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Subtracted Adulthood Mass Index - a new index to predict NAFLD risk in non-obese individuals*

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Abstract

Background and Aim: Nonalcoholic fatty liver disease (NAFLD) is a common chronic liver disease. The aims of the current study are to determine the relationship between NAFLD in non-obese individuals and weight gain during adulthood and develop a new index for the identification of NAFLD risk.

Materials and Methods: For this cross-sectional study, 362 patients who underwent abdominal ultrasonography (USG) in our clinic were included. Seventy-eight individuals were obese (>30 kg/m^2). A history of weight gain during adulthood and systemic metabolic diseases was collected at the time of the study. A new index termed "Subtracted Adulthood Mass Index" (SAMI) was created to estimate the risk of NAFLD development for non-obese people. SAMI is the ratio of the difference between the individual's current weight and his/her weight at 20 years old to his/her height squared (kg/m^2).

Results: When the SAMI cut-off was set at 3 kg/m^2, the sensitivity for predicting NAFLD risk was 85.2%, the specificity was 66.9%, the PPV was 79.1%, and the NPV was 75.4%.

Conclusion: In this innovational study, a new index named SAMI was developed to identify non-obese people who are at risk of developing NAFLD. The SAMI is easy to calculate and appropriate for clinical use.

Keywords: NAFLD; nonalcoholic fatty liver disease; weight gain in adulthood.

Introduction

Nonalcoholic fatty liver disease (NAFLD) is one of the most common liver disorders around the world, especially in industrialized countries where the prevalence is estimated to be around 20% to 30%.[1–3] NAFLD has a wide pathologic spectrum which includes; simple hepatosteatosis, nonalcoholic steatohepatitis (NASH), liver cirrhosis and hepatocellular carcinoma (HCC).[1,4–6]

Although NAFLD is usually associated with obesity, growing number of studies suggest that it can also be observed in non-obese individuals without metabolic syndrome.[7,8] NAFLD in non-obese population has been linked to epigenetic and genetic factors or can be idiopathic.[9] Globally, the reported prevalence of non-obese NAFLD ranges from 3% to 30%. This variability may be attributed to differences in study population, diagnostic modalities, lifestyle and dietary habits of the specific population.[4,10–12] Histology and prognosis of NAFLD in non-obese individuals are always thought to be better than obese people. However, Non-obese and obese individuals' liver biopsies do not show any significant histological difference.[11] Also, prognosis of non-obese individuals with NAFLD are not statistically better than obese people with NAFLD.[1,4] As a matter of fact, NAFLD in non-obese individuals emerges as one of the most probable causes of cryptogenic liver diseases.[12]

NAFLD is accepted as an independent contributing factor to a number of diseases including Type II diabetes, hypertension and coronary artery disease.[13,14] Obese people with NAFLD mostly have other comorbities due to their high body mass index (BMI).[15] Since non-obese individuals, who have NAFLD, do not have many risk factors for other diseases, NAFLD per se causes more mortality and morbidity in this group of patients than in obese individuals with NAFLD.[9]

Visceral fat is regarded as a risk factor for metabolic diseases and NAFLD.[16] Two of the main fat deposition types in a human body are visceral and subcutaneous fat.[17] In childhood, most of the fat is deposited as subcutaneous fat.[17,18] However, as a person ages, percentage of visceral fat in human body increases.[19] Similarly , as the individual gains weight in adulthood, the prevalence of NAFLD in non-obese individuals also increases.[20] Until now, no method has been defined which can predict the risk of NAFLD development in non-obese individuals.

The current study aimed to define an index specific for non-obese people which would estimate the risk of NAFLD development.

Materials and Methods

Study Population

In this cross-sectional study, we included 384 individuals who were referred to the radiology clinic for abdominal ultrasonography by a gastroenterology specialist at Acibadem University between November 2016 and March 2017. All subjects provided written informed consent prior to participating to the study. 22 subjects were excluded because of missing data and exclusion criteria. Starting age of the adulthood

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was set as 20 years for both male and female individuals. Subjects answered surveys, which included age, sex, medical history, drinking habits and subjects' weights when they were 20 years old. Exclusion criteria were pregnancy, chronic liver disease, renal insufficiency, HBsAg or anti-HCV positivity, cancer treatment, being younger than 25 years old and weekly alcohol consumption more than 210 g for males and 140 g for females.

Clinical, Biochemical and Ultrasonographical Evaluation

A total of 362 subjects were clinically evaluated. Subjects' BMI values were calculated and BMI>30 kg/m^2 was accepted as a threshold for obesity as suggested by World Health Organization. Blood samples were obtained after at least 10 hours of fasting and individuals' fasting plasma glucose, ALT, AST, total cholesterol, triglyceride were recorded. Ultrasonographical examinations were performed by an experienced radiologist. The diagnosis was accepted as hepatosteatosis when there was at least 30% increase in liver echogenicity on real-time USG. Grade 1 steatosis refers to minimal diffuse increase in hepatic echogenicity; normal visualization of diaphragm and intrahepatic vessel borders. Grade 2 was described as moderate diffuse increase in hepatic echogenicity; slightly impaired visualization of intrahepatic vessels and diaphragm. Having marked increase in echogenicity; poor penetration of posterior segment of the right liver and poor or nonvisualization of hepatic vessels and diaphragm was defined as grade 3.[21]

The study was approved by the Institutional Review Board of Acıbadem Hospital (or Acıbadem University Ethics Committee).

Statistical Analysis

Statistical analysis was performed by using IBM SPSS program using t-test. P value <0.05 was regarded as statistically significant. Receiver operating characteristic (ROC) curve analysis was carried out to examine the ability of the new index to predict NAFLD risk in individuals.

Results

Characteristics of The Study Population

In total 362 individuals were included in the study. Out of them, 78 individuals were obese (BMI>30 kg/m^2). Most obese subjects were male (%58,9) and their mean age was 46.7±9.1. Out of 284 non-obese subjects 128 (%45) were male and 169 (%59.5) had NAFLD. Average age of the non-obese group was 44.2±11. Demographic characteristics, average BMI and average BMI at the age of 20 years of NAFLD(+) and NAFLD(-) subjects from the non-obese group are shown in Table 1.

Prevalence of type II Diabetes, hypertension and coronary artery disease in non-obese individuals are presented in Table 2.

The Link Between The New Index Called SAMI and NAFLD in Non-obese Individuals

Non-obese NAFLD(+) patients reported they had gained significant amount of weight during their adulthood. This information led us to create a new index named "Subtracted Adulthood Mass Index" (SAMI) to estimate the risk of NAFLD development in non-obese individuals. SAMI is calculated by dividing the difference between the subject's current weight and his/her weight at the age of 20 to his/her height squared (kg/m^2). SAMI values for non-obese subjects were calculated. To assess the relationship between SAMI and NAFLD in non-obese individuals, several cut-off values for SAMI were evaluated. SAMI 3 kg/m^2 and SAMI 4 kg/m^2 were determined as best cut-off values statistically. Sensitivity, specificity, negative predictive value and positive predictive values of SAMI 3 kg/m^2 are presented in Table 3.

A constant relationship between SAMI and NAFLD prevalence was established and it can be seen that as the SAMI values increase, NAFLD prevalence increases consistently. This relationship is presented in Figure 1.

The area under the curve in ROC analysis was 0.846, ROC curve is presented in Figure 2.

Table 1. Demographic characteristics and SAMI values of non-obese individuals

	Non-obese NAFLD (+) subjects n=169 Median (IQR) or %	Non-obese NAFLD (-) subjects n=115 Median (IQR) or %	p
Male gender (%)	57.4	26.9	1.53×10^{-7}<0.05
Age (years)	48.04±10.10	38.73±10.04	4.74×10^{-13}<0.05
SAMI (kg/m^2)	5.87±2.74	2.05±2.50	2.2×10^{-16}<0.05
BMI at 20 years of age (kg/m^2)	20.16±2.55	20.29±3.27	0.0691>0.05

BMI: Body mass index; SAMI: Subtracted Adulthood Mass Index; NAFDL: Nonalcoholic fatty liver disease.

Table 2. Type II diabetes, hypertension, coronary artery disease prevalences in non-obese population

	Non-obese NAFLD (+)	Non-obese NAFLD (-)	p
Type II diabetes	12.4	1.7	1.07×10^{-3}<0.05
Hypertension	16.5	1.7	5.18×10^{-5}<0.05
Coronary artery disease	5.9	1.7	0.0846>0.05

NAFDL: Nonalcoholic fatty liver disease.

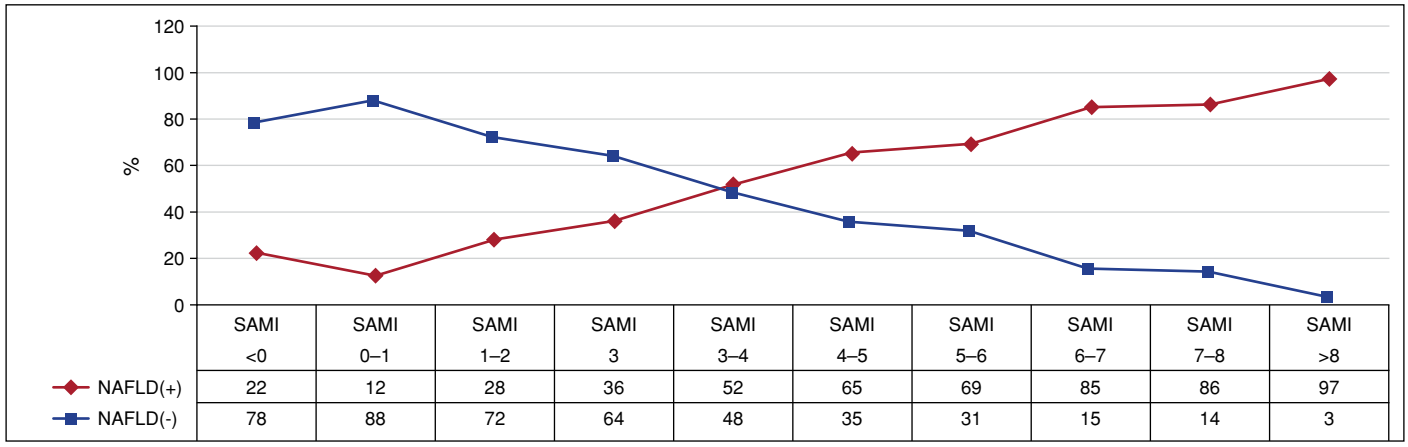
Table 3. Sensitivity, specificity, negative predictive value and positive predictive values of SAMI 3 kg/m^2 and 4 kg/m^2

	SAMI 3 kg/m^2 as a cut-off value %	SAMI 4 kg/m^2 as a cut-off value %
Sensitivity	85.2	76.3
Specificity	66.9	79.1
Negative predictive value	79.1	84.3
Positive predictive value	75.4	69.4

SAMI: Subtracted Adulthood Mass Index.

Discussion

Currently there is no index or method which is being used to predict the risk of NAFLD in non-obese people. This fact decreases the opportuni-



	SAMI <0	SAMI 0–1	SAMI 1–2	SAMI 3	SAMI 3–4	SAMI 4–5	SAMI 5–6	SAMI 6–7	SAMI 7–8	SAMI >8
NAFLD(+)	22	12	28	36	52	65	69	85	86	97
NAFLD(-)	78	88	72	64	48	35	31	15	14	3

Figure 1. Continuous relationship between SAMI and NAFLD prevalence. The area under the curve in Receiver operating characteristic (ROC) analysis was 0.846, ROC curve is presented in Figure 2.

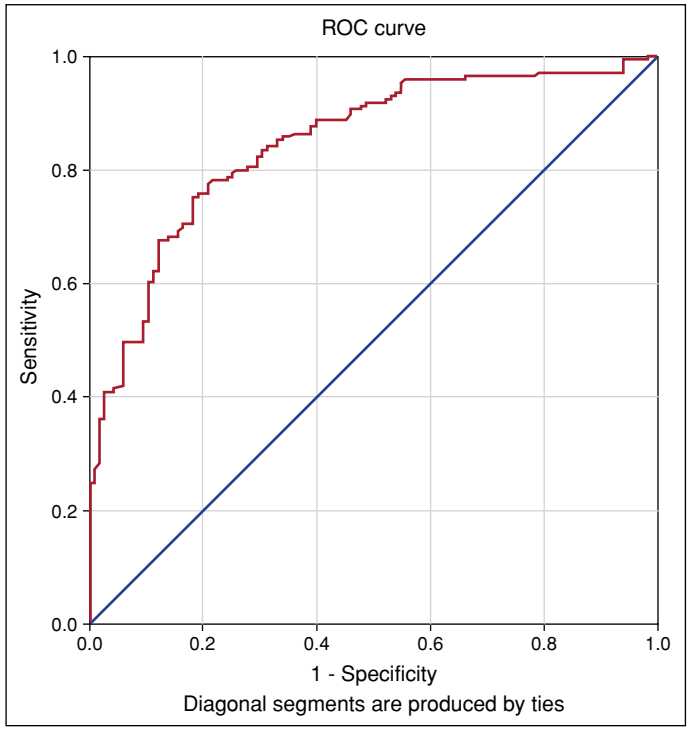


Figure 2. ROC Curve of SAMI.

ty to see the development of morbidities and mortalities associated with NAFLD in non-obese subjects.

In the present study, we aimed to define a new index which will predict the risk of NAFLD development in non-obese individuals and hence will help us to characterize people under the risk of its complications. NAFLD is closely associated with changes in body weight and can regress with weight loss even more dramatically in nonobese NAFLD people. With the new SAMI, we can identify the non-obese individuals who have higher risk of developing NAFLD and plan lifestyle changes such as increased physical activity and dietary modifications which will lead to NAFLD regression.

NASH prevalence in non-obese NAFLD patients is as high as in obese NAFLD(+) individuals.[10,22] Higher levels of ALT/AST values have been observed in non-obese individuals compared to obese individuals.[23] In addition, NAFLD subjects who have elevated ALT levels carry higher risk of NASH development.[24] Taking these into account, one can ask whether non-obese individuals are more susceptible to NASH development and whether the ensuing complications are more severe. The question remains to be answered in future studies in larger groups but also underlines the importance of identifying early the individuals who have higher risk of NAFLD development.

Visceral fat is one of the globally accepted risk factors of metabolic disorders.[25] The amount of excess visceral fat correlates with the risk of metabolic diseases such as type II diabetes, hypertension, and the risk of coronary artery diseases.[25–27] Hepatic fat accumulation which leads to NAFLD is also correlated with the amount of visceral fat deposition in body.[14,28] Reasons behind NAFLD development in non-obese people are still uncertain; however, one of the plausible theories is visceral fat.[29] Kim et al.[30] have suggested four possible factors causing NAFLD in non-obese population, two of them being visceral fat and body weight gain. The results of our study also implicated that weight gain in adulthood with a SAMI value of 3 and visceral fat are the most probable reasons behind NAFLD development in non-obese individuals.

Metabolic syndrome has been the explanation for NAFLD in non-obese population in most studies, however NAFLD is often encountered in non-obese individuals without the presence of metabolic syndrome.[31–34] In our study, we found significant differences between NAFLD(+) non-obese patients and NAFLD(-) non-obese patients regarding the incidence of diabetes mellitus and hypertension. NAFLD(-) non-obese individuals had less diabetes mellitus, hypertension and coronary artery disease (1.7%, 1.7%, 1.7%, respectively) whilst in NAFLD(+) non-obese patients the incidence of diabetes mellitus and coronary artery disease were 12.4%,16.5% and 5.9% respectively. These data led us to think that NAFLD might be the reason behind the metabolic disturbances in these people. Therefore, we claim that these individuals, who are NAFLD(+) and non-obese, are metabolically obese and carry the same health risks as people who are obese by definition.

This research has some limitations. Firstly, there might be a selection bias, because the patients included in this study, were referred to radiologists for abdominal ultrasonography. Secondly, the diagnosis and the grade of NAFLD were established by ultrasonography as a cheaper and noninvasive method compared to liver biopsy. Transient elastography was not available in our unit at the time of the study. Ultrasonography also has

high sensitivity and high specificity in NAFLD patients (85% and 94% respectively).[35] Thirdly, individuals' body weight status at the age of 20 was obtained from the patient's history and not from medical records and this may lead to recall bias. Lastly alcohol consumption of individuals was also based on his personal statement. A study with more precise anthropometric data in larger groups of patients is required to clarify the accuracy of SAMI in NAFLD risk estimation in non-obese population.

In conclusion, non-obese NAFLD patients constitute an important proportion of NAFLD patients. Because of the reasons stated above, risk stratification for NAFLD in non-obese population is especially important due to the fact that non-obese individuals, who are at risk, do not have distinct characteristics of obese patients. With the use of this new Index named SAMI, NAFLD risk in non-obese individuals can be estimated and progression of the disease to NASH, fibrosis and cirrhosis can be prevented by lifestyle changes and possibly by pharmacological agents in the future. SAMI is an easy way to predict the risk of NAFLD development in non-obese people and it can be applied as a screening test by any physician or healthcare personnel, especially in primary healthcare facilities, without any cost and unlike other diagnostic methods, it does not require any professional experience.

Ethics Committee Approval: The study was approved by the Institutional Review Board of Acıbadem Hospital (or Acibadem University Ethics Committee).

Peer-review: Externally peer-reviewed.

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Conflict of Interest: The authors have no conflict of interest to declare.

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