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# Comprehensive assessment of insulin resistance in non-obese Asian Indian and Chinese men

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**Keywords**
Endogenous glucose production, Skeletal muscle insulin sensitivity, Non-obese Asian Indian

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## ABSTRACT

**Aims/Introduction:** Indian individuals are more insulin resistant (IR) than Chinese individuals, even among those with a non-obese body mass index (BMI). However, BMI often underestimates body fat in Indian individuals, and it remains unclear whether Indians would remain more IR than Chinese individuals when both BMI and body fat are equally matched.

**Materials and Methods:** Using the hyperinsulinemic-euglycemic clamp with stable-isotope infusion, we comprehensively assessed IR between 13 non-obese Indian men with 13 Chinese men matched for age, BMI and body fat. We further compared the differences in insulin metabolic clearance rate (MCR) between the two groups and its relationship with various metabolic parameters. The response of lipid and amino acid metabolism to insulin stimulation was also evaluated using metabolomic profiling.

**Results:** The rates of endogenous glucose production during fasting were similar, and endogenous glucose production was completely suppressed during insulin clamp for both ethnic groups. Glucose disappearance during insulin clamp was also similar between the two groups, even after accounting for differences in insulin concentration. Metabolomic profiles of amino acids and various acylcarnitines were similar during both fasting and insulin clamp. However, plasma insulin during clamp was significantly higher in Indian men, indicating that insulin MCR was lower. Insulin MCR correlated significantly with total adiposity and skeletal muscle insulin sensitivity.

**Conclusion:** When equally matched for body fat, non-obese Indian men had similar skeletal muscle insulin sensitivity and endogenous glucose production to Chinese men. The effects of insulin on lipid and amino acid metabolism were also similar. Low insulin MCR is associated with greater adiposity and lower skeletal muscle insulin sensitivity.

## INTRODUCTION

Insulin resistance (IR) or impaired insulin sensitivity describes the impaired action of insulin in maintaining normal blood glucose, and is considered the principal metabolic defect involved in the pathogenesis of type 2 diabetes mellitus. Among the various ethnicities in Singapore, we have shown that Indian individuals are the most IR and Chinese individuals the least[1,2]. As IR is closely linked to the degree of obesity, Indians could be more IR compared with Chinese because of the higher prevalence of obesity, most commonly defined based on the body mass index (BMI)[1]. However, body fat is often underestimated in Indians compared with Chinese with the same BMI[3], and differences in body composition might explain why Indians are more IR. Therefore, it is unclear whether Indians will remain more IR than Chinese when both BMI and body fat are equally matched. Furthermore, IR between the two ethnicities is most disparate when BMI is low[2], suggesting that other non-obesity factors, such as abnormalities in lipid and amino acid metabolism, might be involved[4,5]. These metabolic parameters have not been adequately studied in non-obese Indians and Chinese. Similarly, hyperinsulinemia and the impaired insulin metabolic clearance rate (MCR) might be a harbinger of worsenining IR and future cardiometabolic disorders, even in healthy individuals with non-obese BMI[6].

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However, the influence of impaired insulin MCR on metabolic health in these two ethnic groups remains unclear.

The present study assessed the difference in IR between non-obese Indian men and Chinese men matched for both BMI and body fat using the hyperinsulinemic-euglycemic clamp with stable-isotope labeled glucose infusion. We further compared the differences in insulin MCR between the two groups and its relationship with various adverse metabolic parameters. In addition, we examined the response of amino acid and lipid metabolism to insulin stimulation in the two ethnic groups by carrying out comprehensive profiling of plasma amino acids and acylcarnitines (ACs).

## METHODS

### Participants

This study protocol was approved by the National Healthcare Group Institution Review Board, and written informed consent was obtained from all participants before enrolment into the study. Non-obese Chinese and Indian men, defined by BMI 18.5–25 kg/m$^2$, were recruited from the general population. All participants were required to have normal fasting plasma glucose (<6.0 mmol/L) and glycated hemoglobin (<6%), and no significant changes in dietary habits or bodyweight in the past 3 months. Exclusion criteria included having any first-degree relative with type 2 diabetes mellitus; serum creatinine >125 μmol/L; history of alcohol abuse; serum alanine aminotransferase or aspartate aminotransferase more than twice the upper limit of normal; medications likely to affect fat, glucose or protein metabolism; and active smoking in the past 3 months.

### Study protocol

Participants were first screened before undergoing hyperinsulinemic-euglycemic clamp studies. At screening, fasting blood glucose, glycated hemoglobin, liver, renal and lipid profiles were obtained. BMI was calculated as weight in kg over square of height in meters. For body composition, the total fat mass, fat free mass and fat mass percentage was estimated using tetrapolar bioelectric impedance analysis (Tanita Body Composition scale, model TBF-300; Tanita Corporation, Tokyo, Japan). Matching between Indian and Chinese men was carried out 1:1 for age (±5 years), BMI (±1 kg/m$^2$) and body fat (±5%). Eligible participants were then asked to maintain their usual lifestyle habits and refrain from strenuous physical activities until the completion of the study protocol.

### Hyperinsulinemic-euglycemic clamp with stable-isotope tracer infusion

To standardize the duration of fasting and physical activity, participants were admitted to the National University of Singapore Investigational Medicine Unit 1 day before study day. They were kept fasted from 22.00 h (except water *ad libitum*) until the completion of the protocol the next day. Intravenous catheters were inserted on opposite arms for blood sampling and intravenous infusion.

For the present study, [6,6-$^2H_2$] glucose (99% atom % $^2$H) was purchased as sterile and pyrogen free from Cambridge Isotope Laboratories (Andover, MA, USA). Glucose tracer was dissolved in isotonic saline and passed through a 0.2-μm filter into sterile syringes before administration. After collecting baseline blood samples for background isotopic enrichment, primed-constant infusion of [6,6-$^2H_2$] glucose (2 mg/kg, 3 mg/kg/min) was infused continuously for the next 5 h. After 2 h of glucose tracer infusion, blood samples were taken for the measurement of endogenous glucose production (EGP), insulin and metabolites during the fasted state. Insulin infusion was then started at 40 mU/m$^2$/min for the next 180 min. Blood glucose was measured every 5 min using an on-site glucose analyzer (YSI 2300 STATPLUS; YSI Incorporated, Life Sciences, Yellow Springs, OH, USA), and dextrose 20% was infused at a variable rate to maintain blood glucose at 100 mg/dL with a coefficient of variation of <5%. To maintain a constant plasma isotopic enrichment throughout the clamp, dextrose 20% was enriched with [6,6-$^2H_2$] glucose. Blood taken during the final 30 min of the insulin clamp was used for measurement of EGP and metabolites during the insulin clamp steady state. Indirect calorimetry (Quark RMR; Cosmed, Rome, Italy) was carried out before and during the last 30 min of the insulin clamp to measure the changes in respiratory quotient after insulin stimulation.

### Laboratory analysis

To avoid analytical variation, serum and plasma were stored at −80°C and analyzed as a single batch after completion of the study. Isotopic enrichment of glucose was measured at the Stable Isotope Core Laboratory of the Children's Nutrition Research Center, Baylor College of Medicine, Texas, USA. Penta-acetate derivative of glucose was prepared, and the isotopic enrichment of [6,6-$^2H_2$] glucose was measured by gas chromatography mass spectrometry, as previously described[7]. Profiling of plasma amino acids and AC were carried out using liquid chromatography and tandem mass spectrometry at the Duke-NUS metabolomics core facility to provide a comprehensive overview of substrate metabolism[8]. Free fatty acid concentration was measured using enzymatic methods (Wako, Osaka, Japan) and pyruvate concentration using the gas chromatography mass spectrometry technique.

### Calculations

The total glucose rate of appearance (Ra) was calculated using the standard isotope dilution equation[9].

$$\text{Total glucose Ra} = [Ei/Ep] \times F$$

where $Ei$ and $Ep$ represent the isotopic enrichment of the glucose tracer and plasma, and $F$ the rate of glucose tracer infusion.

In the fasted state, EGP was calculated by subtracting the rate of labeled glucose infused from total glucose Ra. EGP during insulin clamp was calculated by further subtracting the rate of glucose infused to maintain euglycemia. Measurements were normalized by FFM and expressed as mg/kgFFM/min. Under a steady-state condition, glucose Ra is similar to the glucose rate of disappearance (Rd), and when EGP is completely suppressed during insulin clamp, glucose Rd is reflective of skeletal muscle glucose uptake. Because the final insulin concentrations between participants were variable, we further divided glucose Rd by insulin concentration during the insulin clamp steady state ($SS_{Ins}$) as a direct measurement of skeletal muscle insulin sensitivity. MCR of insulin was calculated as the insulin infusion rate divided by the difference between insulin during the insulin clamp and fasting plasma insulin concentration as described by De Fronzo *et al.*[10]

### Statistical analysis

Independent Student's *t*-test was used to compare the clinical and metabolic parameters between the two ethnic groups, and paired Student's *t*-test to examine changes within individuals after insulin stimulation. Univariate regression analysis was used to examine the relationship between insulin MCR with various metabolic markers. Data are represented as mean ± standard deviation or as percentage where appropriate. Statistical analysis was carried out using SPSS version 22 (SPSS Inc., Chicago, IL, USA) and Prism 6 (GraphPad Software Inc., La Jolla, CA, USA). A two-tailed *P*-value ≤0.05 was considered as statistically significant.

## RESULTS

All participants were young and non-obese, with normal blood pressure, liver function, glycated, fasting plasma glucose, triglycerides and high-density lipoprotein cholesterol concentrations. Both the Chinese and Indian groups were well matched for age, BMI, bodyweight, FFM, fat mass and fat mass percentage (Table 1).

In the fasted state, plasma insulin was higher in Indian men compared with Chinese men, but this was not statistically significant. By contrast, steady-state insulin concentration was significantly higher in Indian men, consistent with a lower insulin MCR compared with Chinese men (Table 2). Fasting EGP was similar between Chinese and Indian men, and EGP was completely and equally suppressed in both ethnic groups during insulin clamp (Figure 1). Glucose Rd was not different between Indian and Chinese participants, even after dividing by $SS_{Ins}$ (Table 2). When insulin MCR of the entire cohort was compared with various metabolic parameters, statistically significant correlations were found between insulin MCR with fat mass, fat mass percentage, $SS_{Ins}$, low-density lipoprotein cholesterol, fasting EGP and $Rd/SS_{Ins}$ (Table 3).

Indians and Chinese participants had similar fasting respiratory quotients and plasma pyruvate, and these parameters increased significantly and to the same degree during insulin clamp (Figure 2). In contrast, plasma free fatty acid and 3-hydroxy-butyryl AC decreased during insulin clamp (Figure 2). Plasma concentrations of amino acids, long-, medium-, short- and C2-ACs were also similar in both groups during fasting,

**Table 1** | Baseline characteristics of Chinese and Indian men

| | Chinese ($n$ = 13) | Indian ($n$ = 13) | $P$ |
|---|---|---|---|
| Age (years) | 26.9 ± 5.4 | 26.5 ± 4.2 | 0.809 |
| Systolic blood pressure (mmHg) | 122 ± 8 | 122 ± 9 | 0.384 |
| Diastolic blood pressure (mmHg) | 71 ± 9 | 71 ± 9 | 0.515 |
| Bodyweight (kg) | 69.0 ± 4.1 | 69.3 ± 6.3 | 0.91 |
| Fat mass (kg) | 15.5 ± 1.8 | 17.2 ± 5.5 | 0.303 |
| Fat free mass (kg) | 53.5 ± 4.4 | 52.0 ± 4.0 | 0.377 |
| Fat mass % | 22.5 ± 2.8 | 24.5 ± 6.3 | 0.303 |
| BMI (kg/m$^2$) | 22.5 ± 1.1 | 23.0 ± 1.8 | 0.454 |
| HbA1c (%) | 5.3 ± 0.4 | 5.3 ± 0.4 | 0.963 |
| Fasting glucose (mg/dL) | 84.9 ± 4.6 | 83.1 ± 5,4 | 0.373 |
| Total cholesterol (mmol/L) | 5.0 ± 0.8 | 4.5 ± 0.6 | 0.112 |
| Triglyceride (mmol/L) | 1.0 ± 0.3 | 1.0 ± 0.5 | 0.941 |
| HDL cholesterol (mmol/L) | 1.4 ± 0.3 | 1.3 ± 0.3 | 0.336 |
| LDL cholesterol (mmol/L) | 3.2 ± 0.6 | 2.8 ± 0.5 | 0.139 |
| Alanine transaminase (U/L) | 23.9 ± 6.9 | 22.2 ± 9.1 | 0.605 |
| Aspratate aminotransferase (U/L) | 26.9 ± 7.6 | 24.3 ± 6.2 | 0.361 |
| Alkaline phosphatase (U/L) | 80.0 ± 19.4 | 72.9 ± 14.4 | 0.327 |

Data in mean ± standard deviation. BMI, body mass index; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

**Table 2** | Hyperinsulinemic-euglycemic clamp data in Chinese and Asian Indian men

| | Chinese ($n$ = 13) | Indian ($n$ = 13) | $P$ |
|---|---|---|---|
| Free fatty acid (μmol/L) | | | |
| Fasting | 197.4 ± 93.9 | 175.7 ± 60.8 | 0.491 |
| Clamp | 25.6 ± 13.4 | 29.3 ± 3.7 | 0.486 |
| Glucose (mg/dL) | | | |
| Fasting | 83.4 ± 5.9 | 83.8 ± 4.0 | 0.856 |
| Clamp | 95.9 ± 5.0 | 99.7 ± 5.8 | 0.085 |
| Insulin (μU/mL) | | | |
| Fasting | 7.48 ± 2.5 | 9.56 ± 3.2 | 0.079 |
| Clamp | 96.5 ± 17.0 | 111.7 ± 20.7 | 0.038 |
| Insulin metabolic clearance rate (mL/m$^2$/min) | 458.1 ± 64.8 | 405.4 ± 78.8 | 0.075 |
| Glucose Rd (mg/kgFFM/min) | 10.4 ± 3.6 | 10.8 ± 2.7 | 0.77 |
| $Rd/SS_{Ins}$ (mg/kgFFM/min per μU/mL) | 0.11 ± 0.04 | 0.10 ± 0.04 | 0.517 |

Data in mean ± standard deviation. FFM, fat free mass; Rd, glucose rate of disappearance during insulin clamp; $SS_{Ins}$, insulin concentration during insulin clamp steady state.

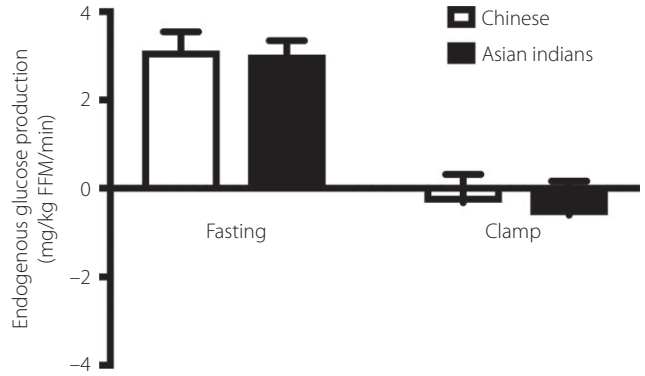


**Figure 1** | Endogenous glucose production in Chinese and Indian men during fasting and insulin clamp steady-state. Rates of endogneous glucose production (EGP) in Chinese and Indian men were measured and compared during fasting and insulin clamp steady-state. No significant between-group differences in EGP were detected in the fasted state, but EGP was completely and equally suppressed in response to insulin infusion. FFM, fat free mass.

**Table 3** | Correlation between insulin metabolic clearance rate of Indian and Chinese men with various metabolic parameters

| | Insulin MCR | |
|---|---|---|
| | *r* | *P*-value |
| Weight | −0.364 | 0.067 |
| BMI | −0.378 | 0.057 |
| Fat mass | −0.418 | 0.034 |
| Fat mass (%) | −0.390 | 0.049 |
| Fasting glucose | 0.031 | 0.88 |
| Fasting insulin | −0.199 | 0.329 |
| HOMA-IR | −0.259 | 0.201 |
| $SS_{Ins}$ | −0.963 | <0.01 |
| Total cholesterol | 0.386 | 0.052 |
| HDL cholesterol | −0.052 | 0.838 |
| Triglycerides | 0.161 | 0.433 |
| LDL cholesterol | 0.442 | 0.024 |
| Fasting EGP | 0.410 | 0.037 |
| Alanine transaminase | −0.101 | −0.64 |
| Aspartate transaminase | −0.258 | 0.204 |
| Rd | 0.084 | 0.683 |
| $Rd/SS_{Ins}$ | 0.524 | 0.006 |

BMI, body mass index; EGP, endogenous glucose production; HDL, high-density lipoprotein; HOMA-IR, homeostatic model assessment of insulin resistance; LDL, low-density lipoprotein; MCR, metabolic clearance rate; Rd, rate of glucose disappearance; $SS_{Ins}$, insulin concentration during insulin clamp steady state.

and decreased to similar magnitudes during insulin clamp (Figures 3 and 4).

## DISCUSSION

In the present study, we used the hyperinsulinemic-euglycemic clamp and stable-isotope labeled glucose infusion method to compare IR between non-obese Indian and Chinese men.

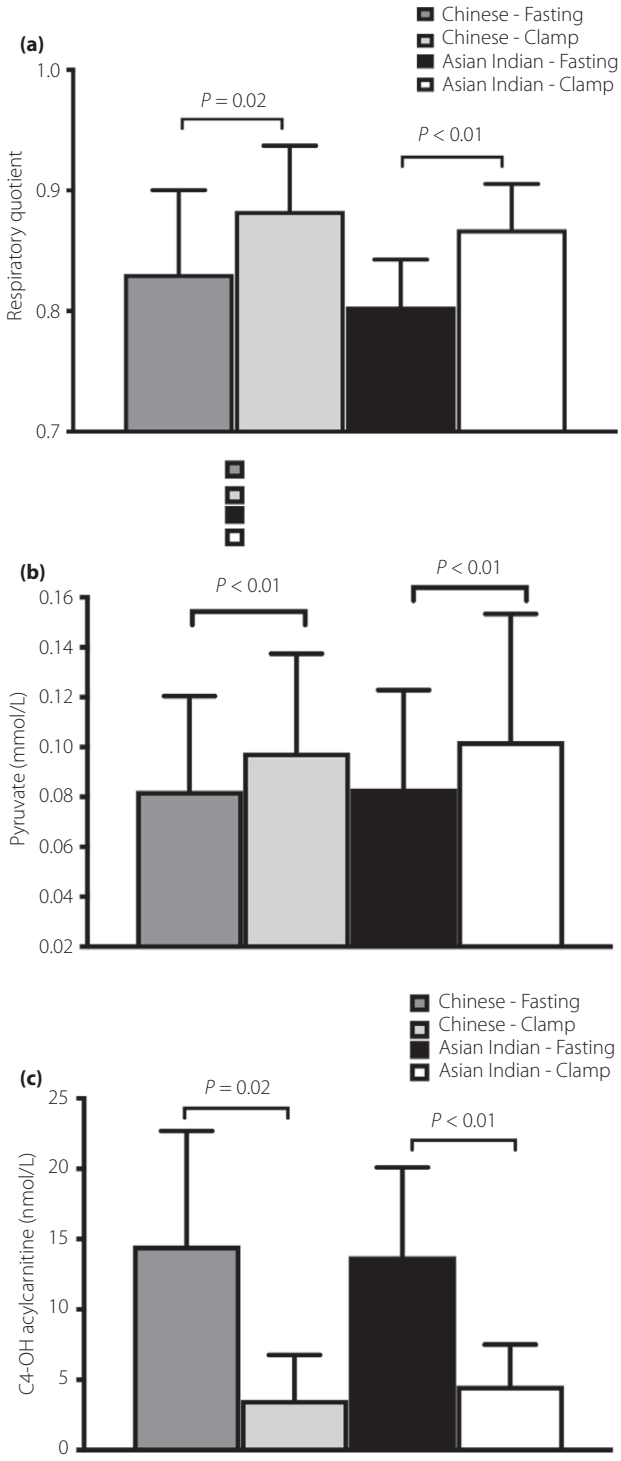


**Figure 2** | Respiratory quotient, plasma pyruvate and 3-hydroxy-butylrate in Indian and Chinese men during the fasted and insulin clamp steady-state. (a) Respiratory quotient, (b) plasma pyruvate and (c) 3-hydroxy-butylrate (4-OH) were measured in Chinese and Indian men in the fasted and insulin clamp steady-state. All measured parameters responded significantly to insulin stimulation, but no significant interethnic differences were detected. Data presented as mean ± standard deviation.

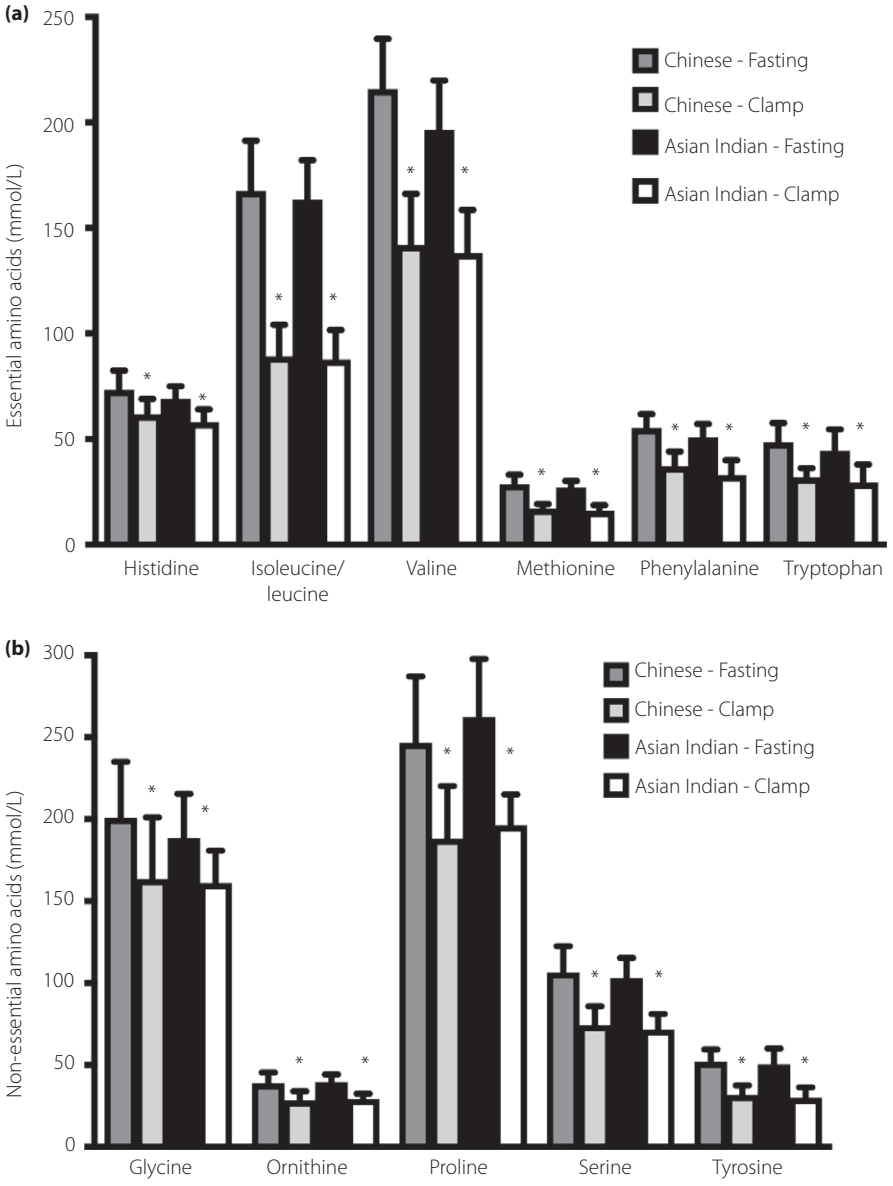


**Figure 3** | Plasma amino acids in Indian and Chinese men at the fasting and during insulin clamp steady-state. (a) Essential and (b) non-essential amino acids in Indian and Chinese men measured after an overnight fast and during insulin clamp steady state. All amino acids decreased significantly in response to insulin infusion. No significant interethnic differences were found in either the fasting or insulin-stimulated state. *$P < 0.05$ of fasting vs insulin clamp.

Previous investigators have found ethnic differences in IR, especially between non-obese Chinese and Indian men. However, these studies did not take into consideration the differences in body composition that might underlie the ethnic differences in IR[2,11]. Also, the findings of ethnic differences in IR at the lower BMI suggest that other obesity-independent pathways might be involved. The present study had several strengths. The non-obese Chinese and Indians men were matched not only for bodyweight and BMI, but also for fat-free mass and fat mass. We incorporated isotope-labeled glucose infusion with hyperinsulinemic-euglycemic clamp to enable the measurements of EGP and glucose Rd. We also examined metabolic flexibility, insulin MCR and carried out comprehensive metabolic profiling (both amino acids and ACs) between non-obese Indian and Chinese participants.

IR is the hallmark for type 2 diabetes mellitus pathogenesis. Indian individuals are known to be more IR compared with Caucasians[12,13] and other Asian ethnicities[1,2,11,14]. Even for the same BMI, Indian individuals are more IR than other ethnicities[2,11], and this might be explained by the limitation of BMI in

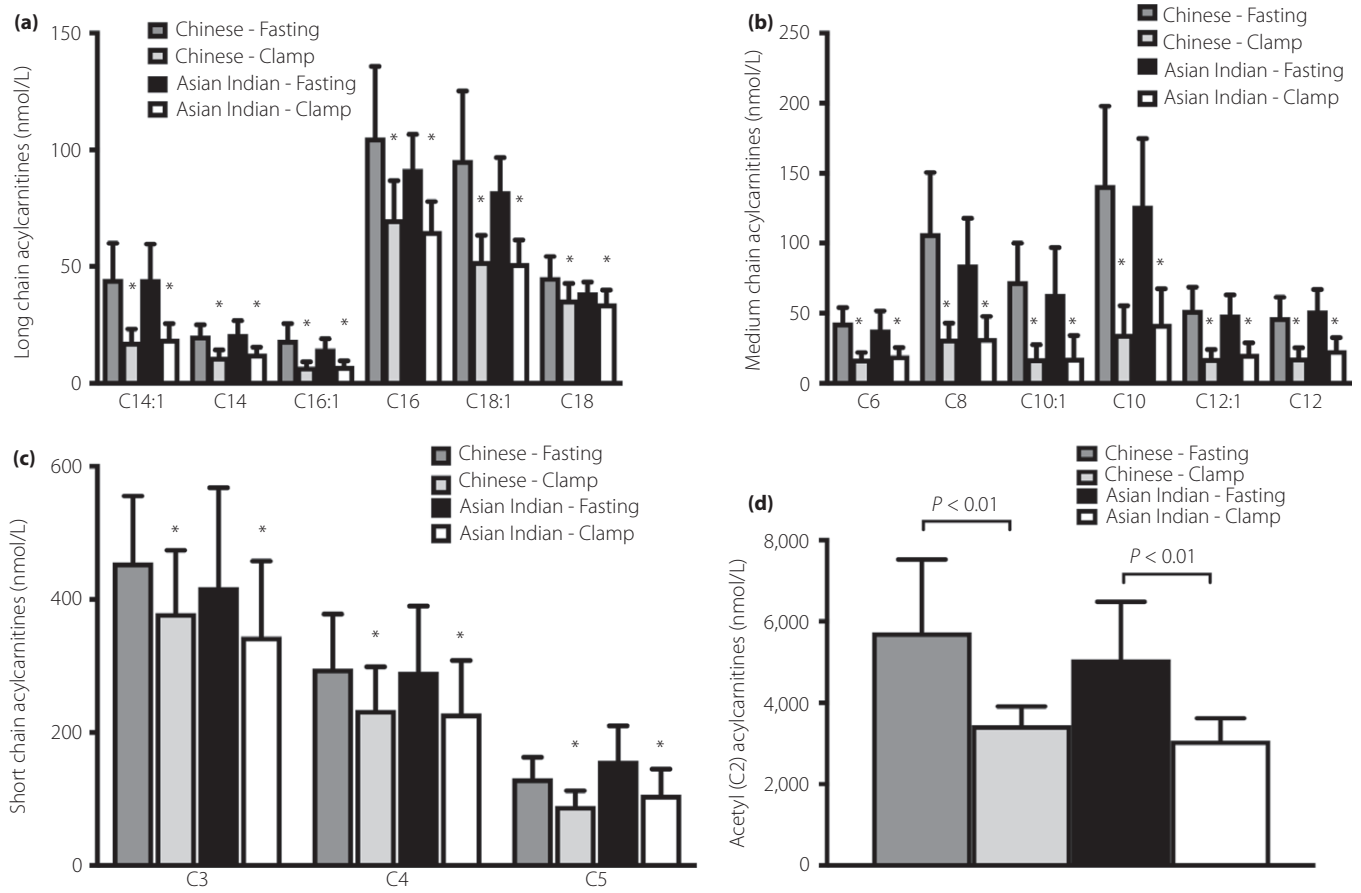


**Figure 4** | Acylcarnitine profiling in Indian and Chinese men during the fasting and insulin clamp steady-state. (a) Plasma measurements of long, (b) intermediate, (c) short and (d) acetyl carnitines in the fasted and insulin clamp steady-state. Insulin stimulation resulted in a statistically significant decrease in various acylcarnitines, but neither the fasting nor insulin clamp steady-state values were different between ethnic groups. The acyl chain length, C, is denoted by the corresponding acyl chain length with C2 (acetyl carnitine), short-chain (C3–C5), intermediate chain (C6–C12), long-chain (C14–C18). *$P < 0.05$ of fasting vs insulin clamp. Data presented as mean ± standard deviation.

the estimation of body fat[3,15,16]. In the present study, we carefully matched our participants for both BMI and body fat, and we found that EGP during the fasting state was similar in the two groups and suppressed completely in response to insulin infusion. When EGP is completely suppressed, glucose Rd during the insulin clamp reflects skeletal muscle glucose uptake, and the glucose Rd was similar in both ethnic groups, even after controlling for $SS_{Ins}$ ($Rd/SS_{Ins}$). Our findings, therefore, indicate that when both BMI and body fat were equally matched, skeletal muscle insulin sensitivity was the same for non-obese Indian and Chinese men. Similar findings have also been reported in other ethnicities, such as between Caucasians and Japanese, where interethnic differences in IR were attributed to the differences in body composition[17].

In agreement with previous studies[11], we found a higher plasma insulin concentration among Indian men compared with Chinese men during the fasting state. This difference became more apparent during the insulin clamp study, reiterating that insulin MCR was indeed lower among Indian men than their Chinese counterparts. The reason and consequence for the lower insulin MCR among Indians is currently unclear. Hyperinsulinemia has often been used as a surrogate marker of IR, but variability in plasma insulin only partially explains differences in IR[18]. Interestingly, impaired insulin clearance and the resulting hyperinsulinemia have been found to predate the development type 2 diabetes mellitus[19,20], leading several investigators to propose that hyperinsulinemia might play a direct mechanistic role in the development of type 2 diabetes mellitus[21,22]. In our cohort of healthy and non-obese participants, we found that insulin MCR correlated significantly with several adverse metabolic parameters, such as total body fat mass, fat mass percentage and glucose $Rd/SS_{Ins}$. Similar findings have also been reported in healthy and non-obese Japanese individuals with low insulin MCR[6]. Thus, the lower insulin MCR could represent the initial event in the natural history of IR and obesity pathogenesis among Indian individuals. However, this idea is at present speculative. Future prospective study is required to clarify the long-term consequence of lower insulin clearance

among Indians who are otherwise non-obese and metabolically healthy.

More recently, abnormalities in the amino acid and lipid metabolism have been implicated in the pathogenesis of IR, and this might occur through weight-independent pathways[5]. Several amino acids, in particular the branched-chain amino acids (leucine, isoleucine and valine) and its related metabolites, have been found to correlate with IR[23]. In animal studies, the branched-chain amino acids have been shown to induce IR through chronic mammalian target of rapamycin stimulation in the setting of lipid overload[5]. ACs are the byproducts of substrate catabolism, and the measurement of various plasma ACs provides a comprehensive overview of intermediary metabolisms at the cellular level. Long- (C16–C22) and intermediate- (C6–C12) even-chain ACs reflect incomplete beta-oxidation of lipids, whereas short-odd chain ACs (C3 and C5 ACs) are formed during amino acid catabolism. The accumulation of these products of incomplete oxidations could also be involved in the pathogenesis of IR[4]. In the present study, we did not find any differences in the fasting plasma concentration of amino acids, free fatty acid or AC species between the two ethnic groups. In addition, these metabolites were suppressed significantly and to a similar extent with insulin infusion, indicating that the anti-proteolytic and anti-lipolytic actions of insulin were intact in our study participants. During insulin clamp, we also found a significant increase in the respiratory quotient and plasma pyruvate consistent with a shift in substrate utilization from lipid oxidation in the fasted state to glucose oxidation during insulin infusion. The shift in substrate selection based on the changes in substrate availability is better known as metabolic flexibility and is a reflection of skeletal muscle insulin sensitivity[24]. The present results show that the metabolite profiles and metabolic flexibility were similar between non-obese Chinese and Indian men, and this further supports the finding of comparable skeletal muscle insulin sensitivity between the ethnic groups, when body composition was matched.

There were several limitations to the present study. The number of participants was small, but comparable with previous studies that showed ethnic differences in IR[11,12]. Our study used an insulin infusion rate of 40 $mU/m^2$.min, as this rate showed lower glucose Rd in non-obese Indian individuals with the same BMI but higher total body fat content than Chinese men[11]. However, when insulin levels were raised ~12-fold higher from baseline in the present study, EGP was completely suppressed. Therefore, we could only compare the differences of insulin sensitivity at the skeletal muscle level and not hepatic IR. This might be important, as IR at skeletal muscle and hepatic tissues could be detected at a lower insulin infusion rate[12,25]. A lower insulin infusion rate or the two-step insulin clamp technique, such as those used by Takeno *et al.*[26], should be used in future studies to clarify tissue-specific insulin sensitivity among Indian individuals with comparable body composition. We did not carry out pancreatic clamp in the present study and blood glucose was 'clamped' at a level that was higher that the fasting values. Therefore, it is possible that endogenous insulin secretion was not completely suppressed. Unfortunately, we did not carry out any measurement for plasma C-peptide for further validation. However, blood glucose concentration during insulin-clamp steady state was similar between the two groups. Hence, calculated results from the clamp would still be valid for comparison between the two ethnic groups. There are several methods used to calculate insulin MCR, and the method we used was comparable with other clinical studies[10,11]. We do recognize that calculations that include the measurement of C-peptide are considered to be more accurate and our findings will need to be verified in future studies. Finally, we measured whole-body total adiposity, but information on fat distribution, such as visceral and hepatic fat, is required provide additional insights into the relationship between fat distribution, ethnicity and IR.

In conclusion, we found that non-obese Indian men had the same skeletal muscle insulin sensitivity as Chinese men when matched for BMI and body fat. Also, metabolic flexibility and the physiological function of insulin on lipid and amino acid metabolism at the fasting and hyperinsulinemic state were similar for both ethnic groups. However, Indian men had lower metabolic clearance of insulin compared with Chinese men, but the implication of this finding is currently not clear.

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## DISCLOSURE

The authors declare no conflict of interest.

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