Observational study of the status of coronary risk biomarkers among Negritos with metabolic syndrome in the east coast of Malaysia

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ABSTRACT

Objectives To determine the prevalence of metabolic syndrome (MS), ascertain the status of coronary risk biomarkers and establish the independent predictors of these biomarkers among the Negritos.

Settings Health screening programme conducted in three inland settlements in the east coast of Malaysia and Peninsular Malaysia.

Subjects 150 Negritos who were still living in three inland settlements in the east coast of Malaysia and 1227 Malays in Peninsular Malaysia. These subjects were then categorised into MS and non-MS groups based on the International Diabetes Federation (IDF) consensus worldwide definition of MS and were recruited between 2010 and 2015. The subjects were randomly selected and on a voluntary basis.

Primary and secondary outcome measures This study was a cross-sectional study. Serum samples were collected for analysis of inflammatory (hsCRP), endothelial activation (sICAM-1) and prothrombogenesis [Lp(a)] biomarkers.

Results MS was significantly higher among the Malays compared with Negritos (27.7% vs 12.0%). Among the Malays, MS subjects had higher hsCRP (p<0.01) and sICAM-1 (p<0.05) than their non-MS counterpart. There were no significant differences in all the biomarkers between MS and the non-MS Negritos. However, when compared between ethnicity, all biomarkers were higher in Negritos compared with Malays (p<0.001). Binary logistic regression analysis affirmed that Negritos were an independent predictor for Lp(a) concentration (p<0.001).

Conclusions This study suggests that there may possibly be a genetic influence other than lifestyle, which could explain the lack of difference in biomarkers concentration between MS and non-MS Negritos and for Negritos predicting Lp(a).

INTRODUCTION

Orang Asli (OA) are the indigenous people believed to be the earliest inhabitants of Peninsular Malaysia. There are 18 OA tribes, categorised under three main groups according to their different languages and customs: Negritos, located in the northern part of the peninsula; Senoi, residing in the Central Region and Proto-Malays (or Aboriginal Malay) living in the southern region. The OA constitutes approximately 0.5% (150 000) of the total Malaysian population with Senoi representing the largest OA population (54%) followed by Proto Malays (43%) and Negritos (3%).

Negrito, known to be the earliest OA tribe to arrive in Peninsular Malaysia, is believed to have occupied this region of Malaysia approximately 25 000 years ago. A substantial group of the Negritos continue to practice nomadic lifestyle for reasons such as illness, food resources and intra-tribal feuds.

The poverty rate among OA is 76.9% with the majority of OA living in the jungles or rural areas, while a minority have moved into urban areas. Although the Malaysian government has taken measures to eradicate the poverty level among the OAs, which subsequently led to the reduction of poverty-associated diseases such as malaria, tuberculosis,
AIDS and dental decay, to name a few, disorders such as metabolic syndrome (MS) and coronary artery disease (CAD) are not well addressed. This could most likely stem from the common misconception that these are ‘diseases of the rich’, when in fact, it is not exclusive to one type of socioeconomic group but transcends all walks of life.4 5 MS, a major public health challenge, is a cluster of metabolic disturbances that result from a complex interaction between genetic and environmental factors.6 MS is associated with increased risk of CAD.7 The metabolic abnormalities that underlie the definition of MS include insulin resistance, central obesity, dyslipidaemia, hypertension and glucose intolerance.8 The prevalence of MS among Malaysians was estimated to be between 37.1% and 42.5% in 2008.9 It has also been well established that MS is associated with enhanced inflammation, endothelial activation and prothrombogenesis that are the key processes in atherosclerosis. Previous studies have documented the association between MS and enhanced inflammation.10 Increases in proinflammatory cytokines such as interleukin-6, resistin and C-reactive protein are due to the overproduction by monocyte-derived macrophages residing in the expanded adipose tissue mass.11 The National Cholesterol Education Program - Adult Treatment Panel (NCEP-ATP) reported higher soluble endothelial adhesion molecules such as intercellular adhesion molecule-1, vascular adhesion molecule-1 and E-selectin among subjects with MS.12 Furthermore, various studies have also shown elevated lipoprotein (a) [Lp(a)] in MS subjects.13 Lp(a) has been found to significantly reduce endogenous clot lysis in plasma ex vivo, possibly to its binding to fibrinogen and attenuating fibrin-mediated enhancement of tissue plasminogen activator of plasminogen.15

Despite MS becoming a major public health concern with extensive data on this syndrome worldwide, reports on its prevalence in Malaysia remain scarce, particularly so among the OA in the country. There have been previous studies addressing factors related to MS globally in Malaysia16; however, the samples used in these studies were not a representative of the Malaysian population as they focused on the major ethnicities in Malaysia – Malay, Chinese and Indian, while the OA population was poorly represented.

To the best of our knowledge, there is only one recent published study that reported the urbanised Orang Seletar (a Proto-Malay subtribe) having the highest prevalence for central obesity (66.1%±5.9%) compared with the other subtribes who are less urbanised (Senoi and Negrito). The study also revealed that the prevalence of hypertension was highest among the Negritos (43.8%±9.3% and 51.2%±15.3%) who resided in most remote areas and were the leanest among the six OA subtribes investigated.1

The lack of data on the prevalence of MS among OA, specifically the Negritos, could most likely stem from the preconceived notion that they are not susceptible to the disorder due to their detachment from urbanisation and their healthier lifestyle. Furthermore, there have been very few studies investigating the status of the biomarkers reflecting inflammation, endothelial activation and prothrombogenesis among the Negritos with MS. In addition, determining the MS components among them will further identify potential modifiable coronary risks such as hypertension, smoking, dyslipidaemia and glucose intolerance through proper education and healthcare services.

Therefore, this study aims to determine the MS components among Negrito, identify their status of inflammation, endothelial activation and prothrombogenesis and ascertain the independent predictors for these biomarkers of coronary risk.

SUBJECTS AND METHODS
Target population and sample collection
One hundred and fifty Negrito subjects were recruited in this cross-sectional study. They were from Bateq and Mendriq sub-tribes, from three inland settlements in Gua Musang, Kelantan, the east coast of Peninsular Malaysia (4.8843°N, 101.9682°E). Also, 1177 Malays were recruited from various national health screening programmes in Peninsular Malaysia. The subjects were randomly selected and on a voluntary basis. These subjects were then categorised into MS and Non-MS groups based on the IDF’s consensus worldwide definition of MS.17 All methods were carried out in accordance with relevant guidelines and regulations.

The sample size was calculated using PS Power and Sample Size Calculations V.3.018 with a power of study at 99% and prevalence of MS among Negritos and Malays at 15.2%±5%19 and 38.8%±5%20 respectively. The minimum sample size calculated for Negritos and Malays are both 125. Due to the significant sample size difference between the two ethnic groups recruited and the relative difficulty in accessing the Negrito’s remote locations of habitat, it is relevant to highlight that this study conducted a within-ethnic group rather than a between-group comparison of the biomarkers of interest when subdivided between MS and non-MS.

Demographic data was gathered by interview questionnaire. Information such as age, gender, tribe, education and occupation, health-related questions such as subjects’ past medical history and social history including smoking status were recorded. Family history of cardiometabolic and infectious diseases were also recorded.

Topography measurements included blood pressure (BP), body mass index (BMI), waist circumference (WC) and waist-to-hip ratio. With the subject in a seated position and following 5–10 min of rest, BP was measured by an automated BP reader (cuff size 12x33 cm, Colin press-mate, Japan). The systolic BP and diastolic BP were measured to the nearest 1 mm Hg. BMI was calculated using the formula: BMI=weight(kg)/height²(m²). WC was measured to the nearest 0.5 cm using a measuring tape at midway between the inferior margin of the last rib and
the iliac crest in a horizontal plane. Hip circumference measurement was taken around the pelvis at the point of maximal protrusion of the buttocks. Any visible stigmata of dyslipidaemia and diabetes mellitus were documented.

Defining MS (IDF Criteria, 2006)

An individual was classified as having MS if central obesity was exhibited along with at least two of the following: (1) elevated triglyceride (TG) concentration of >1.7 mmol/L, (2) reduced high-density lipoprotein cholesterol (HDL-c) of <1.0 or 1.3 mmol/L in male and female respectively, (3) elevated BP of >140/90 mm Hg, and a raised fasting plasma glucose of ≥5.6 mmol/L. Central obesity, using the suggested WC for Asian/South Asians, was defined as ≥90 cm and ≥80 cm for males and females respectively.17

Venous blood sampling and on-site biochemical analysis

Venous blood samples were collected following a non-traumatic venepuncture between 0800 hours and 1500 hours. Serum and plasma were separated by centrifugation at 3500 rpm for 10 min within 1 hour and stored at −20°C before analyse.

Biochemical analysis

Serum samples were sent to Centre for Pathology Diagnostic & Research Laboratories of Faculty of Medicine, Universiti Teknologi MARA, Selangor, Malaysia. All clinical chemistry tests analysed were MS ISO 15189:2014 accredited. Cardiometabolic parameters tested were fasting serum lipids including total cholesterol, TG and HDL-c, which were measured by enzymatic reference methods. Plasma glucose was analysed by hexokinase method. All methods were run on an automated analyser (Cobas Integra 400 PLUS, Roche Diagnostic, Germany) except for low-density lipoprotein cholesterol concentration, which was derived using the Friedewald equation.21

Analyses of biomarkers of inflammation, endothelial activation and prothrombogenesis

The biomarkers analysed included hsCRP, sICAM-1 and Lp(a). Both hsCRP and Lp(a) were measured using turbidimetric method on an automated analyser (Cobas Integra 400 PLUS, Roche Diagnostic, Germany). Serum s-ICAM-1 concentration was determined by enzyme-linked immunosorbent assay based on the measured optical density (eBioscience Bender MedSystems, Vienna Austria).

Data analysis

The associations of all three biomarkers were compared between two groups of MS and non-MS, using independent t-test, SPSS V.20. Binary logistic regression was performed on the independent variables (coronary risk biomarkers) to assess their impact on the likelihood that subjects would fall into each of the MS component (obesity, hypertension, diabetes mellitus, and low HDL-c or high TG concentrations). The specific model estimated from the data was: logit (coronary risk biomarkers) = α +b1(age) +b2(ethnicity) +b3(gender) +b4(smoking status)+b5(BMI) +b6(WC) +b7(SBP) +b8(DBP) +b9(glu-
cose concentration)+b10(HDL-c concentration)+b11(TG concentration), where the dependent variable is logit coronary risk biomarkers, α is the estimate for the intercept and b1, b2,...,b11 are estimates for the coefficients of the 11 predictors.

The variables were represented by two dummy variables to reflect the number of responses and reference categories. They were: ethnicity=Malay (1), Negrito (0), Negrito(reference group); gender, female (1), male (0)=reference group; smoking status, smoking (1) and not smoking (0)=reference group; While for age, BMI, WC, SBP, DBP, glucose, HDL-c and TG concentrations were continuous variables.

Patient and public involvement

Patients were not involved in the recruitment or conduct of the study. Written, informed consent was obtained from all subjects aged 18 years and above, prior to recruitment. Communications were done in Bahasa Malaysia with some input from local translators, either the Department of Orang Asli Development (JAKOA) officers or tribal leaders if and when required. The results of this study were disseminated to subjects through the JAKOA officers or using the postal address if provided. A physician was placed in the settings during the health screening programmes to provide an advice or referral letter when necessary.

RESULTS

Demographic data

Table 1 summarises the demographic parameters for the Malays and Negritos. A total of 326 Malays (27.7%) and 18 Negritos (12.0%) were diagnosed with MS based on the IDF 2006 criteria. On a separate note, among the Negritos, 15.5% of them had diabetes while 1.5% of the Negritos had IFG ≥5.6 mmol/L or random plasma glucose of ≥11.0 mmol/L. We observed that 43.9% of the Malays and 57.2% of the Negritos suffered from hypertension while 58.7% Malays and 14.0% Negritos had central obesity.

Compared with the non-MS Negritos, their MS counterpart had higher TC (5.30±1.05 vs 4.48±0.85 mmol/L, P<0.001 respectively), TG (2.14±0.79 vs 1.41±0.68 mmol/L, P<0.001 respectively) and LDL-c (3.36±0.69 vs 2.80±0.84 mmol/L, P=0.008 respectively). The most frequent criteria diagnosing MS among the Negritos were hypertension, elevated TG and low HDL-c and none of the Negritos diagnosed with MS had any form of glucose intolerance.

Comparison of the biomarkers of inflammation, endothelial activation and prothrombogenesis in Malay and Negrito subjects

As can be seen from table 2 there was no significant differences between MS and non-MS among
Negritos for all biomarkers (P>0.05) whereas MS Malays illustrated higher hsCRP (mean ±SD=1.88±1.16 vs 1.26±1.13 mg/L, p<0.001 respectively) and sICAM-1 (mean ±SD=531.73±185.76 vs 465.46±202.08 ng/mL, p<0.001 respectively) concentrations compared with their non-MS counterpart. When comparing between Negritos and Malays, Negritos showed significantly higher concentrations of hsCRP (mean ±SD=2.27±2.25 vs 1.41±1.17 mg/L, p<0.001 respectively), sICAM-1 (mean ±SD=684.85±388.03 vs 482.25±200.05 ng/mL, p<0.001 respectively) and Lp(a) (mean ±SD=0.22±0.22 vs 0.06±0.04 mg/L, p<0.001 respectively) compared with the Malays.

Independent predictors of the biomarkers of inflammation, endothelial activation and prothrombogenesis in Malay and Negrito subjects

To further determine the independent predictors of these biomarkers, binary logistic regression analyses were performed with the biomarkers as dependent variables (table 3). It was found that BMI (p=0.016), FPG (p<0.001) and DBP (p=0.042) were independent predictors for hsCRP while the Negro determined Lp(a) (p<0.001) when taken account all subjects after adjusting for age, gender, DM, hypertension, smoking status and BMI.

Among the Malays, it was found that male (p<0.001), BMI (p<0.001) and FPG concentration (p<0.001) predicted for hsCRP while male (p=0.040) and FPG (p=0.039) predicted Lp(a) after adjusting for the same parameters. There were no independent predictors for any of these biomarkers among Negritos.

DISCUSSION

MS is defined by an aggregation of atherosclerotic factors, mainly central obesity, hypertension, glucose intolerance and dyslipidaemia, which, in combination, enhance the probability of developing type 2 DM and CAD.22 In two European studies,23 51 the presence of MS predicted

| Parameters | Malays (n=1177) | Negrito (n=150) |
|------------|----------------|-----------------|
| Age (Years)* | 49.53±11.77 | 30.56±11.11 |
| Gender† (Males/Females) | 45.1/54.9 | 5.6/94.4 |
| Diabetes† | 42.1 | 0.00 |
| Plasma glucose*(mmol/L) | 8.22±4.38 | 5.18±1.26 |
| Hypertension† | 83.2 | 83.3 |
| SBP* (mm Hg) | 138.22±17.82 | 133.44±23.06 |
| DBP* (mm Hg) | 83.49±10.63 | 81.39±12.87 |
| Central obesity† | 100 | 100 |
| Waist circumference*(cm) | 97.19±8.93 | 90.81±6.88 |
| BMI* (kg/m²) | 30.57±4.90 | 26.31±3.26 |
| Total cholesterol*(mmol/L) | 5.38±1.00 | 5.30±1.05 |
| Triglyceride*(mmol/L) | 2.70±1.54 | 2.14±0.79 |
| LDL-c* (mmol/L) | 3.10±0.76 | 3.36±0.69 |
| HDL-c * (mmol/L) | 1.08±0.31 | 0.98±0.38 |

*Data expressed as mean ±SD. p-value was significant at p<0.05, T-test was applied.
† Data expressed as percentage. p-value was significant at p<0.05, chi-square test was applied.
BMI, body mass index; DBP, diastolic blood pressure; NS, not significant; SBP, systolic blood pressure.
increased CAD mortality. These findings are not unexpected considering MS comprises established risk factors for CAD such as hypertension, impaired glucose tolerance, low HDL-c concentration, elevated TG concentration and obesity, which enhances endothelial activation and inflammation, key processes in atherogenesis. Furthermore, coronary risk biomarkers are strongly associated with endothelial dysfunction and thrombosis and are elevated in patients with atherosclerosis-related disease such as CAD and peripheral artery disease in previous reports.

There have been several previous reports determining the prevalence of non-communicable diseases (NCDs) such as DM, hypertension, dyslipidaemia and obesity among OA subjects. A previous report on the health status of the Negrito subtribe Lanoh showed that 8.9% were recently diagnosed with hypertension, 6.7% had hypertension and DM and an alarming 26.7% had pre-obesity. A larger population study done identified central obesity and hypertension among OA sampled from seven different subtribes and eight settlements. What is more alarming is the report by Aziz et al, which highlighted the higher percentage of OA having high insulin levels, hsCRP and higher percentage categorised as high risk by the Framingham Risk Score, which forecasts 10-year risk of CAD. These reports strongly imply that NCDs such as hypertension, dyslipidaemia, central obesity and DM, which are clusters of metabolic factors associated with MS, have gradually led to the increase in CAD risk among OA.

Although several reports highlighted the increasing prevalence of NCDs among the OA in Malaysia, there is scarce research that extended to investigate biomarkers for coronary risk among this population. To the best of our knowledge, there is only one other study which reported the status of inflammatory biomarker among OA in Peninsular Malaysia compared with Malays. Our study further explored other biomarkers reflecting atherogenesis such as endothelial activation and prothrombogenesis. This study showed that biomarkers of inflammation (hsCRP) and endothelial activation (sICAM-1) were enhanced in MS Malays compared with their non-MS counterpart. These findings are expected and in keeping with previous studies denoting the higher CAD risk among MS.

Table 3 Predictors for hsCRP and Lp(a)

| Groups | Variables | Independent predictor | Beta | Adjusted OR | 95% CI Lower, Upper | P values |
|--------|-----------|-----------------------|------|-------------|---------------------|----------|
| (a) All subjects | hsCRP | 1. BMI (kg/m²) | 0.05 | 1.05 | 1.01 to 1.10 | 0.016 |
| | | 2. Glucose (mmol/L) | 0.15 | 1.16 | 1.12 to 1.19 | <0.001 |
| | | 3. Diastolic (mm Hg) | 0.01 | 1.01 | 1.00 to 1.02 | 0.042 |
| | Lp(a) | 1. Ethnicity (Negrito) | 1.03 | 2.79 | 1.87 to 4.14 | <0.001 |
| (b) Malays | hsCRP | 1. Gender (male) | −0.64 | 0.53 | 0.39 to 0.71 | <0.001 |
| | | 2. BMI (kg/m²) | 0.18 | 1.20 | 1.16 to 1.24 | <0.001 |
| | | 3. Glucose (mmol/L) | 0.08 | 1.08 | 1.04 to 1.13 | <0.001 |
| | Lp(a) | 1. Gender (Male) | −0.56 | 0.57 | 0.39 to 0.84 | 0.004 |
| | | 2. Glucose (mmol/L) | −0.08 | 0.93 | 0.86 to 1.00 | 0.039 |

The model reasonably fits well. Model assumptions are met. There are no interaction and multicollinearity problem.
biomarkers between Negritos and Malays, we observed higher concentrations of all three biomarkers among the younger aged Negrito subjects compared with the Malays. This suggests that the Negritos may be at higher risk of CAD at a younger age group, hence warranting further investigation.

Furthermore, findings from this study suggest that the MS Negritos despite having coronary risk factors such as hypertension and dyslipidaemia, the failure to exhibit enhanced atherogenesis compared with their non-MS counterpart could possibly be attributed to genetic and/or lifestyle influences, which could play a role in attenuating atherogenesis. The Negritos included in this study were located in remote areas of northern Peninsular Malaysia and to certain extent, still practising the hunter-gatherer lifestyle and living isolated from urbanisation thus may have contributed to the differences observed in the biomarkers between the two ethnicities when comparing with the MS and non-MS counterparts. This is in agreement with previous studies, which reported improved inflammatory endothelial activation and prothrombogenesis status in MS subjects, following aggressive lifestyle modification, which included dietary improvement and initiation and maintenance of exercise.36 37

One possible postulating genetic factor that may contribute to this finding is the genetic variation of the candidate gene CDH13. Recent population genomic studies on the Negritos have identified a strong and consistent positive natural selection signal spanning the genomic region which harbours CDH13.38 39 This implies that the genetic profile of this gene in the Negritos was significantly differentiated from the rest of the populations. CDH13 encodes for protein T-Cadherin, which belongs to the cadherin superfamily of the transmembrane proteins that mediate calcium-dependent intercellular adhesion, is the receptor for the high-molecular-weight adiponectin expressed in the vasculature.40 and cardiac myocytes.41 Genetic variation of this gene has been shown to influence metabolic outcome and possibly provides atherogenesis resistance.39 42 43 Adiponectin plays a crucial role in the metabolic regulation of obesity, insulin sensitivity and atherosclerosis and several studies have indicated its antiatherogenic properties.44 A recent study reported that minor allele of rs12051272 revealed a considerable association with a more favourable metabolic profile, including higher insulin sensitivity, HDL-c, lower DBP, FPG and TG concentrations.42 Given the phenotypic observations and the role of this gene, we postulate a plausibility of CDH13 regulating the phenotype and could explain the findings observed in our study whereby despite fulfilling criteria for MS, these Negritos subjects did not exhibit augmented inflammatory or endothelial activation status when compared with their non-MS counterparts. Future studies exploring expressions of genetic variants of CDH13 in these Negritos cohorts could further shed light on influences of this gene on atherogenesis.

Regression analysis has shown that the Negritos independently predict for Lp(a) in this study. This finding implies that despite hunter-gatherers get more exercise, putting them at a lower risk for heart disease and relatively isolated from modernisation, suggests that serum Lp(a) concentrations are not influenced by diet or lifestyle, but more significantly by variants in the LPA gene. This is in parallel with previous studies that exhibited a significant difference in Lp(a) levels among various populations including Asian Indian, Chinese, non-Hispanic and blacks.15 46 Studies have demonstrated the presence of LPA gene polymorphisms primarily determining levels of Lp(a), without significant dietary or environmental effects.47 Further studies are warranted to identify common polymorphisms in LPA gene among Negritos and other OA tribes, which would further validate these inferences.

The main constraint of this study was the small sample size of the Negrito group, which prevented us from comparing between ethnicities. Although the sample size included was enough to reject the null hypothesis, a larger sample size could provide a better representation of the Negrito population. However, it should be reiterated that Negrito represents only 3% of the total OA population in Malaysia and an even smaller percentage of that embodies the inland dwellers who are not subjected to urbanisation. This along with major physical problems accessing all these remote tribes prevented us from having a larger sample to analyse.

CONCLUSION

This study highlights several key findings that provide further insights into the metabolic differences between the inland-living aboriginal group, Negritos, in Malaysia and urbanised Malays in Malaysia. First, MS and non-MS Negritos failed to show differences in biomarkers of coronary risks as established by previous reports. Although the sample size of the Negrito group, which prevented us from comparing between ethnicities. Although the sample size included was enough to reject the null hypothesis, a larger sample size could provide a better representation of the Negrito population. However, it should be reiterated that Negrito represents only 3% of the total OA population in Malaysia and an even smaller percentage of that embodies the inland dwellers who are not subjected to urbanisation. This along with major physical problems accessing all these remote tribes prevented us from having a larger sample to analyse.

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