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Anthropometric Indices Added the Predictive Ability of Iron Status in Prognosis of Atherosclerosis

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ABSTRACT

Background: Abnormal homeostasis of iron such as deficiency or overload is associated with the pathogenesis of cardiovascular disease (CVD). Another risk factor for CVD is obesity whose added predictive ability to iron status has been assessed by few study. This study aimed to evaluate the effect of adding anthropometric indices to a model based on iron status as risk factors of CVD.

Methods: This cross-sectional study included 140 adult women aged 18-50 years randomly selected from Sheikhorrais Clinic that is one of the Tabriz University sub-specialized clinics in 2011. Anthropometric indices, carotid intima-media thickness (CIMT) and body iron status were measured by standard protocol, non-invasive ultrasound and concentrations of serum iron, ferritin, TIBC (Total iron Binding Capacity) and complete blood cell counts (CBC), respectively. Integrated discriminatory improvement index (IDI) and net reclassification improvement index (NRI) were used as the measures of added predictive ability of anthropometric measures to the iron statues.

Results: IDI (SE) after adding Waist Circumference (WC), Waist to Heap Ratio (WHR), Waist to Height Ratio (WHtR), Body Mass Index (BMI) and Body fat (%) to base model was 0.12 (0.028), 0.09 (0.026), 0.12 (0.028), 0.07 (0.022) and 0.10 (0.026) respectively. The NRI (SE) was 0.10 (0.065) for WC, 0.03 (0.058) for WHR, 0.07 (0.067) for WHtR, 0.05 (0.067) for BMI, and 0.08 (0.064) for Body fat.

Conclusions: Anthropometric indices could significantly add to the predictive ability of the iron statues, with highest IDI when WC and WHtR were added to the base model. It suggests that by adding WC and WHtR to the iron status lead us to a more optimal model for predicting the initial stage of atherosclerosis.

Keywords: Anthropometric, Iron, Atherosclerosis, Predictive Ability, IDI, NRI

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Introduction

Findings of epidemiological studies are controversial according to iron status and risk of cardiovascular disease (CVD) [1]. Sullivan first proposed iron-heart hypothesis

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which is an interaction between body iron pools and its abnormal homeostasis such as lipid per oxidation [2]. Deficiency or overload is associated with the pathogenesis of various chronic diseases, including diabetes and CVD [3, 4]. Iron has oxidative properties and its accumulation in body is a risk factor of atherosclerosis [5]. Atherosclerotic plays an important role in the etiology of CVD. A non-invasive ultrasound measurement of carotid wall intima-media thickness (CIMT) is considered as a general marker for atherosclerosis that correlates with the extent of coronary artery disease in adults and predicts future cardiovascular events [6].

Another risk factor for CVD is obesity. It is associated with diabetes mellitus, hypertension, cardiovascular disease, gall bladder disease, and some types of cancer [7-9]. Anthropometric measurements still play an important role in clinical practice to measure the total body fat and its distributions [10]. Body mass index (BMI) is often used to reflect total body fat amount, while waist circumference (WC), waist-to-hip ratio (WHR) or waist-to height ratio (WHtR) is used as a surrogate of body fat centralization [11].

Few studies have assessed the added predictive ability of the anthropometric measures over iron status for CVD events. If simple anthropometric measures could increases the predictive ability of iron status, this new model can be considered as the best predictor of incident CVD and its complications.

This study aimed to evaluate the effect of adding anthropometric indices to a model, based on iron status as the risk factors of CVD and determined how the addition of anthropometric indices can change the predictive ability of iron status.

Materials and Methods

This cross sectional study included 140 adult women aged 18-50 years randomly selected from Sheikhorrais Clinic, a sub-specialized clinics of Tabriz University of Medical Science, which is one of the most important referral clinics where patients are referred to from the entire province in 2011. Inclusion criteria were to being free from known chronic or acute diseases, i.e. CVD, diabetes, renal disease, hypothyroidism and hyperthyroidism. Pregnant, breastfeeding and menopause women, those treated by steroids, growth hormone, oral contraceptives and any anabolic drug, alcohol or drug users, those with renal disorders, diabetes and hypertension were excluded. Systolic and diastolic blood pressures were measured on the right arm after 15 minutes of rest in sitting position.

The study was approved by the Ethics Committee of Tabriz University of Medical Science [ethical code: 901]. A questionnaire and informed consent form were completed for the subjects.

Anthropometric measurement

Weight, with minimal clothing and without shoes, was measured using digital scales (Seca 707: range 0.1-150 kg) and recorded to the nearest 100 g. Height was measured in a standing position, without shoes while the shoulders were in a normal position to the nearest 0.5 cm. Waist circumference and hip circumference (HC) were measured using un-stretched tape meter in standing position without any pressure to body surface and was recorded to the nearest 0.1 cm. Waist circumference and HC were measured in the middle of lowest gear and the highest part of the pelvis (the most narrow waist circumference) and on the biggest environmental gluteal muscle, respectively. BMI was calculated as weight (kg) divided by squared height (m). WHR was calculated as WC (cm) divided by HC (cm) and WHtR as WC (cm) divided by height (cm). Subcutaneous fat was measured at four regions (biceps, triceps, subscapular, suprailiac) using caliper (Slimguide Model, Creative health, USA). All skinfold measurements were measured three times on the right side of the body and the average was used for analysis. Reliability of anthropometric measurements was assessed in these repetitions by intra class correlation coefficient (All above .80).

Body density defined as body mass / body volume (g/ml), was estimated from Durnin and Womersley equation and then body fat (%) was calculated using the Siri's equation as Body fat (%) = (495/density)–450. The Siri equation is based on the two compartment model that is the body is made up of essentially two components: fat mass (the total fat of an individual) and fat-free mass (everything else: bone, water, lean tissue etc). As density = mass / volume, and the mass of a human is made up of the total of fat mass and fat-free mass, therefore density = (fat mass + fat-free mass) / volume. Following this through and substituting mass/density for volume, and using the values for density above, eventually you get to the Siri equation as listed.

Laboratory measurement

Fasting blood sample was drawn between 7:00 and 9:00 a.m. from all study participants. Serum ferritin was assessed by ELIZA method and commercial kit (Radem, Italy), serum iron and TIBC (Total iron binding capacity) were measured using colorimetric technique (Pars Azmon Inc., Tehran, Iran). Complete blood cell counts (CBC) were assayed using H_1 device as counter cell (Technicon, America).

Common carotid IMT

CIMT was measured using non-invasive ultrasound. All images were taken from the right and left common carotid artery. Medison system (model V10) and 10-MHz Linear transducer was used. All images of the right and left common carotid arteries were captured by the same radiologist who was blinded about clinical condition of the subjects. The participants were asked to lie in the supine position during the ultrasound procedure. Imaging of the left common carotid artery was performed with the subject turning her head 45 degrees to the right and reversely. Imaging was performed in B-mode with transducer movement in longitudinal and latitudinal sections. The transducer was manipulated until maximum thickness in area bolb (1 cm proximal to the common carotid bifurcation) of both carotids was acquired. Then we tried to obtain image with high quality from the desired area in longitudinal section and image was fixed. By placing marker, measurement was performed electronically by the device. The far-wall IMT was measured at three measurement points in right and left that finally maximum thickness was recorded on each side. Based on the CIMT, subjects were classified in "healthy" (CIMT≤0.8 mm) and "at risk" (CIMT >0.8 mm) categories. Precision of ultrasound devices was 0.1 mm.

Statistical analysis

To address the added predictive ability of the anthropometric indices over iron Status as the CVD risk factors, were used integrated discrimination improvement (IDI) and net reclassification improvement (NRI), as two new ways in assessing improvement in model performance offered by a new marker [12]. IDI = Integrated Sensitivity (IS) - Integrated 1-Specificity (IP) which measures the improvement in the average sensitivity with the new marker, and subtracts any increase in the mean 1−specificity.

NRI = ([number of events reclassified higher − number of events reclassified lower]/number of events) _ ([number of non-events reclassified lower− number of no n-events reclassified higher]/number of non-events) which provides a method of quantifying the enhancement in clinically useful risk estimation when a novel marker is added to a standard risk prediction model. This new approach is rapidly being accepted as an important method for evaluating the clinical utility of new risk markers [12].

Area under the ROC Curve (AUC) can be defined as the area under the plot of sensitivity *vs* 'one minus specificity' for all possible cut-off values. The improvement in AUC for a model containing a new marker is defined simply as the difference in AUCs calculated using a model with and without the marker of interest. This increase, however, is often very small in magnitude; studies show simple examples in which enormous odds ratios are required to meaningfully increase the AUC [12]. So we used two new ways of evaluating the usefulness of a new marker.

For this reason a model containing the iron status including serum iron, ferritin, TIBC, RBC (Red Blood Cell), MCV (Mean Cell Volume) and hematocrit was considered as the base model and new models were fitted by adding anthropometric indices including BMI, WHR, WHtR, Body Fat and WC in the separate performances and finally all anthropometric indices simultaneously. In addition IS and IP, standard error (SE) for IDI and NRI and the *P*-value of the test for these indices were presented.

Added-predictive ability SAS macro was used for estimation of IDI and NRI and their SE using SAS software (SAS Institute Inc., Cary, NC, USA). *P*-values <0.05 were considered as to be significant.

Results

One hundred and forty female subjects aged 32.8 (SD = 8.19) years were studied. Anthropometric and biochemical characteristics are shown in Table 1.

Slight increase in the base model AUC was found after adding anthropometric indices to this model.

AUC for the prediction of atherosclerosis was 0.806 using base model and increased to 0.860 by WC additions. However, the greatest increases in AUC was observed when WC (AUC=0.860) and WHtR (AUC= 0.864) were added to the base model. By adding all anthropometric to the base model resulted in the maximum amount of improvement (AUC=0.882) in predicting atherosclerosis.

Table 1: Anthropometric and biochemical factors of subjects

	Mean (SD)
Age (yr)	32.80(8.19)
Weight(kg)	76.30(17.60)
Height(cm)	158.40(5.47)
Waist circumference(cm)	100.40(17.28)
WHR	0.88(0.07)
WHtR	0.63(0.11)
BMI(kg/m^2)	30.46(7.26)
Body fat(%)	32.6(5.68)
Serum iron(µg/dl)	81.60(36.60)
Ferritin (ng/ml)	48.90(29.70)
TIBC(µg/dl)	369.70(63.30)
RBC (M/µL)	4.67(0.42)
MCV(fl)	86.30(6.66)
Hematocrit	39.90(3.14)
Diastolic blood pressure	11.01(1.43)
Systolic blood pressure	7.37(1.15)
CIMT (mm)	0.76(0.25)

†WHR, waist to hip ratio; WHtR, waist to height ratio; BMI, body mass index; TIBC, Total Iron Binding Capacity; RBC, Red Blood Cell; MCV, Mean Cell Volume; CIMT, Carotid artery Intima-Media Thickness

The maximum value of IDI (SE) for predictive ability was after adding WC and WHtRto base model (0.12 (0.028) and 0.12 (0.028) respectively). Based on the test of IDI, for all anthropometric indices significant improvements were observed (IDI = 17% SE= 0.033, *P*<0.05) (Table 2).

Table 2: Summaries for predictive indices and the results of tests for base model by adding anthropometric indices

	AUC-Dif	**IDI (SE)**	***P-value***	**NRI(SE)**	***P-value***
Base model +WC	0.054	0.12 (0.028)	<0.001	0.10 (0.065)	0.109
Base model +WHR	0.038	0.09 (0.026)	0.001	0.03 (0.058)	0.592
Base model +WHtR	0.058	0.12 (0.028)	<0.001	0.07 (0.067)	0.275
Base model +BMI	0.039	0.07 (0.022)	0.001	0.05 (0.067)	0.450
Base model+ Body fat(%)	0.050	0.10 (0.026)	0.001	0.08 (0.064)	0.219
Base model + WC, WHR, WHtR, BMI, Body fat(%)	0.076	0.17 (0.033)	<0.001	0.05 (0.069)	0.443

†Base model (iron Status including serum iron, ferritin, TIBC, RBC MCV and Hematocrit), WC, waist circumference; WHR, waist to hip ratio; WHtR, waist to height ratio; BMI, body mass index; TIBC, Total Iron Binding Capacity; RBC, Red Blood Cell; MCV, Mean Cell Volume; IDI, Integrated Discrimination

Improvement; NRI, Net Reclassification Improvement; SE, Standard Error; AUC, Area Under ROC Curve; AUC-Dif, Difference between new model AUC and base model AUC/

The maximum value of NRI (SE) was 0.10 (0.065) for WC and NRI (SE) was 0.05 (0.069, *P*=443) for all anthropometric indices added to the base model (Table 2).

Discussion

This study demonstrated the predictive performance of anthropometric indices added to iron Status (base model) for predicting risk of atherosclerosis. According to the results, anthropometric indices could significantly add to the predictive ability of the iron Status (base model) based on IDI index. These results suggest that the risk prediction for atherosclerosis improved after anthropometric indices were added into the base model. The highest percentage of IDIs were seen when WC and WHtR were added to the base model. It suggests that adding WC and/or WHtR to the base model create a model with improvement in model for predicting of initial stage of atherosclerosis.

All measures displayed non significant improvements in the NRI estimations. Similar to IDI, the highest percentage of NRI was seen when were added to the base model WC and WHtR and in addition Body fat (%).

Results of this study showed that adding anthropometric indices especially WC and WHtR to iron status create a new and more powerful model to predict atherosclerosis.

Numerous studies applied anthropometric indices as available and feasible tools in CVD screening. However, various anthropometric indices of obesity such as BMI, WHR, WC and WHtR have been suggested as screening tools to identify individuals at risk of CVD [13], as BMI reflecting overall obesity, skin-fold thickness assessing regional obesity, WC, WHR, WHtR demonstrating abdominal fat deposition [14]. Epidemiological evidences show that abdominal obesity is better predictor for CVD than overall obesity [15]. A number of studies have recommended WC as a tool to assess CVD risk factors [16]. WHtR better corresponds to metabolic risk than WHR, WC or BMI [17, 18]. In adults, WHtR seems to be a good indicator of abdominal visceral fat and predictor of cardiovascular risk factors and mortality, both in men and women [19]. WHtR was a better indicator of cardiovascular risk factor in both men and women in comparison with the other three anthropometric indices, as reflected in the calculated area under the ROC curve [20]. Lee et al. [21] support previous claims that measures of central obesity, in particular the WHtR, are better discriminators of cardiovascular disease risk factors compared with BMI. According to our results and similar studies, anthropometric indices especially abdominal indices (WC and WHtR) can improve predictive ability of atherosclerosis.

One another factor related to atherosclerosis is iron statues; there is evidence that the total amount of iron in the body is related to the development of atherosclerotic disease [22]. A prospective study revealed the serum ferritin levels as one of the strongest risk predictors of progression of atherosclerosis [23].

The mechanism by which iron may stimulate atherogenesis is unclear. The catalytic role of iron in lipid peroxidation may be an important factor in the formation of atherosclerotic lesions [22].

Although little conclusive evidence exists to support the role of ferritin or plasma iron in CVD risk, it seems plausible that free iron would be increased with elevated ferritin and potentially contributes to oxidative stress [24].

Since, for measuring anthropometric indices were used from handle device and for measuring iron status was used from kits and biochemical factors and has less error than anthropometric indices and according to previous studies that showed effect of iron Status on CVD risk and atherosclerosis and predictive ability of iron status to prognosis CVD risk. In this study we used iron status as the base model.

Only female subjects were used, which was the first limitation of this study. Further studies including both females and males are recommended for better generalization of results. In addition, it is highly suggested to perform the multicenter studies on different ethnicity groups for further generalization of the results.

One of advantage of this study was to use the advance indices of IDI and NRI in predicting atherosclerosis by using iron Status and anthropometric.

Our results based on IDI index, suggest that each of the anthropometric indices can increase predictive power of iron status in predicting atherosclerosis but improvement of prognosis ability of adding WC and WHtR as abdominal anthropometric indices to the iron status are higher than others.

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