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Research Article

Lipid Accumulation Product is a Novel Index Associated with Osteoporosis: Evidence from Two Independent Cross-sectional Chinese Populations

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Abstract

Objectives: The relationships between osteoporosis and obesity-related indices have been extensively investigated, but for the newly developed index, lipid accumulation product (LAP), its relationship with osteoporosis is unknown. This study aimed to explore the relationship between LAP and osteoporosis.

Methods: A total of 2,128 and 3,384 elderly subjects were recruited from two Community Health Service Centers. These participants received anthropometric measurements, questionnaire investigations, bone density measurements, body composition measurements, and blood biochemical tests. Correlation analysis and multiple linear regression analysis were performed. Integrated discrimination improvement (IDI) and net reclassification improvement (NRI) were calculated to evaluate the risk prediction capabilities.

Results: LAP and all conventional obesity-related indices positively correlated with bone mineral density (BMD) at the total hip and lumbar spine (LS) (P<0.001) in all subjects and in sex-classified subgroups. After adjustment for percentage fat mass, the positive correlation between LAP and BMD at the two sites was still statistically significant (P<0.05) (except for LS-BMD in females of Sample 1). Furthermore, IDI and NRI analyses indicated that the addition of LAP would significantly improve the ability to predict osteoporosis.

Conclusion: Taken together, evidence from two independent cross-sectional Chinese populations indicates that LAP is a novel index associated with osteoporosis.

Keywords: osteoporosis, obesity, lipid accumulation product

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1 INTRODUCTION

Osteoporosis is a widespread disorder that affects more than 200 million people worldwide[1].Osteoporosis is a multifactorial condition characterized by changes in bone homeostasis, which result in reduced bone mass, impaired bone quality, and an increased propensity for fractures[2].As life expectancy continues to rise due to technological improvements, osteoporosis has become a

significant public health concern[3].Obesity and osteoporosis are two complex and closely related diseases. Previous epidemiological studies have extensively investigated the relationship between osteoporosis and many conventional obesity-related indices, including waist circumference (WC), waist-to-hip ratio (WHR), body mass index (BMI), fat mass (FM), percentage fat mass (PFM), and visceral fat rating (VFR). These indices have been developed to evaluate obesity from various aspects and have several endogenous advantages and limitations in the evaluation of obesity. Apart from these conventional anthropometric indices, some obesity-related indices have been newly developed, such as lipid accumulation product (LAP).

LAP is a simple but effective index of visceral obesity, calculated by using WC and triglycerides (TGs)[4]. LAP can reflect overall fat accumulation and visceral fat function. LAP has shown potential for predicting the risk of hypertension, renal function decline, impaired fasting glucose, and even diabetes and cardiovascular disease[5]. Several published studies have explored the value of LAP in disease prediction. For example, Chiang et al.[6] explored the accuracy of LAP in predicting metabolic syndrome in Chinese middle-aged and elderly people. LAP was proven to be a simple index with significantly higher predictability. Similar results were found in the Iranian population[7]. However, LAP, as a novel obesity-related index, has not been evaluated with regard to its relationship with osteoporosis.

The purpose of this study was to analyze the correlation between LAP and osteoporosis and to compare the correlation between LAP and osteoporosis with a series of conventional obesity-related indices in two independent large Chinese populations. Furthermore, this study also evaluated whether the newly developed index LAP improved the ability to predict the risk of osteoporosis.This study also provides new clues for researchers and clinical doctors to plan and manage future work. So as to better prevent osteoporosis.

2 MATERIALS AND METHODS

2.1 Study Subjects

The study subjects were community-dwelling adults 65 years or older who were recruited by two Community Health Service Centers in Southeast China. The subjects were invited to attend the regular medical examination and our osteoporosis project. All the subjects received anthropometric measurements, questionnaire investigations, bone mineral density (BMD) measurements, body composition measurements, and blood biochemical tests. Since blood biochemical tests were carried out using different machines at the two health service centers, subjects were analyzed as two independent populations. Originally, 2,128 (Sample 1) and 3,384 (Sample 2) subjects from two Community Health Service Centers were included in this study, respectively.

The following exclusion criteria were adopted to exclude the subjects: (1) history of endocrine diseases, including hyperparathyroidism and hypothyroidism; (2) history of major gastrointestinal surgery; (3) history of severe renal insufficiency; (4) severe anemia; (5) depression and malignant tumors; (6)use of corticosteroids. Using the exclusion criteria, 423 and 256 subjects were excluded from Sample 1 and Sample 2 in the following analyses, respectively. Finally, a total of 4,833 eligible subjects with 1,705 from Sample 1 and 3,128 from Sample 2 were involved in the following analyses. This study was approved by the institutional review boards of the authors' affiliated institutions. Written consent was obtained from all study participants.

2.2 Anthropometric Measurement and Questionnaire Investigation

Each participant received face-to-face interviews with a questionnaire to obtain basic information, including demographics, lifestyle, family history, and medical history. Standing height and weight were measured using standard procedures. Using inelastic tape, the WC was evaluated at the umbilical level, and the hip was determined at the maximum extension of the horizontal plane of the buttocks. BMI was calculated using the following formula.

$$BMI = weight / height^2 (kg/m^2)$$

2.3 BMD and Body Composition Measurement

The BMDs (g/cm^2) at the total hip (TH) and lumbar spine (LS) were determined using a dual-energy X-ray absorptiometry bone densitometer (Hologic Inc., Waltham, MA, USA). The LS prosthesis was used for quality control daily before the participants were tested for BMD. The accuracy of BMD measurements was based on three replicate measurements of thirty volunteers expressed as the root mean square coefficient of variation (RMS-CV). For the BMD measurements of TH and LS, the RMS-CV was 2.50% and 2.05%, respectively. Body composition was measured using a bioelectrical impedance analyzer (MC 780A, TANITA, Tokyo, Japan). All participants had to wear light clothing and take off their shoes and socks. PFM (%), FM, lean mass and VFR were automatically calculated by the machine. The fat mass index (FMI) and lean mass index (LMI) were calculated using the following formulas.

$$FMI = fat\ mass / height^2 (kg/m^2)$$
$$LMI = lean\ mass / height^2 (kg/m^2)$$

2.4 The Test of Serum TG and The Calculation of LAP

Fasting peripheral blood was drawn from each subject by a certified phlebotomist from the antecubital fossa vein in the early morning of the test. Serum TG was tested by using Siemens ADVIA 2,400 and Mindray BS-360 biomedical analyzers. LAP is a sex-specific index.

$$Male\ LAP = (WC-65) * TG\ (cm{\cdot}mmol/L)$$
$$Female\ LAP = (WC-58) * TG\ (cm{\cdot}mmol/L)$$

Table 1. Basic Characteristics of the Study Subjects

	Total (*n*=4,833)	Sample 1 (*n*=1,705)	Sample 2 (*n*=3,128)	*P*
Age (year)	72.44±5.71	72.01±5.17	72.68±5.98	0.014
LAP (cm·mmol/L)	42.61±35.93	44.55±35.68	41.55±36.02	<0.001
TH-BMD (g/cm^2)	0.79±0.16	0.80±0.15	0.79±0.16	<0.001
LS-BMD (g/cm^2)	0.90±0.19	0.89±0.19	0.90±0.19	0.054
WC (cm)	85.30±9.86	85.05±8.93	85.43±10.33	0.098
Weight (kg)	60.79±10.34	60.73±10.28	60.8±10.38	0.754
Height (m)	1.59±0.13	1.57±0.19	1.60±0.09	<0.001
BMI (kg/m^2)	23.78±3.27	23.93±3.24	23.69±3.28	0.003
PFM (%)	27.48±8.41	28.74±8.16	26.80±8.47	<0.001
FMI (kg/m^2)	6.64±2.73	7.04±2.72	6.41±2.70	<0.001
LMI (kg/m^2)	15.94±1.81	15.93±1.73	15.94±1.85	0.858
VFR	10.54±4.02	10.91±3.94	10.33±4.04	<0.001
TG (mmol/L)	1.69±1.11	1.80±1.07	1.63±1.13	<0.001

Notes: Values are the mean±SD for continuous variables and *n* (%) for categorical variables.

2.5 Statistical Analyses

Descriptive statistics are used to characterize the distribution of all parameters. Continuous variables such as age, height, and other obesity indices are expressed as the mean and standard deviation (SD). The T test or Wilcoxon rank sum test was used to compare the differences between Sample 1 and Sample 2 and between male and female groups of each sample. Bivariate Spearman correlation analyses were used to study the association of BMD with sex, age, and obesity-related indices at both sites. If age and sex were significantly associated with BMD (P<0.05), these significant confounding factors were included in multiple linear regression analyses at the corresponding sites. If the variance inflation factor is > 10, it indicates collinearity between obesity-related phenotypes and covariates. The receiver operating characteristic curve (ROC) and area under the ROC were used to assess the extent of the predictive model for osteoporosis. Integrated discrimination improvement (IDI) and net reclassification improvement (NRI) were used to assess the extent to which the newly added index LAP improved the prediction accuracy of the new model. P<0.05 was considered to be significant. All analyses were performed using SAS 9.4.

3 RESULTS

As shown in Table 1, there were significant differences in age, LAP, TH-BMD, height, BMI, PFM, VFR and TG between the two samples (P<0.05).

Then, the data from the two independent samples were analyzed separately. Table 2 shows the Spearman correlation results between obesity-related indices and BMD. Since sex has a significant effect on BMD, this study also analyzed their correlations in the sex-classified subgroups in further analyses (Table 2). In all subjects, under no adjustment, the LAP was associated with BMD in Sample 2 but not in Sample 1. LAP was significantly associated with BMD in both males and females in the two samples (P<0.001). In both total subjects and gender-stratified subjects, BMD at both TH and femoral neck was significantly associated with obesity-related indices (e.g., WC, PFM, FMI, LMI and VFR) (P<0.001).

When sex and/or age were adjusted as covariates in multiple linear regression analyses (Table 3), LAP and all conventional obesity-related indices were positively and consistently correlated with BMD either in total subjects or in the sex-stratified subgroups, but the standardized regression coefficients of LAP were smaller than some conventional obesity-related indices (e.g., BMI, WC, PFM and VFR) in the total sample, males and females. The association results were similar in the two samples.

To further evaluate whether the correlation for LAP is independent of the conventional obesity-related indices, this study performed multiple regression analyses with involvement of sex and/or age and a single conventional obesity-related index as covariates. Table 4 presents the standardized regression coefficients and the corresponding *P*-values for LAP in the regression analyses. As shown in Table 4, the positive correlations between LAP and TH-BMD and LS-BMD were still statistically significant (P<0.05) when adjusting PFM (except for LS-BMD in females of Sample 1). However, when adjusting for FMI, LMI, WC, BMI or VFR, the associations between LAP and BMD were not significant in many situations, e.g., for WC and TH-BMD in the total sample or for BMI and LS-BMD in the total sample.

This study used the ROC curve to evaluate the predictive power of LAP for osteoporosis (BMD T score<-2.5 SD diagnosed as osteoporosis). The lowest area under curve(AUC) in Model 1 was 0.627, which suggested a lower prediction of PFM in osteoporosis. When LAP was added to Model 1 to form Model 2, all AUCs in Model 2 were

Table 2. Spearman Correlation Analysis between Obesity-related Index and BMD

	Total		Male	
	TH-BMD	LS-BMD	TH-BMD	LS-BMD
Sample 1				
Sex	0.576***	0.588***		
Age (year)	-0.166***	0.0001	-0.149***	0.029
LAP (cm·mmol/L)	0.019	0.017	0.263***	0.254***
WC (cm)	0.260***	0.270***	0.252***	0.250***
BMI (kg/m^2)	0.287***	0.263	0.379***	0.347***
PFM (%)	-0.254***	-0.253***	0.198***	0.210***
FMI (kg/m^2)	-0.095***	-0.102***	0.277***	0.273***
LMI (kg/m^2)	0.642***	0.598***	0.417***	0.334***
VFR	0.577***	0.588***	0.340***	0.352***
Sample 2				
Sex	0.505***	0.551***		
Age (year)	-0.175***	0.013	-0.162***	0.049
LAP (cm·mmol/L)	0.093***	0.059**	0.245***	0.199***
WC (cm)	0.288***	0.319***	0.240***	0.238***
BMI (kg/m^2)	0.306***	0.287***	0.339***	0.288***
PFM (%)	-0.180***	-0.207***	0.160***	0.172***
FMI (kg/m^2)	-0.036*	-0.063**	0.238***	0.223***
LMI (kg/m^2)	0.547***	0.552***	0.349***	0.279***
VFR	0.517***	0.557***	0.270***	0.275***

Notes: The value listed in the table is the correlation coefficient. * represents $P<0.05$, ** represents $P<0.01$, *** represents $P<0.001$.

Table 3. The β Value in the Regression Analysis Adjusted by Sex & Age or Age

	Total		Male		Female	
	TH-BMD	LS-BMD	TH-BMD	LS-BMD	TH-BMD	LS-BMD
Sample 1						
LAP (cm·mmol/L)	0.145	0.134	0.223	0.224	0.148	0.123
WC (cm)	0.201	0.199	0.262	0.234	0.239	0.249
BMI (kg/m^2)	0.297	0.270	0.404	0.333	0.330	0.315
PFM (%)	0.248	0.231	0.225	0.185	0.233	0.239
FMI (kg/m^2)	0.015	0.017	0.020	0.022	0.012	0.015
LMI (kg/m^2)	0.036	0.041	0.038	0.042	0.039	0.045
VFR	0.383	0.347	0.393	0.337	0.309	0.312
Sample 2						
LAP (cm·mmol/L)	0.123	0.150	0.083	0.150	0.171	0.201
WC (cm)	0.165	0.204	0.151	0.194	0.212	0.283
BMI (kg/m^2)	0.222	0.247	0.168	0.271	0.322	0.316
PFM (%)	0.191	0.229	0.140	0.165	0.185	0.262
FMI (kg/m^2)	0.013	0.017	0.016	0.020	0.011	0.015
LMI (kg/m^2)	0.028	0.034	0.026	0.035	0.032	0.035
VFR	0.307	0.314	0.189	0.278	0.322	0.280

Notes: The adjusted covariates are sex & age in the total sample, and age in the males or females. β represents standardized regression coefficient. All the tests are significant with $P<0.001$.

increased compared with those in Model 1 at TH and LS, but the differences in AUCs between the two models were not statistically significant (Table 5) (except for those in males of Sample 2). Furthermore, both IDI and NRI demonstrated significant results, which suggests that the newly added LAP significantly improved the prediction accuracy of the new model (except for NRI in the females of Sample 2 at TH).

4 DISCUSSION

Conventional obesity-related indices have some

Table 4. Standardized Regression Coefficients and the Corresponding *P*-values in the Regression Analysis

Adjusted Conventional Indices	Total				Male				Female			
	TH-BMD		LS-BMD		TH-BMD		LS-BMD		TH-BMD		LS-BMD	
	β	*P*	β	*P*	β	*P*	β	*P*	β	*P*	β	*P*
Sample 1												
PFM (%)	0.087	<0.001	0.079	<0.001	0.165	<0.001	0.177	<0.001	0.080	0.015	0.049	0.161
FMI (kg/m^2)	0.063	0.003	0.053	0.020	0.099	0.018	0.138	0.001	0.066	0.037	0.028	0.406
LMI (kg/m^2)	0.044	0.032	0.041	0.065	0.042	0.286	0.086	0.031	0.057	0.067	0.027	0.431
WC (cm)	0.045	0.071	0.029	0.259	0.095	0.060	0.119	0.020	0.038	0.297	0.000	0.998
BMI (kg/m^2)	0.019	0.380	0.020	0.395	0.009	0.826	0.059	0.181	0.030	0.354	0.004	0.906
VFR	0.046	0.029	0.036	0.104	0.024	0.569	0.067	0.114	0.077	0.015	0.033	0.328
Sample 2												
PFM (%)	0.074	<0.001	0.093	<0.001	0.114	<0.001	0.104	<0.001	0.064	0.015	0.114	<0.001
FMI (kg/m^2)	0.056	0.002	0.076	<0.001	0.084	0.005	0.087	0.005	0.049	0.065	0.094	<0.001
LMI (kg/m^2)	0.060	<0.001	0.086	<0.001	0.070	0.011	0.068	0.018	0.061	0.015	0.132	<0.001
WC (cm)	0.045	0.026	0.054	0.005	0.069	0.041	0.059	0.081	0.040	0.172	0.066	0.022
BMI (kg/m^2)	0.029	0.117	0.048	0.005	0.032	0.282	0.037	0.229	0.033	0.223	0.075	0.005
VFR	0.027	0.142	0.062	<0.001	0.027	0.366	0.038	0.208	0.030	0.253	0.104	<0.001

Notes: β represents standardized regression coefficient.

Table 5. The Predictive Effect of PFM alone Versus PFM & LAP on Osteoporosis

Group	Sites	AUC Model 1	AUC Model 2	AUC Difference	*P* for AUC Differences	IDI (%)	*P* for IDI	NRI (%)	*P* for NRI
Sample 1 total	TH	0.831	0.836	0.005	0.223	1.556	0.004	34.193	<0.001
Sample 1 total	LS	0.750	0.754	0.004	0.130	0.400	0.023	22.070	<0.001
Sample 2 total	TH	0.789	0.792	0.003	0.165	0.296	0.028	16.630	0.002
Sample 2 total	LS	0.749	0.752	0.003	0.112	0.454	<0.001	19.474	<0.001
Sample 1 male	TH	0.694	0.792	0.098	0.046	1.290	0.003	89.051	0.002
Sample 1 male	LS	0.655	0.682	0.028	0.130	1.748	<0.001	37.927	0.001
Sample 2 male	TH	0.712	0.753	0.041	0.007	1.028	0.013	48.306	<0.001
Sample 2 male	LS	0.627	0.658	0.030	0.010	0.839	<0.001	28.943	<0.001
Sample 1 female	TH	0.743	0.751	0.008	0.326	1.721	0.002	25.963	0.003
Sample 2 female	TH	0.719	0.721	0.002	0.389	0.249	0.042	6.665	0.263

Notes: Model 1: The regression analysis includes PFM, and age and/or sex that were significantly associated with BMD; Model 2: The regression analysis includes the corresponding variables in Model 1 and LAP.

endogenous advantages and limitations in the evaluation of obesity. BMI is a simple and commonly used index in evaluating the total amount of fat accumulation, but BMI cannot be used to assess the distribution of body fat. The amount of body muscle is an important misleading factor in obesity evaluation when BMI is used. WC is currently considered to be the simplest and most practical index for measuring abdominal adipose accumulation. However, WC cannot distinguish between subcutaneous fat and visceral fat. LAP is a simple and effective integration index that reflects not only the overall accumulation of abdominal FM but also the index of FM metabolism. Previous studies have shown that LAP is a simple and accurate predictor of metabolic syndrome, hypertension, diabetes and cardiovascular disease. This study represents the first effort to investigate the relationship between LAP and osteoporosis.

LAP is associated with metabolic syndrome and some cardiac metabolic risk factors. A study of Taiwanese individuals aged 50 years and over showed that LAP has a higher predictive value for metabolic syndrome than BMI, WC, WHR, and waist-height ratio[6]. LAP may be a useful tool for predicting the risk of cardiovascular disease and metabolic syndrome in postmenopausal women[8]. Kahn believes that LAP is better at identifying diabetes than BMI[9]. A subsequent follow-up study demonstrated this in young people[10]. Elevated LAP is significantly associated with hypertension risk in Chinese Han adults, and LAP is better at predicting hypertension risk than other obesity indices[11].It is well established that obesity interacts with bone metabolism through mechanical, hormonal, and inflammatory factors[12]. Therefore, as an indicator of visceral obesity, LAP is more suitable than other obesity indicators to assess the association between central obesity and osteoporosis.

The present study found that LAP was a novel index associated with osteoporosis based on the following evidence: (1) When sex and/or age were adjusted as covariates in multiple linear regression analyses, LAP and all conventional obesity-related indices were positively and consistently correlated with BMD either in total subjects or in the sex-stratified subgroups; (2) the associations between LAP and BMD were still significant even under adjustment of PFM; (3) both IDI and NRI, demonstrating that the newly added LAP significantly improved the prediction accuracy of the new model.

The positive correlations between LAP and BMD were still statistically significant when adjusting for PFM but not significant in many situations when adjusting for WC, BMI or VFR. The possible explanation for this observation is that LAP formed by WC and TG is regarded as a composite index of visceral adiposity; when the adjustment of other indices (e.g., WC, BMI, and VFR), the effect of LAP on BMD would be adjusted due to the strong correlation between LAP and other indices. It is reasonable that the correlation disappeared after adjustment for conventional obesity-related indices (e.g., WC, BMI or VFR) in some situations. Comparatively, the correlation between LAP and BMD was more independent of PFM than other indices. LAP and all conventional obesity-related indices were significantly positively correlated with TH-BMD and LS-BMD, but the standardized regression coefficients of LAP were smaller than some other conventional obesity-related indices in the total sample, males and females.

AUC is a common method to determine the predicted value. This method is based on the test performance of different "diagnostic thresholds" and is used to summarize the test performance of all thresholds[13,14]. However, the ROC curve and AUC are of little significance to clinicians and patients[15]. NRI and IDI provide a new AUC alternative for measurement model identification. In the case where the model already has a medium to strong AUC, they better reflect the degree of model improvement than AUC[16-18]. IDI summarizes how much the new model increases the average risk of events and reduces the average risk of nonevents[19]. The NRI directly represents the cost of correct and incorrect classification and incorporates adjustments in prevalence because the study data are expressed in the diagnosis of false negative and false positive patients, and the effects are also clinically relevant and easy to interpret.

From this, this study used AUC, IDI, and NRI to evaluate how the newly added indices improved the predictive accuracy. Using the ROC curve of the entire population, it can be seen that the addition of a new index to the risk prediction model has not reached significance, but both IDI and NRI proved that the newly added index LAP improved the prediction of the model. In addition, the differences in AUCs in some sites were remarkable in males, but in the total participants and females, the differences in AUCs were not significant. The IDIs and NRIs in males were higher than those in all participants, except for Sample 1 at the TH site. Therefore, it can be considered that LAP was more valuable in improving the accuracy of PFM in predicting osteoporosis in males, and the results in females were inconsistent. Larger independent samples are needed to verify this conclusion.

At the same time, this study also considered possible reasons for the correlation between LAP and osteoporosis. LAP is a powerful index of insulin resistance, and its ability to identify insulin resistance in nondiabetic individuals is stronger than that of BMI and WC[20]. BMD is associated with insulin resistance. Insulin resistance leads to higher plasma insulin and excessive production of androgens and estrogen in the ovary, resulting in a decrease in the production of liver sex hormone-binding globulin. As a result, it increases the level of sex hormones, inhibits osteoclast activity, enhances osteoblast activity, and ultimately manifests as increased bone mass.

5 CONCLUSION

This study represents the first effort to explore the association between the new obesity-related index LAP and osteoporosis, detect the change of relationship after adjustment of conventional obesity-related indices, and evaluate the accuracy in prediction osteoporosis after addition of LAP. Taken together, the evidence from two independent cross-sectional Chinese populations indicates that LAP is a novel index associated with osteoporosis.

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Conflicts of Interest

The authors declared no conflict of interest.

Ethical Statement

This study was approved by the institutional review boards of the authors' affiliated institutions. Written consent was obtained from all study participants.

Author Contribution

Zhu D and Ge B were responsible for data collection. Tang H and Pei H were responsible for analysis. Tang H and Pei H were responsible for writing. Tang H, Liu X, Pei H et al. were responsible for editorial assistance. Tang H and Pei H analysed the data for completeness.

Abbreviation List

AUC, Area under curve
BMD, Bone mineral density
BMI, Body mass index

FM, Fat mass
FMI, Fat mass index
IDI, Integrated discrimination improvement
LAP, Lipid accumulation product
LMI, Lean mass index
NRI, Net reclassification improvement
ROC, Receiver operating characteristic curve
RMS-CV, Root mean square coefficient of variation
LS, Lumbar spine
PFM, Percentage fat mass
TG, Triglyceride
TH, Total hip
VFR, Visceral fat rating
WC, Waist circumference
WHR, Waist-to-hip ratio

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