Insulin resistance syndrome (metabolic syndrome) and Asian Indians

Anoop Misra* and Naval K. Vikram

Department of Medicine, All India Institute of Medical Sciences, New Delhi 110 029, India

Diabetes mellitus and coronary heart disease are prevalent and predicted to increase sharply in Asian Indians. The data over the last decade suggest that insulin resistance is common in this ethnic group and operates as a 'common soil' for development of glucose intolerance and atherosclerosis. Obesity phenotype of Asian Indians; high percent body fat and higher truncal and abdominal fat at a lower lean body mass, may be important in generation of insulin resistance. The metabolic abnormalities significantly associated with insulin resistance in Asian Indians include dyslipidemia (hypertriglyceridemia, low levels of high-density lipoprotein cholesterol and high levels of small-dense low-density lipoprotein), procoagulant tendency, increased proinflammatory cytokines and endothelial dysfunction. Interestingly, such a phenotype and metabolic perturbations are particularly seen in immigrant Asian Indians and also in intra-country migrants from rural areas settled in urban slums. In comparative data including other ethnic groups, Asian Indians had significantly adverse body composition and metabolic profile. Even with the similar amount of body fat, Asian Indians are reported to be more insulin resistant as compared to Caucasians. These data suggest genetic factors in addition to lifestyle and other factors in inducing insulin resistance in Asian Indians. Some of these abnormalities are also evident at young age, particularly in children with low birth weight. Thus, clustering of cardiovascular risk factors and significant insulin resistance are prime factors for early, widespread and severe atherosclerosis in this ethnic group.

THE coexistence of obesity, glucose intolerance, dyslipidemia, and hypertension, is termed as insulin resistance syndrome (IRS, metabolic syndrome, Syndrome X). Gerald Reaven[1] initially proposed that resistance to insulin-mediated glucose disposal (and consequent hyperinsulinemia) is the pathophysiological interface for several complex metabolic alterations and diseases (Table 1). Interestingly, 13 years after its initial description, its scope and dimensions continue to evolve. The clinical presentation of IRS, however, may be dominated by one of its components. Further, some or all of the clinical and metabolic abnormalities may occur at any given time in an individual.

Clinically, insulin resistance should be suspected in the presence of abdominal obesity, hypertension, dyslipidemia (hypertriglyceridemia and low levels of high-density lipoprotein cholesterol [HDL-C]), family history of type 2 diabetes, and in individuals of certain ethnic groups (Hispanics, Asian Indians) particularly if they are obese. Clinical diagnosis of IRS can be made according to the recently proposed criteria by an Expert Panel of National Cholesterol Education Program (NCEP), Adult Treatment Panel III (Table 2)[2]. It is of note that the defining levels for waist circumference as given by the NCEP Expert Panel may not be applicable to Asian Indians.

Several laboratory investigations can be carried out to assess the magnitude of hyperinsulinemia and insulin resistance (Table 3). Hyperinsulinemic euglycemic insulin clamp technique is the reference method to assess insulin resistance. It is ideal for experimental purposes, but is expensive, lengthy and has poor acceptance among patients due to multiple blood sampling involved in the procedure. Other methods assess surrogate markers of insulin resistance, e.g. fasting hyperinsulinemia, ratio of fasting blood glucose and insulin levels, insulin area under the curve on glucose tolerance test and various ratios of insulin and glucose. These measures are simple to perform and often used in clinical and epidemiological studies.

Asian Indians are particularly predisposed to develop diabetes mellitus[3] and coronary heart disease (CHD)[4,5]. Several reports emphasize striking increase in their prevalence in the next two decades. This has brought IRS, which contributes significantly to the pathogenesis of diabetes mellitus and CHD, in particularly sharp focus as evidenced by a substantial increase in the number of published studies in this area. For example out of 41 studies (quoted in Tables 4 and 5), 31 have been published during the last five years. Researchers in USA and other countries are now academically sensitized to this research issue partly because of rapid growth of the Asian Indian immigrant community in these countries.

The pathophysiology of IRS has been reviewed elsewhere[6,7] and will not be discussed. In the following section we shall present evidence-based arguments in context of IRS and its components in Asian Indians. The literature search on the topic has been carried out using

*For correspondence. (e-mail: Anoop.Misra@UTsouthwestern.edu)

Table 1. Components of insulin resistance syndrome

Original description	Additions
Resistance to insulin-stimulated glucose uptake	Central obesity
Hyperinsulinemia	Microalbuminuria
Glucose intolerance	High levels of small dense low-density lipoprotein
Hypertension	Post-prandial lipemia
High levels of very low-density lipoprotein triglyceride	High levels of plasminogen activator inhibitor-1
Low levels of high-density lipoprotein cholesterol	Increased levels of proinsulin
	Hyperleptinemia
	Endothelial dysfunction
	Polycystic ovary syndrome
	Hyperactive sympathetic nervous system
	High intra-myocellular lipids[a]
	Hepatic steatosis (non-alcoholic)[a]
	Sub-clinical inflammation[a]
	Low levels of serum adiponectin[a]

[a]Possible additions as suggested by the evolving evidence.

Table 2. Clinical identification of metabolic syndrome[a] (insulin resistance syndrome). See ref. 2

Risk factor	Defining level
Abdominal obesity	Waist circumference
• Males	> 102 cm (> 40 inches)
• Females	> 88 cm (> 35 inches)
Serum triglycerides	≥ 150 mg/dl
High-density lipoprotein cholesterol	
• Males	< 40 mg/dl
• Females	< 50 mg/dl
Blood pressure	≥ 130/≥ 85 mm Hg
Fasting blood glucose	≥ 110 mg/dl

[a]The preferred name by the Expert Panel (ATPIII)[2].

Table 3. Laboratory methods for the assessment of insulin sensitivity

Hyperinsulinemic euglycemic clamp technique (gold standard)
Fasting insulin levels and insulin/glucose ratio; homeostatic model assessment (HOMA)
Insulin values or area under the curve during oral glucose tolerance test
Intravenous glucose tolerance test (IVGTT), minimal model analysis
Constant infusion of glucose with model assessment (CIGMA)

the terms 'Insulin resistance or hyperinsulinemia in Asian Indians or South Asians' in the medical search databases *Medline*, *Pubmed* and *Current Contents*, in addition to the manual search of the quoted references from the published articles.

Hyperinsulinemia and insulin resistance: Clinical studies

Hyperinsulinemia, both fasting and post-glucose load is reported more frequently in healthy immigrant Asian Indians[8–13] and in Indians in India[14]. This may result in earlier onset of glucose intolerance[15]. Overall, the prevalence of insulin resistance in Asian Indians (~ 5–50%) is reported to be highly variable (Tables 4 and 5). This could be due to different methodologies employed by various scientists for the assessment of insulin resistance. Moreover, tremendous heterogeneity of Asian Indians in terms of their geographical location and partial adaptation of lifestyle of the country of residence, in addition to variations due to age, gender, and socio-economic strata may also contribute. Important and consistent observations related to high prevalence of insulin resistance in Asian Indians are, however, presence of excess body fat and abdominal obesity.

Obesity and body fat distribution

Obesity is the most important factor associated with insulin resistance. Increase of ~ 1/3rd over ideal body weight decreases insulin sensitivity by 40% (ref. 16). It is important to note that all obese individuals are not insulin resistant. Obesity is frequently associated with insulin resistance in Asian Indians settled in other countries[17–19], and in India[20,21].

Asian Indian obesity phenotype

The typical obesity phenotype observed in Asian Indians (Table 6) consists of higher percentage of body fat at a lower value of body mass index (BMI), high waist–hip ratio (W–HR) at a relatively low waist circumference and less lean body mass as compared to Caucasians[22,23] and other Asian ethnic groups[24]. Asian Indians in UK[8] and USA[22] were reported to have higher values of BMI and W–HR and thicker skinfolds[8] as compared to urban subjects in India[20,23] (Figure 1 *a*, *b*). Though the values of BMI in immigrant Asian Indians were comparable to those of Caucasians (Figure 1 *a*), values of

Table 4. Measures of insulin resistance in Asian Indians (living in India)

Author and ref. no.	Study group	*N*	Geographic location	Type of study	Measure of IR	Observations	Other associations with IR
Ramachandran *et al.*[117]	Non-diabetic men and women	144	Chennai, Southern India	Cross-sectional	Immunoreactive insulin levels	No significant correlation between leptin and insulin	
Snehalatha *et al.*[118]	Non-diabetic subjects Men Women	 21 19	Chennai, Southern India	Cross-sectional	FI levels	VF correlated with insulin secretion in men	
Malhotra *et al.*[119]	HTN Controls[a]	68 140	Chandigarh, Northern India	Cross-sectional	FI levels and OGTT	↑ FI (32.3% subjects) and post glucose load insulin (70.6% subjects) associated with HTN	↑BMI, ↑W-HR with HTN, clustering of risk factors
Misra *et al.*[46]	ISH HTN Controls	15 15 14	New Delhi, Northern India	Case-control	OGTT[b], AUC insulin	↑ levels of insulin at 60 min and↑ AUC in ISH and HTN than in controls	
Ramachandran *et al.*[120]	Offspring of DM patients NGT IGT DM Controls	 20 20 20 20	Chennai, Southern India	Cross-sectional	FI, 120 min insulin, and proinsulin levels, HOMA IR	IR ↑ from NGT to DM, insulin and proinsulin at 120 min ↑ from NGT to IGT and ↓ with development of DM	
Ramachandran *et al.*[82]	Men and Women[c]	953	Chennai, South India	Cross-sectional population survey	FI and 120 min insulin levels	~ 55% age-adjusted prevalence of high 2 h insulin levels	Clustering of risk factors, central obesity highest
Marita *et al.*[47]	HTN Non-HTN	38 26	Mumbai, Western India	Case-control	Insulin response to oral glucose, AUC glucose/ AUC insulin ratio	insulin r esponse in HTN with ECG changes, AUC glucose/AUC insulin ratio in subjects with abnormal ECG	50% reduction in insulin receptor number in HTN patients as compared to non-HTN controls[d]
Misra *et al.*[49]	Healthy offspring of; HTN parents Non-HTN parents	 38 18	New Delhi, Northern India	Case-control	OGTT[b]	↑ FI and 2 h post-glucose load insulin levels in the healthy offspring of HTN parents	
Marita *et al.*[121]	HTN (OB&NOB) Non-HTN (OB&NOB)	28 28	Mumbai, Western India	Case-control	OGTT[e], HOMA IR, AUC insulin	↑ Basal and post OGTT[f] insulin in OB non-HTN and ↑ basal insulin in OB HTN	
Snehalatha *et al.*[14]	Non-diabetic	260	Chennai, Southern India	Cross-sectional	OGTT, HOMA IR, IGI	↑ IR in OB IGT, ↓ IGI with increase in glucose intolerance	
Bavdekar *et al.*[78]	8-y-old children	477	Pune, Western India	Prospective	FI and 32–33 PI, 30-min post glucose insulin levels, HOMA	values of all parameters, calculated IR associated with LBW	levels of IRS variables in BF with LBW children
Snehalatha *et al.*[122]	Non-diabetic subjects	654	Chennai, Southern India	Cross-sectional	OGTT, HOMA IR	↑ FI in 53.6% (F), 37% (M); ↑ 2-h insulin in 71.6% (F), 51% (M), IR in 11.1% (M), 13.6% (F)	BMI (+), 2-h glucose (+), DBP (+)

(*Continued*)

Table 4. (*Continued*)

Author and ref. no.	Study group	*N*	Geographic location	Type of study	Measure of IR	Observations	Other associations with IR
Mohan *et al.*[83]	Middle and low-income groups	479 783	Chennai, Southern India	Cross-sectional	FI levels	FI levels in middle income group	High prevalence of other components of IRS in middle income group
Snehalatha *et al.*[123]	Non-diabetic subjects[g] NGT IGT	 48 51	Chennai, Southern India	Cross-sectional	HOMA IR	HOMA IR in IGT	IMT not associated with IR
Misra A. *et al.*[20]	Women residing in urban slums	80	New Delhi, Northern India	Cross-sectional	HOMA IR	High HOMA IR in 22.5%, High FI levels in 26%	%BF (+), FI levels higher in presence of at least one risk factor
Deepa *et al.*[84]	Subjects from upper and low SES	107 0	Chennai, South India	Cross-sectional	HOMA IR	IR 18.7% in high SES, 6.6% in low SES	Age (+), BMI (+), SES (+)

[a]58 genetically related members of hypertensives also included as controls; [b]Insulin levels assessed at 0, 30, 60, 90 and 120 min; [c]Aged 40 years; [d]Measured by I (125) binding to erythrocytes; [e]Insulin levels assessed at 0, 30, 60 and 120 min; [f]Value at 60 min;, [g]Subjects with NGT and IGT matched for BMI and W–HR. +, Positive association; AUC, area under curve; BF, body fat; BMI, body mass index; DBP, diastolic blood pressure; DM, diabetes mellitus; ECG, electrocardiogram; F, females; FI, fasting insulin; HOMA IR, homeostatic model analysis of insulin resistance; HTN, hypertension; IGT, impaired glucose tolerance; IGI, insulinogenic index; IMT, intima media thickness; IR, insulin resistance; IRS, insulin resistance syndrome; ISH, isolated systolic hypertension; LBW, low birth weight; M, males; NGT, normal glucose tolerance; NOB, non-obese; OB, obese; OGTT, oral glucose tolerance test; PI, proinsulin; SES, socioeconomic status; VF, visceral fat; W–HR, waist–hip ratio.

W–HR were higher (Figure 1 *b*), even when compared to other Asian ethnic groups[25]. Similarly, Asian Indian men had significantly thicker truncal skinfolds as compared to Caucasians[17].

High body fat, often at BMI values that are in non-obese range is another characteristic phenotypic feature of Asian Indians, reported by several groups, including Banerji *et al.*[22] in Asian Indians in USA (mean BMI, 24.5 kg/m^2, body fat ~ 33%) and by Dudeja *et al.*[23] in Asian Indians in India (mean BMI 23.3 kg/m^2, body fat ~ 35%). Similarly, non-obese hyperlipidemic Asian Indians had excess body fat and high W–HR (ref. 26). Some data indicate that intra-abdominal fat is more in Asian Indians as compared to other ethnic groups[22,27] which may contribute to increased insulin resistance[28,29]. Further, less muscle mass, particularly in the regions of hips and lower limbs has been reported[30]. Increased body fat and decreased lean body mass approximately compensate each other not allowing appreciable increase in the value of BMI. This may be an important reason why BMI does not reflect adiposity accurately in Asian Indians. Such BMI-defined non-obese individuals may have adverse metabolic effects of excess adiposity.

Insulin resistance in non-obese subjects

Not all insulin-resistant subjects are overweight or obese. Non-obese subjects (as defined by BMI) may be 'metabolically obese' having insulin resistance and dyslipidemia. The common denominator of metabolic abnormalities appears to be high body fat[31]. According to Banerji *et al.*[22], 66% of non-obese immigrant Asian Indian males had high body fat and were insulin resistant. Contribution of other factors in the development of IRS in non-obese subjects is not clear. For example, intramyocellular lipids (IMCL) that are pathophysiologically correlated to insulin resistance[32], may be high in non-obese Asian Indians[33], however significance of the observations are not known. It is interesting to speculate that insulin resistance may be at the level of skeletal muscles that are structurally and physiologically altered by poor nutrition in non-obese Asian Indians but it remains to be investigated. Yet another plausible hypothesis is that Asian Indians may have a primary genetic susceptibility to develop IRS. Chandalia *et al.*[17] showed that Asian Indian men had higher insulin resistance than Caucasian men independently of generalized or truncal obesity indicating a *de novo* insulin resistance.

Dyslipidemia and insulin resistance

Abnormalities of lipolysis and free fatty acid turnover, triglyceride metabolism and secretion are characteristic of insulin resistance. The association of hyperinsulinemia with hypertriglyceridemia and low levels of HDL-C is well known[34]. This combination of lipid abnormalities is

Table 5. Measures of insulin resistance in Asian Indians (residing in other countries)

Author and ref. no.	Study group	*N*	Geographic location	Type of study	Measure of IR	Observations	Other associations with IR
Mohan *et al.*[10]	AIs[a] Europeans[a]	45 72	London, UK	Case-control	OGTT	basal insulin levels and total insulin r esponse in non-diabetic and diabetic AIs than Europeans	BMI and race predicted insulin response
Dowse *et al.*[12]	AIs Creoles Chinese	2741 1160 377	Mauritius	Cross-sectional	FPG and FI levels	Highest â-cell function in Indians, IR with glucose intolerance	BMI (+), W–HR (+), physical inactivity (+), female gender (+)
McKeigue *et al.*[8]	South Asians[b] Europeans Afro-Caribbeans	1761 1712 209	London, UK	Cross-sectional	OGTT	FI and post -glucose insulin levels in AIs as compared to Europeans	W–HR (+)
McKeigue *et al.*[9]	South Asians[b] Europeans	1712 1716	London, UK	Cross-sectional	OGTT	Variation in 2-h insulin levels more with W–HR than BMI in AIs	
Simmons *et al.*[15]	South Asians Europeans	4395 5328	Coventry, UK	Cross-sectional	OGTT, Insulin levels	FI and 2-h insulin levels in South Asia ns at all ages[c]	Earlier onset of diabetes in South Asians
Zimmet *et al.*[124]	Asian Indians Creoles Chinese	3214 1306 409	Mauritius	Cross-sectional	OGTT, FI and 2-h insulin - levels	FI and 2 -h insulin levels correlated with generalized and upper-body obesity	Insulin levels higher in presence of risk factors
Sevak *et al.*[125]	South Asians[b] European men	92 81	London, UK	Cross-sectional	FI and 2-h post glucose insulin levels	FI and 2 -h insulin levels positively associated with carbohydrate intake	mean energy and total fat intake and starch, PUFA and fiber intake in South Asians
Laws *et al.*[19]	AIs Europeans	22 22	California, USA	Case-control	Insulin suppression test, OGTT	glucose and insulin responses to OGTT, 60% higher steady-state plasma glucose levels during insulin suppression test in AIs	TG and HDL levels in AIs, plasma FFAs and glycerol in response to mixed meals in AI women
Berger *et al.*[81]	Healthy AI women Premenopausal Postmenopausal	 102 75	Durban, South Africa	Cross-sectional	FI levels	Markedly FI levels in postmenopausal women	Menopause, W–HR, apo E genotype, and testosterone/SHBG ratio independent predictors of insulin levels
Hodge *et al.*[126]	AIs Creoles Chinese	4394 1746 425	Mauritius	Cross-sectional	FI, 1-h, and 2-h post glucose insulin levels	Insulin levels not consistently highest in AIs	W –HR with lesser BMI and HDL levels in AIs
Chowdhary *et al.*[30]	AI men Swedish men	10 10	Goteborg, Sweden	Case-control	FI levels	80% higher insulin AUC in AIs with similar glucose AUC	VAT/TAT volume ratio (+) in AIs
Hughes *et al.*[25]	AIs Malays Chinese	284 240 294	Singapore	Cross-sectional	FI levels	FI levels and glucose intolerance in Indians	BMI (+), W–HR (+), abdominal diameter (+), TG (+), PAI-1 (+), tPA (+), HDL (–)

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Table 5. (*Continued*)

Author and ref. no.	Study group	*N*	Geographic location	Type of study	Measure of IR	Observations	Other associations with IR
Banerji *et al.*[22]	Healthy AI men	20	New York, USA	Cross-sectional	HEC	IR in 66% of NOB subjects	Inverse correlation with VAT, TG (+), HDL (+)
Chandalia *et al.*[17]	Healthy AIs[d] Caucasians[d]	21 23	Dallas, USA	Cross-sectional	HEC	↓ Rd in AIs even after adjustment for BF	ISI(–) with BF and truncal skinfolds
Forouhi *et al.*[63]	Non-diabetic men South Asians[b] Europeans	 20 20	London, UK	Cross-sectional	SITT	Lower insulin sensitivity in South Asians	South Asians had higher IMCL not correlated to insulin sensitivity
Kulkarni *et al.*[40]	AIs Caucasians (matched)	39 39	Alabama USA	Cross-sectional	FI levels	FI levels similar in two groups, small dense LDL more in AIs	FI levels higher in those with high levels of small-dense LDL
Tai *et al.*[13]	AIs[e] Chinese[e] Malays[e]	439 1791 508	Singapore	Cross-sectional	OGTT, HOMA IR	↑ IR in AI	IGT (+), DM (+), BP (+)[f], TC (+), LDL (+), TG (+), HDL (–), LDL/apo B ratio (–)
Zoratti *et al.*[41]	Healthy men South Asians Afro-Caribbeans Europeans	 31 30 31	London, UK	Cross-sectional		Similar insulin resistance in South Asians and Afro-Caribbeans but higher than Europeans. AIs had less favourable lipid profile	
Raji *et al.*[27]	Healthy AIs[g] Caucasians[g]	12 12	Massachusetts, USA	Cross-sectional	OGTT, HEC	FI levels, glucose and insulin levels during OGTT, Rd	Fat mass and PAI-1 levels inversely correlated with Rd in AI
Forouhi *et al.*[127]	Healthy South Asians[b] Europeans	 56 57	London, UK	Cross-sectional	Insulin levels during OGTT	CRP levels significantly associated with FI and 2-h insulin	W–HR and visceral fat area strongly associated with CRP in South Asians
Kalhan *et al.*[43]	Offspring of immigrant South Asians[h] Europeans[h]	 32 29	Cleveland, USA	Cross-sectional	FI levels	↑ FI in South Asians as compared to Europeans	Plasma leptin levels significantly correlated with insulin levels
Cruz *et al.*[42]	South Asians[i] Northern Europeans[i] Latin Americans[i]	8 9 8	Oxford, UK	Cross-sectional	FI and post high-fat meal insulin levels[j], SITT	postprandial glucose AUC (0–120 min), AUC log insulin in South Asians, ability of exogenous insulin to lower blood glucose in South Asians	% BF responsible for variation in insulin sensitivity in South Asians
Kain *et al.*[101]	Relatives of South Asians with ischemic stroke South Asian controls	143 146	West Yorkshire, UK	Case-control	FI, HOMA IR	FI and HOMA IR in relatives of stroke patients	BMI (+), HDL (+), TG (+), tPA (+), SBP (+)[k], W–HR (+)[j], DBP (+)[l]
Kain *et al.*[100]	South Asians with ischemic stroke South Asians without history of stroke	80 80	Bradford, UK	Case-control	HOMA IR	Insulin levels similar in both groups but IR in stroke patients	

(*Continued*)

Table 5. (*Continued*)

Author and ref. no.	Study group	*N*	Geographic location	Type of study	Measure of IR	Observations	Other associations with IR
Whincup *et al.*[55]	Children[m] AIs[b] British	 73 1287	London, UK	Cross-sectional	FI and post glucose insulin levels	Mean insulin levels higher in AI children	Mean heart rate, and levels of TG, and fibrinogen higher in AI children

[a]All groups were control matched; [b]People of heterogenous ethnicities (e.g. from India, Pakistan, Bangladesh and Sri Lanka); [c]Fasting insulin values available in 322 Europeans and 298 South Asians, 2 h insulin values available in 286 Europeans and 300 South Asians; [d]Matched for age and body fat; [e]Only subjects with normal glucose tolerance included; [f]In women; [g]Matched for age and body mass index; [h]Age 18–32 y, [i]Age 22–40 y; [j]Values at 20, 40, 60, 90, 120, 180, 240, 300, 360, 420 and 480 min; [k]Only in relatives of stroke patients; [l]Only in South Asian controls, [m]8–11 years of age. AI, Asian Indians; apo B, apolipoprotein B; apo E, apolipoprotein E; AUC, area under curve; BF, body fat; BMI, body mass index; BP, blood pressure; CRP, C-reactive protein; DBP, diastolic blood pressure; DM, diabetes mellitus; FFA, free fatty acids; FI, fasting insulin; FPG, fasting plasma glucose; HDL, high-density lipoprotein cholesterol; HEC, hyperinsulinemic-euglycemic clamp; HOMA IR, homeostatic model analysis of insulin resistance; IMCL, Intramyocellular lipids; IR, insulin resistance; ISI, insulin sensitivity index; LDL, low-density lipoprotein cholesterol; NOB, non-obese; OGTT, oral glucose tolerance test; PAI-1, plasminogen activator inhibitor-1; PUFA, polyunsaturated fatty acid; Rd, glucose disposal rate; SBP, systolic blood pressure; SHBG, sex-hormone binding globulin; SITT, short insulin tolerance test; TAT, total adipose tissue, TC, total cholesterol; TG, triglycerides; tPA, tissue plasminogen activator; VAT, visceral adipose tissue; W–HR, waist–hip ratio.

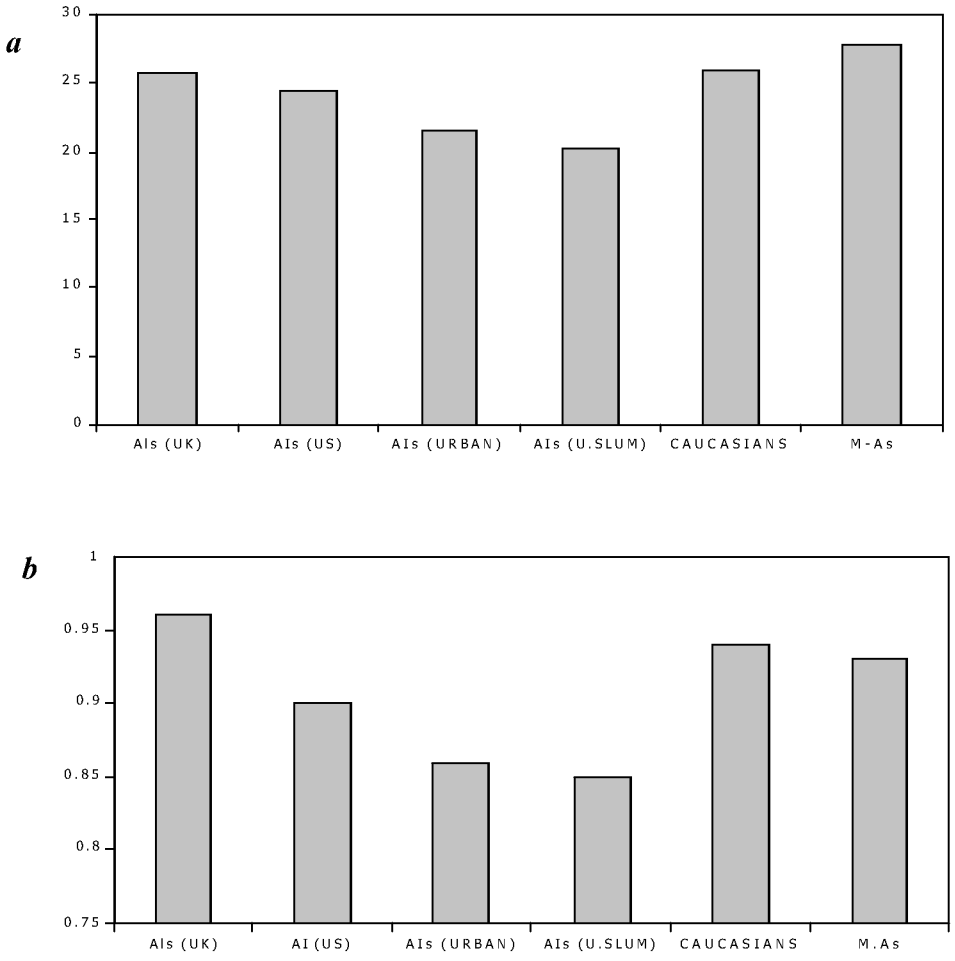

Figure 1. Comparisons of anthropometric profiles of Asian Indians in different geographical locations vs ethnic groups. ***a***, Body mass index; ***b***, Waist-to-hip ratio. AIs, Asian Indians; U. Slum, urban slum; MAs, Mexican Americans; AIs (UK), McKeigue *et al.*[8]; AIs (US), Chandalia *et al.*[17]; AIs (Urban), Dudeja *et al.*[23]; AIs (U. Slum), Misra *et al.*[35]; Caucasians, McKeigue *et al.*[8]; MAs, Haffner *et al.*[134].

the most important manifestation of IRS. The typical lipid profile in Asian Indians is characterized by hypertriglyceridemia, low levels of HDL-C, and high levels of small-dense low-density lipoprotein (LDL)[4,20,35–37]. Such lipoprotein abnormalities, characteristic of insulin resistance and considered to be conducive to atherogenesis, are termed as 'atherogenic dyslipidemia'[38]. Small-dense LDL associated with insulin resistance is considered as a stronger risk factor for CHD than large LDL (ref. 39) and reported to be high in insulin-resistant Asian Indians[40]. Lipoprotein abnormalities with insulin resistance are commonly reported in immigrant Indians[41,42] and their young offspring[43].

Insulin resistance and hypertension

Hypertension is one of the defining diseases for IRS when described initially. A strong relationship of fasting hyperinsulinemia and hypertension was shown in a meta-analysis[44]. Insulin resistance in hypertension has been reported from western India[45] and northern India[46], and may occur irrespective of obesity[47] and associated with asymptomatic CHD. Hyperinsulinemia was also demonstrable in isolated systolic hypertension[46] now known to be a strong predictor of cardiovascular mortality[48]. Early onset of hyperinsulinemia and its familial occurrence was shown in young non-obese offspring of hypertensive parents[49].

However, not all recent reports support the strong relationship of insulin resistance and hypertension[50,51]. It is generally believed that ~ 50% of the hypertensive individuals may have insulin resistance.

Evidence-based arguments for other IRS-associated factors

These arguments for IRS-associated factors in Asian Indians (Table 7) are as follows:

1. Procoagulant tendency due to increased thrombotic factors and/or less of fibrinolytic factors correlate to cardiovascular events. Levels of plasminogen activator inhibitor-1 (PAI-1) are known to be increased in hyperinsulinemia[52]. Higher levels of PAI-1 were recorded in Asian Indians in Singapore[25] and South Asians in UK[53] as compared to other ethnic groups and correlated to fasting insulin levels[25]. High PAI-1 activity was also observed in non-diabetic hypertriglyceridemic patients having obesity and hyperinsulinemia[54]. Higher fibrinogen levels were recorded in Asian Indian women in Singapore[25], in South Asian subjects in UK[53], and in South Asian children[55] and the levels were significantly more than the subjects of other ethnic groups.
2. Cytokines secreted by the adipose tissue may also contribute to insulin resistance. Tumour necrosis factor (TNF)-α, a pro-inflammatory cytokine, adversely affects glucose homeostasis and β-cell function by disrupting insulin-signaling pathways[56]. A preliminary communication reported high levels of TNF-α and interleukin-6 in urban slum dwellers from western India[57]. Importance of these observations and their relationship to insulin resistance for Asian Indians is not known.
3. IRS is associated with endothelial dysfunction, as indicated and measured by upregulation of cellular adhesion molecules[58] and inability of medium-size arteries to dilate in response to physiological and pharmacological stimuli[59]. Recently high levels of soluble inter-cellular adhesion molecule-1 (sICAM-1) were reported in Asian Indians in India belonging to poor socioeconomic strata having one or more cardiovascular risk factor(s)[60] (Figure 2). Interestingly, healthy subjects also had equally high levels of sICAM-1 (ref. 60). These observations suggested widespread endothelial dysfunction but its cause remains to be investigated. Flow-mediated, endothelium-dependent dilatation of brachial artery was also reported to be reduced more in insulin resistant Asian Indians as compared to Europeans[61].

Table 6. The Asian Indian obesity phenotype

Higher body fat with relatively less body BMI
Less lean body mass[a]
High BF/BMI ratio[b]
High waist–hip ratio[c]
Variable subscapular/triceps ratio
High intramyocellular lipids[d]

[a]Particularly in lower limbs; [b]Higher body fat per unit BMI; [c]Absolute value of waist circumference may not be excessive; [d]Insufficient evidence.

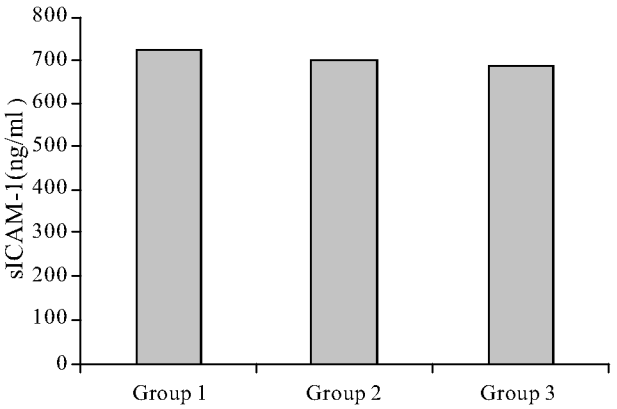

Figure 2. Serum soluble inter-cellular adhesion molecule-1 (sICAM-1) levels in people belonging to low socio-economic strata residing in urban slums of New Delhi. Group 1, Subjects from urban slums having at least one risk factor for coronary heart disease; Group-2, Non-diabetic, normolipidemic and normotensive subjects from urban slums; Group 3, Non-diabetic, normolipidemic and normotensive subjects from urban non-slum areas (healthy medical students). Adapted from Sethi *et al.*[60].

Table 7. Insulin resistance and related disorders in Asian Indians: Evidence from published literature

Insulin resistance and related disorders	Author and reference no.
Insulin resistance	
(a) Resistance to insulin-mediated glucose uptake using hyperinsulinemic euglycemic clamp	Sharp *et al.*[128], Kooner *et al.*[92], Banerji *et al.*[22], Chandalia *et al.*[17], Raji *et al.*[27]
(b) Hyperinsulinemia and other surrogate measures of insulin resistance	
(i) Adults	Mohan *et al.*[10], Dowse *et al.*[12], Mckeigue *et al.*[8], McKeigue *et al.*[9], Dhawan *et al.*[18], Hughes *et al.*[25], Ramachandran *et al.*[117], Snehalatha *et al.*[118], Misra *et al.*[46], Ramachandran *et al.*[82,120], Misra *et al.*[97], Marita *et al.*[121], Snehalatha *et al.*[14], Forouhi *et al.*[63], Misra *et al.*[95], Snehalatha *et al.*[122], Mohan *et al.*[83], Snehalatha *et al.*[123], Misra *et al.*[20], Deepa *et al.*[84]
(ii) Children	Misra *et al.*[49], Whincup *et al.*[55]
(c) Increased levels of proinsulin	Ramachandran *et al.*[120]
Dyslipidemia	
(a) High levels of TG and low levels of HDL-C	Laws *et al.*[19], Hodge *et al.*[126], Banerji *et al.*[22], Tai *et al.*[13], Misra *et al.*[35], Misra *et al.*[20]
(b) Isolated low levels of HDL-C	Tai *et al.*[13]
(c) Increased levels of small-dense low-density lipoprotein	Kulkarni *et al.*[40]
Glucose intolerance	Dowse *et al.*[12], Hughes *et al.*[25], Ramachandran *et al.*[120], Snehalatha *et al.*[14], Misra *et al.*[97], Tai *et al.*[13], Misra *et al.*[35], Misra *et al.*[20]
Hypertension	Malhotra *et al.*[119], Misra *et al.*[46,49], Marita *et al.*[47], Marita *et al.*[121]
Central obesity and abnormal fat distribution	
(a) High W–HR or WC	Dowse *et al.*[12], McKeigue *et al.*[8], Hodge *et al.*[126], Hughes *et al.*[25], Misra *et al.*[35], Misra *et al.*[20]
(b) Increased truncal fat[a]	Chandalia *et al.*[17]
(c) High abdominal fat and visceral fat[b]	Raji *et al.*[27]
(d) High body fat at relatively lower BMI	Forouhi *et al.*[63], Banerji *et al.*[22], Yap *et al.*[24], Dudeja *et al.*[23], Misra *et al.*[35], Vikram *et al.*[129], Misra *et al.*[20]
Microalbuminuria	No studies
Impaired suppression of non-esterified fatty acids	Kooner *et al.*[c,92], Frost *et al.*[93]
Increased procoagulant factors	
(a) High plasminogen activator inhibitor-1 levels	Hughes *et al.*[25], Sarkar *et al.*[54], Kain *et al.*[101]
(b) High fibrinogen levels	Kain *et al.*[101], Whincup *et al.*[d,55], Kain *et al.*[100]
Hyperleptinemia	Ramachandran *et al.*[117], Misra *et al.*[130]
Endothelial dysfunction	
(a) Flow-mediated endothelium dependent dilatation	Chambers *et al.*[e,61], Caballero *et al.*[59]
(b) High levels of inter-cellular adhesion molecule-1	Sethi *et al.*[60]
Low birth weight	Yajnik *et al.*[131], Fall *et al.*[132], Bavdekar *et al.*[78], Yajnik *et al.*[133]
Inflammatory markers and proinflammatory cytokines	
(a) High C-reactive protein levels	Chambers *et al.*[e,64]
(b) High levels of tumour necrosis factor-*á* and interleukin-6	Yudkin *et al.*[57]
High intramyocellular lipids	Forouhi *et al.*[63], Sinha *et al.*[33]
Hepatic steatosis (non-alcoholic)	No studies
Increased (basal) heart rate	Whinecup *et al.*[d,55]
Clustering of risk factors	Ramachandran *et al.*[82], Malhotra *et al.*[119], Mohan *et al.*[83], Misra *et al.*[20], Deepa *et al.*[84]

[a]As measured by multiple truncal skinfolds, significant as compared to Caucasians; [b]As measured by CT scans or MRI scans, [c]During hyperinsulinemic euglycemic clamp procedure; [d]Study in children aged 10–11 years, significantly higher values as compared to British children; [e]As compared to European whites. TG, Serum triglycerides; HDL-C, high-density lipoprotein cholesterol; W–HR, waist–hip ratio; WC, waist circumference.

4. Increased oxidative stress, as indicated by plasma total 8-epi-PGF2alpha, was recorded in Asian Indians in Mauritius, closely correlating to fasting levels of glucose and triglycerides and insulin resistance[62].
5. IMCL content of the soleus muscle is reported to be high in South Asian men as compared to Europeans in UK[63] and in non-obese healthy men and diabetic patients in India[33] (Figure 3), whereas correlation of IMCL content of soleus muscle with the insulin sensitivity was shown in Caucasians[33] but not in Asian Indians[33,63]. However, since both the studies had small number of subjects, more data are needed for Asian Indians particularly since IMCL is rapidly emerging as a close correlate of insulin resistance in other ethnic groups.
6. Chronic sub-clinical inflammation, particularly intraplaque inflammation may be important in destabilization of the fibrous cap leading to plaque rupture that may trigger an acute coronary event. High values of C-reactive protein (CRP), white blood counts and erythrocyte sedimentation rate signify ongoing inflammation. Currently, some data in Asian Indians suggest that inflammation and IRS are closely associated. For example, immigrant Asian Indians had 17% higher levels of CRP than Europeans that correlated strongly with BMI and W–HR (ref. 64). Further, elevated CRP levels were associated with 14% increased CHD risk in Asian Indians as compared to Europeans[64]. Of considerable concern, ~ 12% adolescents and young adults in New Delhi had high CRP levels that correlated positively with BMI and W–HR (Misra *et al.*, manuscript under preparation).

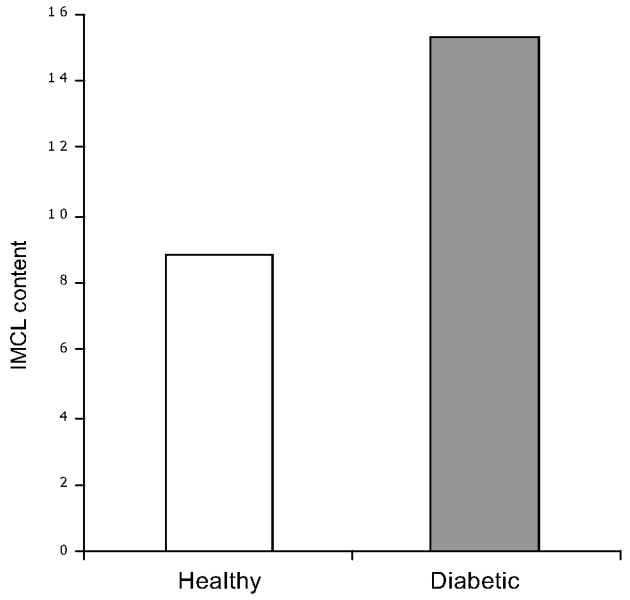

Figure 3. Intramyocellular lipid (IMCL) content as estimated by proton magnetic resonance spectroscopy of soleus muscle in healthy and diabetic subjects. [a]IMCL content given as: percent of intensity of water resonance peak. Adapted from Sinha *et al.*[33].

7. Increasing evidence suggests that adiponectin, a protein secreted by adipose tissue, plays an important role in insulin sensitivity[65,66]. Though much needed, currently no data on Asian Indians is available. Similarly, there is a strong need for research on the relationship of hepatic steatosis and insulin resistance in Asian Indians.

Insulin resistance in special situations

Children and adolescents

Insulin resistance and dyslipidemia are early life phenomena[67,68]. It is known that childhood obesity is a powerful predictor of development of IRS and type 2 diabetes in adulthood[69,70]. Unfortunately data for Asian Indians are scarce. A recent study showed markedly high levels of both fasting and post-glucose load insulin in South Asian children as compared to British white children[55]. Some reports indicate high levels of triglyceride and low levels of HDL-C in non-obese, normotensive offspring of hypertensive parents[49], and low levels of HDL-C in healthy urban adolescents and young adults (age 14–24 years) in India[71] and high levels of triglycerides in South Asian children in UK[55]. Furthermore, our group observed high prevalence of overweight (23% in males and ~ 25% in females), excess body fat (~ 31% in males and ~ 24% in females) in healthy adolescents[72]. Similar findings have been reported in children aged 10–16 years[73].

Children with low birth weight

Several reports indicate that adverse environment during fetal life leads to development of insulin resistance in adult life[74,75]. These observations assume greater significance in Asian Indians because of prevalent maternal malnutrition and low mean birth weight[76]. The calorie deposition in the adverse environment is predominantly stored in the adipose tissues while there is attrition of the muscle mass[77]. Yajnik and coworkers[78], in a series of studies, have reported important observations. Specifically, low birth weight was significantly associated with insulin resistance and other risk factors, particularly in those with high body fat mass at 8 years age. Further, in a case-control study, levels of total cholesterol and LDL-C were significantly higher in term low-birth weight children as compared to children matched for age, sex and socio-economic strata[79].

Women

Recent reports suggest a high prevalence of generalized obesity, abdominal obesity, high values of skinfolds, and excess body fat associated with high prevalence of

dyslipidemia and hypertension in Asian Indian women[23,35]. Furthermore, ~65% women belonging to poor socio-economic strata had at least one coronary risk factor and ~25% were insulin resistant[20] (Figure 4). Specifically, a significant association was shown between percent body fat and serum insulin levels. These metabolic perturbations were particularly common in postmenopausal Asian Indian women[80,81]. One of the important reasons for obesity in women could be physical inactivity. Certainly, this issue needs further studies.

Socio-economic strata and insulin resistance

High prevalence of obesity[21] and IRS in urban population is well known[82,83]. In an important recent study, Deepa *et al.*[84] report 18.7% prevalence of IRS in upper socio-economic strata in South India, while it was 6.5% in the low socio-economic strata. The data on rural–urban differences in prevalence of IRS parallel the prevalence of type 2 diabetes in rural and urban areas[85,86].

Particularly interesting population for research is intra-country migrant population that resides in urban slums. These subjects had a high prevalence of type 2 diabetes (10.3%), obesity (13.9%), excess body fat (30.7%), hypertension (11.7%), hypercholesterolemia (21.1%), hypertriglyceridemia (14.5%), high levels of LDL-C (25.7%), low levels of HDL-C (16.2%), and high prevalence of insulin resistance (22.5–26%)[20,35]. It is not clear why subjects who were previously physically active and consumed simple diets should develop a cluster of abnormalities upon migration to urban areas. A simple explanation could be marked changes in their diets and lifestyle. Some data suggest that diets presently consumed by them were highly imbalanced. Specifically, the dietary consumptions of saturated fat and cholesterol were high and fiber and antioxidants were low[87]. Maladaptation, 'stress response' causing hypothalamic-pituitary activation, increased smoking and alcohol drinking may be additional contributory factors.

High prevalence of obesity and IRS in these subjects is a significant but alarming observation. However, these data also provide a unique opportunity to study an intra-country migrant population, changes in their diet and lifestyle factors in comparison to the pre-migration status, and their metabolic adverse effects. Though speculative, similar mechanism(s) might be operative for development of obesity and insulin resistance in inter-country Asian Indian migrants to other countries.

Patients with CHD

Nearly 15–16% of global mortality due to CHD is contributed by India[88]. High prevalence of CHD has been observed in immigrant Asian Indians[89,90]. Though some debate continues, insulin resistance and its metabolic consequences are increasingly being recognized as risk factors for CHD (ref. 91).

In a study involving British Asians (Punjabi Sikhs) impairment of insulin-mediated glucose disposal and suppression of non-esterified fatty acid (NEFA) were

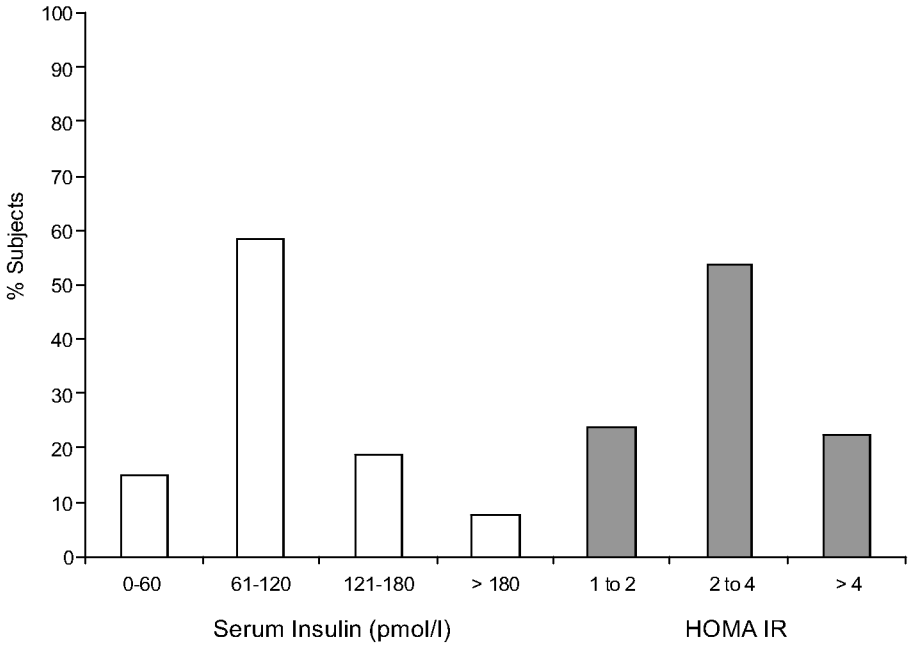

Figure 4. Fasting hyperinsulinemia and HOMA-IR in women belonging to low socio-economic strata residing in urban slums of New Delhi. HOMA IR, Homeostatic model assessment of insulin resistance. (Adapted from Misra *et al.*[20]).

observed more in survivors of premature myocardial infarction (MI) as compared to ethnic controls. British white MI patients had similar metabolic abnormalities except NEFA suppression[92]. Non-diabetic first-degree relatives of Sikh MI patients also manifested abdominal obesity and insulin resistance. In another case-control study, higher fasting insulin values and lower insulin-stimulated glucose uptake in adipocytes were observed in Asian Indians with CHD as compared to Caucasians[93]. Hyperinsulinemia has also been observed in Asian Indians having ECG abnormalities[94], acute coronary event[95], MI (ref. 96), premature MI (ref. 97), and with low left ventricular mass and high arterial compliance[98].

Overall, hyperinsulinemia, insulin resistance and other metabolic abnormalities were more often observed in Asian Indians with CHD as compared to other ethnic groups, and similar observations have been recorded in patients with CHD and premature MI in India. However, no investigation of long-term relationship of insulin resistance and hyperinsulinemia to CHD has been carried out.

Patients with ischaemic cerebrovascular diseases

Higher prevalence of cerebrovascular disease has been recorded in Asian Indians as compared to white population[99]. Increased insulin resistance along with abnormalities in fibrinolytic system may account for this increase in cerebrovascular disease. Higher levels of fibrinogen, von Willebrand factor and tissue plasminogen activator were observed in patients with ischaemic stroke as compared to age-matched ethnic controls in UK. These differences were abolished after adjusting for features of IRS stressing its primary role[100]. Further, the relatives of South Asian patients with ischaemic stroke had hyperinsulinemia, increased insulin resistance and increased levels of tissue plasminogen activator as compared to ethnic controls[101] again underlining familial predisposition to develop IRS. This line of research has not been done on Asian Indians in India.

Measures for prevention and treatment

Optimal management strategy should include emphasis on each component of IRS. In particular, obesity should be targeted from childhood.

Therapeutic lifestyle changes

These constitute the most important aspect of management. Caloric restriction leads to decrease in body weight, reductions in total, abdominal subcutaneous and visceral fat[102] and blood pressure[103] associated with reduction in insulin levels, and improvements in the lipid profile[104,105]. Significant improvement in insulin resistance with diet alone[106], combined diet and exercise regimens[106] and regular physical activity without caloric restriction[107] has been reported. Regular physical exercise improves insulin sensitivity and glucose tolerance due to upregulation of muscle GLUT-4. Beneficial effects of meditation and yoga have been reported in patients with CHD (ref. 108), however, its role in the management of IRS without CHD is not known. Progression from impaired glucose tolerance to diabetes can also be effectively prevented by lifestyle interventions[109].

Pharmacotherapy for insulin resistance

Currently no drug is approved for treatment of IRS. The following drugs given for different indications additionally have some beneficial effects on insulin resistance.

(a) Weight-reducing drugs: Currently approved drugs sibutramine and orlistat may have beneficial effects on insulin resistance due to loss of weight[110,111].

(b) Biguanides: Metformin, a biguanide leads to increased hepatic and peripheral insulin sensitivity[112]. Furthermore, modest weight reduction, improvement in lipid profile[113], and favourable effects on endothelial function[114] has been reported.

(c) Thiazolidinediones: These drugs increase insulin sensitivity by increasing skeletal muscle glucose uptake and by reducing plasma free fatty acids. They may also reduce cytokine production from the adipose tissue[115]. A combination of metformin and thiazolidinediones may be superior to either drug alone[116]. However, their long-term benefits and adverse effects are not known.

Lacunae and future directions

In view of high prevalence of CHD, insulin resistance, and type 2 diabetes in Asian Indians, the current research efforts seem to be inadequate. In particular there is a singular lack of prospective cohort studies. Furthermore, there is dearth of data on genetic predisposition to develop peculiar body fat pattern and insulin resistance. Although there are encouraging research trends in the last few years, much needs to be done for elucidation of etiological factor(s) and to assure proper diagnosis and treatment of IRS and related disorders in Asian Indians.

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