ORIGINAL ARTICLE

Lean People with Dysglycemia Have a Worse Metabolic Profile Than Centrally Obese People Without Dysglycemia

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Abstract

Aim: This study compared metabolic profiles of Asian Indians with normal waist circumference (WC) and dysglycemia versus those with high WC without dysglycemia.

Subjects and Methods: In 2,350 subjects ≥ 20 years of age from the Chennai Urban Rural Epidemiology Study with full anthropometric and biochemical characterization, high WC was defined as ≥ 90 cm in males and ≥ 80 cm in females. Dysglycemia was defined as prediabetes (fasting plasma glucose ≥ 100 mg/dL and/or 2-h plasma glucose ≥ 140 mg/dL) or diabetes (fasting plasma glucose ≥ 126 mg/dL, 2-h plasma glucose ≥ 200 mg/dL, or treatment for diagnosed diabetes). Coronary artery disease (CAD) was defined as known myocardial infarction or Q waves on electrocardiography. Multi-variable logistic regression models were used to explore factors associated with CAD.

Results: Of the subjects, 260 (11.1%) had dysglycemia with normal WC, and 679 (28.9%), had high WC without dysglycemia. Compared with subjects with high WC without dysglycemia, those with dysglycemia/normal WC, adjusted for age, were more likely to be males ($P < 0.001$) and have higher systolic blood pressure ($P < 0.05$), higher serum triglycerides ($P < 0.001$), higher tumor necrosis factor- α ($P < 0.001$), lower high-density lipoprotein cholesterol ($P < 0.05$), and higher prevalence of CAD (6.3% vs. 2.0%; odds ratio 3.25 [95% confidence interval 1.52–6.94]; $P = 0.002$).

Conclusions: Dysglycemia is associated with a worse cardiometabolic profile than central obesity alone.

Introduction

GLOBALLY, THE PREVALENCE of type 2 diabetes is growing at an alarming rate. Propelling the upsurge in diabetes is the growing prevalence of overweight and obesity both in developed and in developing nations.¹

Although overweight, obesity, and, in particular, central obesity are very strongly correlated with the risk of diabetes, there are emerging data for subphenotypes of obesity that appear to deviate from the apparent monotonous relationship with adverse metabolic outcomes.^{4–8} For example, there is a group referred to as “metabolically obese, normal weight” individuals.^{9–15} There are both grossly overweight individuals who manifest all the classical abnormalities associated with adult-onset obesity, whereas at the other end of the spectrum are normal weight individuals who have the metabolic abnormalities usually associated with obesity.¹⁶ Yet, there is also some discordance: type 2 diabetes also occurs in

nonobese people, especially frequently in some ethnic groups (e.g., Asian Indians),¹⁷ and metabolic abnormalities that are usually associated with obesity do not affect all obese people.^{11,18} To study this paradox better, we used data from a population-based study in Chennai, India, to compare metabolic profiles of people with dysglycemia/normal waist circumference (WC) and high WC/no dysglycemia.

Research Design and Methods

The Chennai Urban Rural Epidemiology Study (CURES) is a large cross-sectional epidemiological study done on a representative population of Chennai (formerly Madras) city in southern India ($n = 26,001$). The study's methodology has been published elsewhere.¹⁹ Informed consent was obtained from all participating subjects, and institutional ethical committee approval was obtained. In brief, the city of Chennai was divided into 155 corporation wards representing a

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socioeconomic diverse group. In Phase 1 of CURES, 46 of the 155 wards in Chennai were screened via systematic sampling techniques, providing a total sample size of 26,001 individuals ≥ 20 years of age. Subsequently, every 10th subject recruited in Phase 1 ($n=2,600$) was invited for detailed testing; 90.4% (2,350/2,600) of subjects participated.

All of these participants, except those with known diabetes ($n=46$), had a 75-g oral glucose tolerance test ($n=2,304$). Anthropometric measurements included height, weight, and waist measurements,¹⁹ obtained using standardized techniques, from which body mass index was calculated. Blood pressure was recorded in the sitting position in the right arm to the nearest 2 mm Hg with a mercury sphygmomanometer (Diamond Deluxe BP apparatus; Diamond, Pune, India). Two readings were taken in a resting position 5 min apart, and the mean of the two was used.

Dietary intakes were assessed using a previously validated and published interviewer-administered meal-based semi-quantitative food frequency questionnaire containing 222 food items to estimate the usual food intake over the past year.²⁰ Interviews were conducted by well-trained nutritionists, and the participants were asked to estimate the usual frequency (number of times per day/week/month/year or never) and their usual serving size of the various food items in the food frequency questionnaire.

Levels of plasma glucose (glucose oxidase-peroxidase method), serum cholesterol (cholesterol oxidase-peroxidase amidopyrine method), serum triglycerides (glycerol-3-phosphate oxidase-*p*-aminophenazone method), and high-density lipoprotein (HDL) cholesterol (direct method) were estimated using a Hitachi-912 autoanalyzer (Hitachi, Mannheim, Germany). Low-density lipoprotein (LDL) cholesterol was calculated using the equation of Friedewald et al.²¹ Glycated hemoglobin (HbA1c) was measured using a VariantTM machine (Bio-Rad, Hercules, CA). The intra- and interassay coefficients of variants (CVs) for the biochemical assays ranged from 3.1% to 7.6%. High-sensitivity C-reactive protein (Bio Check, Foster City, CA) (intra- and interassay CVs of 4.0 and 7.8%, respectively) and tumor necrosis factor (TNF)- α (Biosource Europe, Nivelles, Belgium) (intra- and interassay CVs ranged from 3.4% to 7.7%) concentrations were measured by enzyme-linked immunosorbent assay. Total serum adiponectin was measured by radioimmunoassay (catalog number HADP-61 HK; Linco Research, St. Charles, MO) (intra- and interassay CVs of 0.38 and 0.74%, respectively). Resting 12-lead electrocardiography was done, and Minnesota coding was used to grade electrocardiograms.

Definitions

Dysglycemia was defined as the presence of either prediabetes (fasting plasma glucose of 100–125 mg/dL²² and/or 2-h plasma glucose of 140–199 mg/dL²³) or diabetes (fasting plasma glucose of ≥ 126 mg/dL and/or 2-h plasma glucose of ≥ 200 mg/dL) or on medication for diabetes. Asia-Pacific guidelines²⁴ were used to define central obesity as WC ≥ 90 cm for males and ≥ 80 cm for females.

Coronary artery disease (CAD) was defined as a documented history of myocardial infarction, medication post-myocardial infarction, and/or Minnesota codes for CAD from 1-1-1 to 1-1-7 (Q wave changes), 4-1 to 4-2 (ST segment depression), or 5-1 to 5-3 (T wave abnormalities).²⁵

Analysis

All statistical analyses were performed using SPSS version 15.0 (SPSS, Inc., Chicago, IL) for Windows. We compared metabolic and clinical parameters in high WC/no dysglycemia and dysglycemia/normal WC subjects using one-way analysis of variance for continuous variables and χ^2 tests for categorical variables. As there is a significant difference in the mean age of the two groups studied, the mean values were presented after adjusting for age. Multivariable logistic regression was used to evaluate the factors associated with high WC/no dysglycemia and dysglycemia/normal WC. Calculations in Table 1 were adjusted only for age, whereas in Table 2 calculations on multivariable logistic regression are similar but were adjusted for multiple key variables, and the differences between the two groups are presented. The variables that were significantly different between the groups in Table 1 and the clinically important variables were chosen for the model for adjustment in Table 2, which includes age, gender, systolic blood pressure, triglycerides, HDL cholesterol, TNF- α , energy intake, and physical activity. Multiple logistic regression was also used to assess the association between high WC/no dysglycemia and dysglycemia/normal WC and CAD controlled for age, sex, cholesterol, triglycerides, HDL cholesterol, systolic blood pressure, and smoking in separate models.

Results

Of 2,350 participants, 260 (11.1%) had dysglycemia/normal WC, and 679 (28.9%) had high WC/no dysglycemia. The 260 subjects with dysglycemia/normal WC comprised 46 (17.7%) with self-reported diabetes, 83 (31.9%) with newly diagnosed diabetes, and 92 (35.4%) with impaired glucose tolerance. Compared with subjects with high WC/no dysglycemia, participants with dysglycemia/normal WC, adjusted for age, were more likely to be male (32.5% vs. 65%, $P<0.001$), have higher systolic blood pressure (120 ± 15 vs. 123 ± 21 mm Hg, $P=0.003$), higher serum triglycerides (1.3 vs. 1.5 mmol/L, $P<0.001$), higher TNF- α (3.4 ± 2.2 vs. 4.4 ± 2.2 pg/mL, $P=0.017$), lower HDL cholesterol (1.09 ± 0.23 vs. 1.06 ± 0.23 mmol/L, $P=0.007$), lower adiponectin (7.5 ± 3.8 vs. 6.5 ± 3.0 μ g/mL, $P=0.032$), and lower energy intake ($2,661 \pm 559$ vs. $2,473 \pm 722$ Kcal, $P=0.003$) (Table 1). Also, participants with dysglycemia/normal WC had comparatively lower levels of carbohydrates ($P<0.001$), protein ($P=0.009$), fat, and glycemic load ($P=0.001$). There were no significant difference in the carotid intima-medial thickness and physical activity, although there were significantly higher proportions of people involved in sedentary activity ($P=0.021$). More smokers were found among participants with dysglycemia/normal WC than among those with high WC/no dysglycemia ($P<0.001$). In the multivariable logistic regression (Table 2), after adjusting for age, gender, systolic blood pressure, triglycerides, HDL cholesterol, TNF- α , energy intake, and physical activity, the two groups were similar. Adiponectin still differed ($P=0.048$).

In regression models, dysglycemia/normal WC participants had higher odds of CAD (3.25; 95% confidence interval 1.52–6.94) than those with high WC/no dysglycemia (Table 3). When sequentially controlled for age, gender, cholesterol, triglycerides, HDL cholesterol, systolic blood pressure, and smoking, the odds were 2.22 (95% confidence interval 0.99–4.97), 2.21

TABLE 1. AGE-ADJUSTED CLINICAL AND BIOCHEMICAL CHARACTERISTICS OF THE GROUPS WITH DYSGLYCEMIA/NORMAL WAIST CIRCUMFERENCE AND HIGH WAIST CIRCUMFERENCE/NO DYSGLYCEMIA

Variable	Dysglycemia /normal WC	High WC/no dysglycemia	P value
<i>n</i>	260	679	
Male (%)	169 (65.0)	221 (32.5)	<0.001
Age (years)	45 ± 14	38 ± 11	<0.001
Family history of diabetes [<i>n</i> (%)]			
One parent with diabetes	64 (24.6)	138 (20.3)	0.152
Both parents with diabetes	16 (6.2)	36 (5.3)	0.075
BMI (kg/m ²) ^a	22.1 ± 2.7	25.3 ± 3.3	<0.001
Waist circumference (cm) ^a			
Male	82.7 ± 6.1	96.6 ± 6.0	<0.001
Female	74.4 ± 4.8	88.8 ± 7.1	<0.001
Blood pressure (mm Hg) ^a			
Systolic	123 ± 21	120 ± 15	0.003
Diastolic	76 ± 11	76 ± 10	0.883
Fasting plasma glucose (mmol/L) ^a	7.3 ± 3.4	4.7 ± 0.4	<0.001
HbA1c (%) ^a	7.4 ± 2.4	5.6 ± 0.5	<0.001
Cholesterol (mmol/L) ^a	4.8 ± 1.1	4.8 ± 0.9	0.257
Triglycerides (mmol/L) ^b	1.5	1.3	<0.001
HDL cholesterol (mmol/L) ^a	1.06 ± 0.23	1.09 ± 0.23	0.007
Carotid intima-medial thickness (mm) ^a	0.73 ± 0.18	0.71 ± 0.17	0.278
Inflammatory markers ^a			
Hs-CRP (mg/L)	3.3 ± 3.2 (<i>n</i> = 95)	3.0 ± 3.2 (<i>n</i> = 147)	0.484
TNF-α (pg/mL)	4.4 ± 2.2 (<i>n</i> = 41)	3.4 ± 2.2 (<i>n</i> = 76)	0.017
Adiponectin (μg/mL) ^a	6.5 ± 3.0 (<i>n</i> = 75)	7.5 ± 3.8 (<i>n</i> = 229)	0.032
Energy per unit of BMI (Kcal) ^a	116 ± 37	97 ± 21	<0.001
Carbohydrate (g) ^a	393.3 ± 121.4	433.0 ± 97.4	<0.001
Protein (g) ^a	69.7 ± 20.2	74.5 ± 16.5	0.009
Fat (g) ^a	64.7 ± 23.5	68.1 ± 18.9	0.108
Glycemic load ^a	220.1 ± 75.8	243.9 ± 63.8	0.001
Physical activity [<i>n</i> (%)]			
Sedentary	205 (78.8)	578 (85.1)	0.021
Moderate	50 (19.2)	96 (14.1)	0.054
Heavy	5 (1.9)	5 (0.7)	0.113
Current smokers [<i>n</i> (%)]	45 (17.3)	56 (8.2)	<0.001
Coronary artery disease [<i>n</i> (%)]	15 (6.3)	13 (2.0)	0.001

Dysglycemia/normal waist circumference (WC) was defined as a waist measurement of <90 cm for males and <80 cm for females, along with fasting plasma glucose of ≥5.6 mmol/L, 2-h plasma glucose of ≥7.8 mmol/L, or diabetes. High WC/no dysglycemia was defined as a waist measurement of ≥90 cm for men and ≥80 cm for females, along with fasting plasma glucose of <5.6 mmol/L and 2-h plasma glucose of <7.8 mmol/L.

^aThese data are presented as age-adjusted mean ± SD values.

^bData are presented as geometric mean values.

BMI, body mass index; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; Hs-CRP, high-sensitivity C-reactive protein; TNF, tumor necrosis factor.

(0.96–5.12), 2.19 (0.96–5.03), 2.07 (0.89–4.82), 2.06 (0.89–4.81), 2.04 (0.87–4.78), and 2.02 (0.86–4.74), respectively.

Discussion

This study showed the following findings: (1) 11.1% of urban Asian Indians had dysglycemia/normal WC, and 28.9% had high WC/no dysglycemia, and (2) the dysglycemia/normal WC group had worse metabolic and cardiovascular profiles than the high WC/no dysglycemia group.

Similar distributions of weight and metabolic abnormalities have been observed previously. In a study from Korea²⁶ in 2009, the prevalence of metabolically obese normal weight was 8.7%, whereas the prevalence of the metabolically healthy obese phenotype was 15.2%, leading to the proposal that regardless of weight gain, metabolic profile should be looked

for. A recent study in Canada²⁷ estimated that nearly 25% of normal-weight individuals display abnormal metabolic profiles. We previously reported that in the Chennai population, the prevalence of metabolically obese normal weight was 15.1% and that of metabolically healthy obese was 13.3,²⁸ and metabolic obesity may have different clinical implications than phenotypic obesity. In the current study, 11.1% exhibit the dysglycemia/normal WC profile, which translates to nearly 420,000 people with this profile in Chennai city alone. These figures are clinically important as these individuals are frequently undetected because of normal waist size.

Asian Indians have an increased susceptibility to type 2 diabetes and premature CAD,^{1,29} the so-called “Asian Indian phenotype,”^{30–32} which includes increased insulin resistance, high central (visceral) adiposity, and increased levels of pro-inflammatory markers despite having generalized obesity as

TABLE 2. MULTIVARIABLE ADJUSTED CLINICAL AND BIOCHEMICAL CHARACTERISTICS OF THE GROUPS WITH DYSGLYCEMIA/NORMAL WAIST CIRCUMFERENCE AND HIGH WAIST CIRCUMFERENCE/NO DYSGLYCEMIA

Variable	Dysglycemia/ normal WC	High WC/no dysglycemia	P value
<i>n</i>	260	679	
Blood pressure (mm Hg)			
Systolic	125±3.3	121±3.4	0.431
Diastolic	76±1.4	76±1.4	0.925
Cholesterol (mmol/L)	4.8±0.19	4.8±0.19	0.997
Triglycerides (mmol/L)	1.8±0.28	1.7±0.29	0.890
HDL cholesterol (mmol/L)	1.09±0.04	1.09±0.04	0.969
Inflammatory markers			
Hs-CRP (mg/L)	2.9±0.6	3.7±0.6	0.365
TNF- α (pg/mL)	4.3±0.4	3.4±0.4	0.181
Adiponectin (μ g/mL)	7.8±0.8	10.7±1.0	0.048
Energy per unit of BMI (Kcal)	112±6.8	95±7.0	0.115
Carbohydrate (g)	402.5±8.7	396.9±8.9	0.677
Protein (g)	71.6±1.4	69.2±1.4	0.252
Fat (g)	64.2±3.2	65.4±3.3	0.807
Glycemic load	230.3±8.4	221.3±8.6	0.490

Dysglycemia/normal waist circumference (WC) was defined as a waist measurement of <90 cm for males and <80 cm for females, along with fasting plasma glucose of ≥ 5.6 mmol/L, 2-h plasma glucose of ≥ 7.8 mmol/L, or diabetes. High WC/no dysglycemia was defined as a waist measurement of ≥ 90 cm for men and ≥ 80 cm for females, along with fasting plasma glucose of <5.6 mmol/L and 2-h plasma glucose of <7.8 mmol/L. All variables are adjusted for age, gender, systolic blood pressure, triglycerides, high-density lipoprotein (HDL) cholesterol, tumor necrosis factor (TNF)- α , energy intake, and physical activity and presented as adjusted mean $\pm$ SE values.

BMI, body mass index; Hs-CRP, high-sensitivity C-reactive protein.

measured by body mass index. The group with dysglycemia/normal WC had greater dyslipidemia in comparison with the group with high WC/no dysglycemia.¹⁸ It is usually believed that visceral adiposity is common in Asian Indians, unrelated to overall increased body mass index,^{17,33} and drives hyperinsulinemia and a greater propensity to cardiometabolic risk factors.¹⁷ In our models, however, the elevated levels of pro-

inflammatory/pro-atherogenic markers were more common in the dysglycemia/normal WC subjects, which appeared to account for the higher odds of CAD in this group. Our data imply that identification of people with these profiles and implementation of preventive measures may help prevent or at least delay progression to CAD. Furthermore, our data point to the need for more detailed study of fat quantity and distribution (e.g., visceral vs. subcutaneous) and its relationship with disease.

Earlier studies have suggested that familial aggregation of diabetes may have a strong influence in the development of dysglycemia in our population.^{34,35} However, in the present study, in the group with dysglycemia, family history of diabetes was not different from that of the group with high WC/no dysglycemia. It has been shown that normal-weight individuals with dysglycemia have impaired first-phase insulin secretion compared with those with normoglycemia.³⁶ The finding of elevated levels of inflammatory markers in the subjects with dysglycemia supports the pro-inflammatory/pro-atherogenic state of this subgroup. Thus, if these people are appropriately identified and preventive measures are implemented, one could prevent or at least delay their conversion to overt type 2 diabetes mellitus.

After adjusting for age and sex, the odds ratio for CAD was reduced from 3.25 to 2.21 and lost statistical significance. This implies that age and sex are important contributors to dysglycemia/normal WC. *P* values alone do not permit any direct statement about the risk between the groups; however, confidence intervals indicate the direction of the effect studied. Hence, it is possible that the relatively small sample size of the study might have led to the statistical insignificance. Strong evidence exists that Indians have age-associated risk for diabetes and that the onset occurs at a younger age compared with developed Western countries.³⁷ The ICMR-India DIABetes (ICMR-INDIAB) study, a large epidemiological study on the prevalence of diabetes and prediabetes in four regions of India, also reported age as being one of its significant risk factors for diabetes.³⁸ In the Indian Diabetes Risk Score we developed,³⁹ age had the highest score for diabetes, compared with other risk factors. Although there is no clear gender predisposition, in general, differences do exist in the

TABLE 3. MULTIPLE REGRESSION ANALYSIS OF ASSOCIATION WITH CORONARY ARTERY DISEASE

Variable	Odds ratio for CAD (95% CI)	P value
High WC/no dysglycemia (reference)	1.00	
Dysglycemia/normal WC		
Model 1: unadjusted	3.25 (1.52–6.94)	0.002
Model 2: adjusted for age	2.22 (0.99–4.97)	0.053
Model 3: adjusted for age and sex	2.21 (0.96–5.12)	0.063
Model 4: adjusted for age, sex, and cholesterol	2.19 (0.96–5.03)	0.064
Model 5: adjusted for age, sex, cholesterol, and triglycerides	2.07 (0.89–4.82)	0.090
Model 6: adjusted for age, sex, cholesterol, triglycerides, and HDL-C	2.06 (0.89–4.81)	0.094
Model 7: adjusted for age, sex, cholesterol, triglycerides, HDL-C, and systolic blood pressure	2.04 (0.87–4.78)	0.100
Model 8: adjusted for age, sex, cholesterol, triglycerides, HDL-C, systolic blood pressure, and smoking	2.02 (0.86–4.74)	0.106

Dysglycemia/normal waist circumference (WC) was defined as a waist measurement of <90 cm for males and <80 cm for females, along with fasting plasma glucose of ≥ 5.6 mmol/L, 2-h plasma glucose of ≥ 7.8 mmol/L, or diabetes. High WC/no dysglycemia was defined as a waist measurement of ≥ 90 cm for men and ≥ 80 cm for females, along with fasting plasma glucose of <5.6 mmol/L and 2-h plasma glucose of <7.8 mmol/L.

CAD, coronary artery disease; CI, confidence interval; HDL-C, high-density lipoprotein cholesterol.

rates of dysglycemia. In the ICMR-INDIAB Study, the dysglycemia prevalence was higher in males compared with females.³⁸ In the current study also, a significantly higher proportion of males had dysglycemia/normal WC compared with females. This could possibly be one of the reasons that the dysglycemia/normal WC group has a higher proportion of smokers, as in India smoking is very uncommon among females. Earlier studies have shown that active smoking is associated with an increased risk of diabetes.⁴⁰

Our study is limited by its cross-sectional nature, precluding any causal inferences. In addition, β -cell function, insulin resistance, and visceral and total body fat were not measured in these subjects. However, the strengths of the study are that it is population-based, large, and representative of the local population with a good response rate.

In conclusion, even in the absence of central obesity, dysglycemia is associated with poor cardiometabolic profiles, and clustering of cardiovascular risk factors or the components of metabolic syndrome are more common in Asian Indians with dysglycemia/normal WC. Therefore, when evaluating Asian Indians, physicians should look for metabolic abnormalities not only in the centrally obese, but also in nonobese, people.

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References

- Unwin N, Whiting D, Guariguata L, Ghyoot G, Gan D, eds. *Diabetes Atlas*, 5th ed. Brussels: International Diabetes Federation, 2011:11–74.
- Danaei G, Finucane MM, Lu Y, Singh GM, Cowan MJ, Paciorek CJ, Lin JK, Farzadfar F, Khang YH, Stevens GA, Rao M, Ali MK, Riley LM, Robinson CA, Ezzati M; Global Burden of Metabolic Risk Factors of Chronic Diseases Collaborating Group (Blood Glucose): National, regional, and global trends in fasting plasma glucose and diabetes prevalence since 1980: systematic analysis of health examination surveys and epidemiological studies with 370 country-years and 2.7 million participants. *Lancet* 2011;378:31–40.
- Finucane MM, Stevens GA, Cowan MJ, Danaei G, Lin JK, Paciorek CJ, Singh GM, Gutierrez HR, Lu Y, Bahalim AN, Farzadfar F, Riley LM, Ezzati M; Global Burden of Metabolic Risk Factors of Chronic Diseases Collaborating Group (Body Mass Index): National, regional, and global trends in body-mass index since 1980: systematic analysis of health examination surveys and epidemiological studies with 960 country-years and 9.1 million participants. *Lancet* 2011;377:557–567.
- Brochu M, Tchernof A, Dionne IJ, Sites CK, Eltabbakh GH, Sims EA, Poehlman ET: What are the physical characteristics associated with a normal metabolic profile despite a high level of obesity in postmenopausal women? *J Clin Endocrinol Metab* 2001;86:1020–1025.
- Sims EA: Are there persons who are obese, but metabolically healthy? *Metabolism* 2001;50:1499–1504.
- Bonora E, Kiechl S, Willeit J, Oberhollenzer F, Egger G, Targher G, Alberiche M, Bonadonna RC, Muggeo M: Prevalence of insulin resistance in metabolic disorders: the Bruneck Study. *Diabetes* 1998;47:1643–1649.
- Karelis AD, St-Pierre DH, Conus F, Rabasa-Lhoret R, Poehlman ET: Metabolic and body composition factors in subgroups of obesity: what do we know? *J Clin Endocrinol Metab* 2004;89:2569–2575.
- Karelis AD, Brochu M, Rabasa-Lhoret R: Can we identify metabolically healthy but obese individuals (MHO)? *Diabetes Metab* 2004;30:569–572.
- Hollenbeck CB, Reaven G: Variations in insulin-stimulated glucose uptake in healthy individual with normal glucose tolerance. *J Clin Endocrinol Metab* 1987;64:1169–1173.
- Zavaroni I, Bonora E, Pagliara M, Dall'Aglio E, Luchetti L, Buonanno G, Bonati PA, Bergonzani M, Gnudi L, Passeri M, Reaven G: Risk factors for coronary artery disease in healthy persons with hyperinsulinemia and normal glucose tolerance. *N Engl J Med* 1989;320:702–726.
- Ruderman N, Chrisholm D, Pi-Sunyer X, Schneider S: The metabolically obese normal weight individual revisited. *Diabetes* 1998;47:699–713.
- Ruderman NB, Berchtold P, Schneider SH: Obesity associated disorders in normal weight individuals: some speculations. *Int J Obes* 1982;6:151–157.
- Reaven GM: Banting Lecture: role of insulin resistance in human disease. *Diabetes* 1988;37:1595–1607.
- Caro JF: Insulin resistance in obese and non obese men. *J Clin Endocrinol Metab* 1991;73:691–695.
- Wajchenberg BL, Malerbi DA, Rocha MS, Lerario AC, Santomauro AT: Syndrome X: a syndrome of insulin resistance. Epidemiological and clinical evidence. *Diabetes Metab Rev* 1994;10:19–29.
- Ruderman NB, Schneider SH, Berchtold P: The “metabolically-obese,” normal-weight individual. *Am J Clin Nutr* 1981;34:1617–1621.
- 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;86:5366–5371.
- Pajunen P, Kotronen A, Korpi-Hyövälti E, Keinänen-Kiukaanniemi S, Oksa H, Niskanen L, Saaristo T, Saltevo JT, Sundvall J, Vanhala M, Uusitupa M, Peltonen M: Metabolically healthy and unhealthy obesity phenotypes in the general population: the FIN-D2D Survey. *BMC Public Health* 2011;11:754.
- Deepa M, Pradeepa R, Rema M, Mohan A, Deepa R, Shanthirani S, Mohan V: The Chennai Urban Rural Epidemiology study (CURES)—study design and methodology (Urban Component) (CURES 1). *J Assoc Physicians India* 2003;51:862–870.
- Sudha V, Radhika G, Sathya RM, Ganesan A, Mohan V: Reproducibility and validity of an interviewer administered semi-quantitative food frequency questionnaire to assess dietary intake of urban adults in Southern India. *Int J Food Sci Nutr* 2006;57:481–493.

21. Friedewald WT, Levy RI, Fredrickson DS: Estimation of the concentration of low-density lipoprotein cholesterol in plasma without use of the preparative ultracentrifuge. *Clin Chem* 1972;18:499–502.
22. Genuth S, Alberti KG, Bennett P, Buse J, DeFronzo R, Kahn R, Kitzmiller J, Knowler WC, Lebovitz H, Lernmark A, Nathan D, Palmer J, Rizza R, Saudek C, Shaw J, Steffes M, Stern M, Tuomilehto J, Zimmet P; Expert Committee on the Diagnosis and Classification of Diabetes Mellitus: Follow-up report on the diagnosis of diabetes mellitus. *Diabetes Care* 2003;26:3160–3167.
23. World Health Organization: Definition, Diagnosis and Classification of Diabetes Mellitus and Its Complications. Report of a WHO Consultation. Part 1: Diagnosis and Classification of Diabetes Mellitus. Geneva: Department of Noncommunicable Disease Surveillance, 1999.
24. World Health Organization: The Asia Pacific Perspective. Redefining Obesity and Its Treatment. Melbourne: World Health Organization, International Association for the Study of Obesity and International Obesity Task Force, and International Diabetes Institute, 2000.
25. Deepa M, Farooq S, Datta M, Deepa R, Mohan V: The prevalence of metabolic syndrome using WHO, ATP III and IDF definitions in Asian Indians. *CURES-34. Diabetes Metab Res Rev* 2007;23:127–134.
26. Lee K: Metabolically obese but normal weight (MONW) and metabolically healthy obese (MHO) phenotypes in Koreans: characteristics and health behaviors. *Asia Pac J Clin Nutr* 2009;18:280–284.
27. Shea JL, King MT, Yi Y, Gulliver W, Sun G: Body fat percentage is associated with cardiometabolic dysregulation in BMI-defined normal weight subjects. *Nutr Metab Cardiovasc Dis* 2012;22:741–747.
28. Geetha L, Deepa M, Anjana RM, Mohan V: Prevalence and clinical profile of metabolic obesity and phenotypic obesity in Asian Indians. *J Diabetes Sci Technol* 2011;5:439–446.
29. Anand SS, Yusuf S, Vuksan V, Devanese S, Teo KK, Montague PA, Kelemen L, Yi C, Lonn E, Gerstein H, Hegele RA, McQueen M: Differences in risk factors, atherosclerosis, and cardiovascular disease between ethnic groups in Canada: the Study of Health Assessment and Risk in Ethnic groups (SHARE). *Lancet* 2000;356:279–284.
30. Deepa R, Sandeep S, Mohan V: Abdominal obesity, visceral fat and Type 2 diabetes—"Asian Indian phenotype." In: Mohan V, Gundu HR Rao, eds. *Type 2 Diabetes in South Asians: Epidemiology, Risk Factors and Prevention*. New Delhi: Jaypee Brothers Medical Publishers, 2006:138–152.
31. McKeigue PM, Shah B, Marmott MG: Relationship of central obesity and insulin resistance with high diabetes prevalence and cardiovascular risk in South Asians. *Lancet* 1991;337:382–386.
32. Mohan V, Sharp PS, Cloke HR, Burrin JM, Schumer B, Kohnner 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;29:235–237.
33. Sandeep S, Gokulakrishnan K, Velmurugan K, Deepa M, Mohan V: Visceral & subcutaneous abdominal fat in relation to insulin resistance & metabolic syndrome in non-diabetic south Indians. *Indian J Med Res* 2010;131:629–635.
34. Mohan V, Sharp PS, Aber V, Mather HM, Kohnner EM: Family histories of Asian Indian and European NIDDM patients. *Pract Diabetes* 1986;3:254–256.
35. Viswanathan M, Mohan V, Snehalatha C, Ramachandran A: High prevalence of type 2 (non-insulin dependent) diabetes among the offspring of conjugal type 2 diabetic parents in India. *Diabetologia* 1985;28:907–910.
36. Kahn SE, Hull RL, Utzschneider KM: Mechanisms linking obesity to insulin resistance and type 2 diabetes. *Nature* 2006;444:840–846.
37. Nakagami T, Qiao Q, Carstensen B, Nhr-Hansen C, Hu G, Tuomilehto J, Balkau B, Borch-Johnsen K; the DECODE-DECODA Study Group: Age, body mass index and Type 2 diabetes-associations modified by ethnicity. *Diabetologia* 2003;46:1063–1070.
38. Anjana RM, Pradeepa R, Deepa M, Datta M, Sudha V, Unnikrishnan R, Bhansali A, Joshi SR, Joshi PP, Yajnik CS, Dhandhanika VK, Nath LM, Das AK, Rao PV, Madhu SV, Shukla DK, Kaur T, Priya M, Nirmal E, Parvathi SJ, Subhashini S, Subashini R, Ali MK, Mohan V; ICMR-INDIAB Collaborative Study Group: Prevalence of diabetes and prediabetes (impaired fasting glucose and/or impaired glucose tolerance) in urban and rural India: phase I results of the Indian Council of Medical Research-India DIABetes (ICMR-INDIAB) study. *Diabetologia* 2011;54:3022–3027.
39. Mohan V, Deepa R, Deepa M, Somannavar S, Datta M: A simplified Indian Diabetes Risk Score for screening for undiagnosed diabetic subjects. *J Assoc Physicians India* 2005;53:759–763.
40. Manson J, Ajani U, Liu S, Nathan DM, Hennekens CH: A prospective study of cigarette smoking and the incidence of diabetes mellitus among US male physicians. *Am J Med* 2000;109:538–542.

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