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Cut-off levels for hyperandrogenemia among Samoan women: An improved methodology for deriving normative data in an obese population

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ABSTRACT

Objective: To define biochemical hyperandrogenemia (HA) among a population-based sample of reproductive-aged Samoan women, taking into consideration their high BMI levels.

Design and methods: A secondary analysis was performed among a cross-sectional sample of Samoan women aged 25–39 years (n = 494) who were part of a larger genome-wide association study (GWAS) of adiposity. Women indicating pregnancy/lactation, hysterectomy, oophorectomy, cancer treatment, or use of contraceptive injections were excluded from the study.

We analyzed the distribution of free androgen index (FAI) values to establish normative androgen data among Samoan women of reproductive age. Using the lowest tertile of body mass index (BMI), we defined HA as free androgen index (FAI) values > 95th FAI percentile in that subsample. We compared the anthropometric and metabolic characteristics of women with HA to women with normal androgen levels.

Results: HA was defined as FAI > 8.5. Using this definition, 14% of women were classified as hyperandrogenemic. Women with HA had significantly higher average BMI values, abdominal circumferences, fasting triglycerides, and insulin levels as well as significantly lower adiponectin levels.

Conclusion: This study is the first to define normative androgen values among Samoan women with a quantitative assessment of the relationship between adiposity and androgen levels. The uniquely high BMI levels in the population not only provide important clinical insight into normative androgen values among Samoan women, but they also serve as references for the clinical assessment of HA, taking into consideration BMI, in other populations.

1. Introduction

The prevalence of overweight and obesity among adults in Samoa is one of the highest in the world, with a higher prevalence among women compared to men. In a 2010 survey, 91.3% of women and 80.4% of men were overweight or obese, based on Polynesian cut-offs for body mass index (BMI; BMI ≥ 26 kg/m^2) [1]. Despite the increasing burden of obesity among women in developing countries, the impact of obesity on reproductive health is not well-understood. As a result, a standardized approach to clinical diagnosis and treatment for health issues such as endocrine disorders among obese women is lacking.

Adiposity in adult women is associated with hyperandrogenemia (HA) in the literature [2,3,4,5]. HA can be established clinically or biochemically. Hirsutism, a clinical manifestation of hyperandrogenemia, can be assessed using the modified Ferriman–Gallwey (mF–G) scoring system, but assessments are often subjective and normal body hair amounts and distribution can vary by ethnicity [6]. Biochemical assessment is most conducive to standardization, but a consensus has not been reached on the methodology with which to define a specific cut-off point for HA in a given population [7]. The most commonly used method is a percentile cut-off among a pre-defined “healthy” group [8,9,10,11]. However, there is inconsistency in selecting a percentile cut-off as well as in defining what constitutes a healthy group in the literature. Using pre-determined percentile cut-offs without exploratory analyses into patterns of androgen distribution does not necessarily capture physiologically normative data [12].

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Considering the rise in overweight and obesity in women of reproductive age globally, the high prevalence of these conditions and the wide range of BMIs among Samoan women can contribute to a better understanding of associations between women's adiposity and androgen levels globally. The purpose of this report is to define hyperandrogenemia among Samoan women and establish the relationship between biochemical hyperandrogenemia and cardiometabolic risk factors.

2. Materials and methods

2.1. Study population & data collection

The data for this study were derived from a parent population-based genome wide association study (GWAS) of adiposity and cardiometabolic risk factors conducted in 2010 among Samoans. The GWAS recruited adults of Samoan descent (four Samoan grandparents), aged 24.5 to <65 years, from thirty-three villages in independent Samoa [1].

Health questionnaires, anthropometric measurements, and fasting serum samples were collected. The health questionnaire included menstrual patterns and contraceptive use, but clinical signs of hyperandrogenemia were not collected. After a minimum of ten hours fasting overnight, venous whole blood specimens were collected in vacutainers spray-coated with silica and containing polymer gel for serum separation. The specimens were separated by centrifugation in the field, and serum was stored at −40°C in Samoa. Samples were shipped in bulk on dry ice to Northwest Lipid Labs, Seattle, WA for lipid and metabolic hormone assays.

2.2. Cross-sectional sample selection

A total of 3504 participants enrolled in the parent study. For this analysis, participants who had not completed the health questionnaire were excluded (n = 7). Men (n = 1416) were excluded, and only women of reproductive age, 25–39 years, were included (n = 759). The upper age limit was deliberately conservative to avoid peri-menopausal as well as postmenopausal conditions [13]. Women with normal physiologic causes of menstrual irregularity, namely pregnancy/lactation (n = 17), hysterectomy or oophorectomy (n = 14), and cancer treatment (n = 1), were excluded. Women who did not report their menstrual cycle data (n = 10) or who lacked anthropometric measurements (n = 1) or fasting serum samples (n = 49) were also excluded. Because using exogenous hormone injections for contraception can result in irregular menstruation and altered androgen levels [14], we excluded women who indicated ever using contraceptive injections (n = 173). The final study sample size for this analysis was n = 494.

2.3. Anthropometric measures

The standard procedures for anthropometric measurements have been described by Hawley et al. [1]. Categorical definitions of BMI based upon body composition measures among Polynesians were used to define overweight (BMI 26–32 kg/m^2) and obesity (BMI > 32 kg/m^2), cut-offs equivalent to the standard World Health Organization (WHO) cut-offs of 25 and 30 kg/m^2, respectively, after taking into account the greater lean mass of Polynesians [15].

Abdominal circumference was taken at the level of the umbilicus. Due to the difficulty in locating the bony markers necessary to assess waist circumference in a population with a high prevalence of overweight and obesity, abdominal circumference was used as a substitute for waist circumference in calculating the ratios abdominal circumference-to-hip ratio (AHR) and abdominal circumference-to-height ratio (AHtR). For central obesity, the WHO cut-offs are abdominal circumference >88 cm, waist-to-hip ratio >0.85, and waist-to-height ratio >0.5 [16]. Mid-upper arm and calf circumferences were used as measures of peripheral obesity.

2.4. Cardiometabolic measures

Cholesterol, triglycerides, insulin, glucose, and adiponectin assays were undertaken by Northwest Lipid Labs in Seattle, WA, USA. The analytic methods are described by Hawley et al. [1].

The variable homeostasis model assessment-estimated insulin resistance (HOMA-IR) was calculated as: HOMA-IR = fasting plasma insulin (μU/mL) × glucose (mg/dL) / 405 [17]. Because of the general similarities in body size and adiposity of Mexican Americans and Samoans, we used, albeit cautiously, the insulin resistance cut-off of HOMA-IR >3.80 recommended among Mexican Americans by Qu et al. [18].

Type 2 diabetes was defined as either a fasting glucose level of ≥126 mg/dL or self-report of taking medication for diabetes. We excluded diabetic women (n = 21) when analyzing glucose, insulin, and HOMA-IR values in the study.

2.5. Reproductive hormones

Serum levels of total testosterone (TT) and sex hormone binding globulin (SHBG) were determined by automated chemiluminescent immunoassay (Siemens, Los Angeles, CA) at Women & Infants Hospital in Providence, RI, USA. SHBG values exceeding the maximum sensitivity range of 180 nmol/L (n = 20) were diluted and re-assayed. For TT, the lower limit of detection was 0.694 nmol/L, and values at or below this level (n = 55) were assigned 0.694 nmol/L for analysis. The inter-assay coefficients of variation for TT and SHBG were less than 8.7% and 4.1%, respectively.

The free androgen index (FAI), defined as (TT × 100) / SHBG, was calculated for each sample. FAI adjusts TT values for abnormalities in SHBG, and studies have shown that FAI is a more sensitive and reliable index for assessing HA [19]. Given the variability of the TT assays currently available, using FAI provides a better estimate of TT concentration by incorporating the more accurate results of the SHBG assays [20,21].

2.6. Statistical analyses

All metabolic and reproductive hormones were subject to a log-10 transformation prior to statistical analyses to account for the highly right-skewed nature of these distributions, and comparisons are reported as median (log standard deviation). We calculated Pearson's correlation coefficients between androgen measurements and anthropometric measurements.

In order to better quantify the association of BMI and androgens in a predominantly overweight population, FAI was stratified by equal tertiles of BMI rather than by pre-defined obesity categories.

As described above, standard biochemical cut points for defining HA are not well-defined in the literature [12,22]. We defined HA here to be FAI above the 95th FAI percentile among women in the lowest BMI tertile. The 95th percentile is an accepted approach to defining biological cut-offs, but it is important that this approach be used among a subset in the population with low BMI given the strong association of BMI and FAI [4,12]. In order to have robust statistical power, we use the 95th FAI percentile in the lowest BMI tertile (n=165) instead of in the normal BMI group (BMI < 26 kg/m^2) in which there were only n = 55 women.

Differences in metabolic parameters between androgen groups were assessed using independent samples t-test or a Chi-squared test. A pairwise exclusion was used for missing data. Statistical significance was two-tailed at the p = 0.05 level.

2.7. Ethical approval

The Brown University Institutional Review Board and the Health Research Committee of the Samoan Ministry of Health approved the parent research protocol and informed consent process.