regulation of body weight as it links the adipose tissue to the central nervous system for the control of appetite and energy

expenditure.<sup>13</sup> In addition to adipocytokines, pro-inflammatory markers like tumour necrosis factor- $\alpha$  [TNF- $\alpha$ ] inhibit insulin signaling in human adipocytes,<sup>14</sup> enhance insulin resistance and increase the risk for diabetes. Recent reports show that Indians have low levels of adiponectin compared to their Caucasian counterparts.<sup>15</sup>

In this issue of JAPI, Lele and Joshi<sup>16</sup> report on interesting new information on the relation of adipocytokines with diabetes in urban western Indians. They show that adiponectin and leptin have a reciprocal association with diabetes. In a south Indian population, we showed that low adiponectin levels are associated with hypertriglyceridemia, low HDL cholesterol, insulin resistance and other components of the metabolic syndrome.<sup>17</sup> As low levels of adiponectin have been demonstrated in migrant Indians, one could speculate that this could be one of the mechanisms for the increased diabetic tendency observed in Indians. It is of interest that in the study by Lele and Joshi,<sup>16</sup> leptin had a positive association with obesity indices but a negative association with diabetes. This has been earlier documented in Caucasians.<sup>18</sup> It is possible that adipocytokines secreted from different fat depots may have differential effects on diabetes.

Another interesting observation in the study conducted by Lele and Joshi<sup>16</sup> is that proinsulin showed a positive association with diabetes and an inverse association with adiponectin. It is well known that compensatory hyperinsulinemia observed in pre-diabetic stage is followed by decreased insulin secretion. Indeed, at the time of clinical diagnosis of type 2 diabetes, only 50% of the beta cell function is present.<sup>19</sup> In this regard, the link between adiponectin and beta cell dysfunction shown in this study adds a new dimension to the pathophysiology of diabetes in Indians.

Recent studies have shown increased levels of inflammatory markers like C-reactive protein in Indians compared to Caucasians.<sup>20</sup> It was also shown that in south Indians inflammatory markers are linked to diabetes and this link is probably mediated through body fat.<sup>21</sup> Though hsCRP, an inflammatory predictor for diabetes is associated with diabetes, TNF- $\alpha$  failed to show an association with diabetes in the study by Lele and Joshi.<sup>16</sup> The Asian Indian Phenotype could perhaps

Madras Diabetes Research Foundation and Dr. Mohan's Diabetes Specialities Centre, Chennai, India.

be expanded further to include decreased adiponectin and increased hsCRP as possible additional components of this phenotype seen in Indians.

India is currently experiencing an increasing obesity epidemic. This is in contrast to the 1990's where the National Nutrition Monitoring Bureau documented the prevalence of obesity in Indian women to be 4.1%<sup>22</sup> and the National Family Health Survey (NFHS) reported obesity prevalence rates ranging between 3.5% to 4.1%.<sup>23</sup> Today, over 20% of men and 30% of women in urban areas have generalized obesity and nearly 40% of females have abdominal obesity.<sup>24</sup> It is further predicted that the prevalence of obesity in India would further increase by 89% in males and 82% in females between 2002 and 2010.<sup>25</sup>

As India is presently facing a double threat due to the obesity and diabetes epidemics, urgent measures are necessary to tackle the twin epidemics. Though both these diseases have a strong genetic background, lifestyle modification with increased physical activity, healthy eating habits and modest weight loss has been shown to prevent diabetes in several studies. However, the applicability and feasibility of these studies to the community at large needs to be studied. National policies need to be formulated to tackle the twin epidemics of diabetes and obesity before they grow out of hand.

## REFERENCES

- Mohan V, Deepa M, Deepa R, et al. Secular trends in the prevalence of diabetes and impaired glucose tolerance in urban South India-the Chennai Urban Rural Epidemiology Study (CURES-17). *Diabetologia* 2006;49:1175-78.
- Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes, estimates for the year 2000 and projections for 2030. *Diabetes Care* 2004;27:1047-53.
- Ramaiya KL, Kodali VRR, Alberti KGMM. Epidemiology of Diabetes in Asians of the Indian Sub-continent. *Intnl J Diab Dev Countries* 1991;2:15-36.
- Mohan V, Sharp PS, Cloke HR, Burrin JM, Schumer B, Kohner EM. Serum immunoreactive insulin responses to a glucose load in Asian Indian and European type 2 (non-insulin-dependent) diabetic patients and control subjects. *Diabetologia* 1986;29:235-37.
- Sharp PS, Mohan V, Levy JC, Mather HM, Kohner EM. Insulin resistance in patients of Asian Indian and European origin with non-insulin dependent diabetes. *Horm Metab Res* 1987;19:84-85.
- Misra A, Vikram NK. Insulin resistance syndrome (metabolic syndrome) and Asian Indians. *Current Science* 2002;83:1483-96.
- Ramachandran A, Snehalatha C, Viswanathan V, Viswanathan M, Haffner SM. Risk of noninsulin dependent diabetes mellitus conferred by obesity and central adiposity in different ethnic groups: a comparative analysis between Asian Indians, Mexican Americans and Whites. *Diabetes Res Clin Pract* 1997;36:121-25.
- Raji A, Seely EW, Arky RA, Simonson DC. Body fat distribution and insulin resistance in healthy Asian Indians and Caucasians. *J Clin Endocrinol Metab* 2001;86:5366-71.
- Yajnik CS, Fall CH, Coyaji KJ, et al. Neonatal anthropometry: the thin-fat Indian baby. The Pune Maternal Nutrition Study. *Int J Obes Relat Metab Disord* 2003;27:173-80.
- Joshi R. Metabolic syndrome - Emerging clusters of the Indian Phenotype. *J Assoc Physicians India* 2003;51:445-46.
- Scherer PE. Adipose tissue: from lipid storage compartment to endocrine organ. *Diabetes* 2006;55:1537-45.
- Arner P. Resistin: yet another adipokine tells us that men are not mice. *Diabetologia* 2005;48:2203-05.
- Friedman JM, Halaas JL. Leptin and the regulation of body weight in mammals. *Nature* 1998;395:763-70.
- Hotamisligil GS, Arner P, Caro JF, Atkinson RL, Spiegelman BM. Increased adipose tissue expression of tumor necrosis factor in human obesity and insulin resistance. *J Clin Invest* 1995;95:2409-15.
- Abate N, Chandalia M, Snell PG, Grundy SM. Adipose tissue metabolites and insulin resistance in nondiabetic Asian Indian men. *J Clin Endocrinol Metab* 2004;89:2750-55.
- Lele RD, Joshi SR, Gupte A. Association of adipocytokines, TNF alpha and proinsulin with diabetes - The Mumbai obesity project (MOP). *J Assoc Physicians India* 2006;54:689-96.
- Mohan V, Deepa R, Pradeepa R, et al. Association of low adiponectin levels with the metabolic syndrome - The Chennai Urban Rural Epidemiology Study (CURES - 4). *Metabolism* 2005;54:476-81.
- Liu J, Askari H, Dagogo-Jack S. Basal and stimulated plasma leptin in diabetic subjects. *Obes Res* 1999;7:537-44.
- UK Prospective Diabetes Study Group. UK Prospective Diabetes Study XII. Difference between Asian, Afrocaribbean and White Caucasian Type 2 diabetic patients at diagnosis of diabetes. *Diabet Med* 1994;11:670-77.
- Chambers JC, Eda S, Bassett P, et al. C-reactive protein, insulin resistance, central obesity, and coronary heart disease risk in Indian Asians from the United Kingdom compared with European whites. *Circulation* 2001;104:145-50.
- Mohan V, Deepa R, Velmurugan K, Premalatha G. Association of C-reactive Protein with body fat, diabetes and coronary artery disease in Asian Indians - The Chennai Urban Rural Epidemiology Study (CURES - 6). *Diabet Med* 2005;22:863-70.
- Naidu AN, Rao NP. Body mass index: a measure of the nutritional status in Indian populations. *Eur J Clin Nutr* 1994;48:S131-40.
- International Institute for Population Sciences and ORC Macro. National Family Health Survey India 1998/99. IIPS, Mumbai, India, 2000.
- Mohan V, Shanthirani S, Deepa R, Premalatha G, Sastry NG, Saroja R. Intra urban differences in the prevalence of the metabolic syndrome in southern India - The Chennai Urban Population Study (CUPS-4). *Diabet Med* 2001;18:280-87.
- Yach D, Stuckler D, Brownell KD. Epidemiologic and economic consequences of the global epidemics of obesity and diabetes. *Nat Med* 2006;12:62-66.