EBioMedicine 2 (2015) 1513–1522

Contents lists available at ScienceDirect

EBioMedicine

journal homepage: www.ebiomedicine.com

Research Article

Circulating Unsaturated Fatty Acids Delineate the Metabolic Status of Obese Individuals

Yan Ni [a,b,1], Linjing Zhao [a,b,1], Haoyong Yu [c], Xiaojing Ma [c], Yuqian Bao [a,c], Cynthia Rajani [b], Lenora W.M. Loo [b], Yurii B. Shvetsov [b], Herbert Yu [b], Tianlu Chen [a], Yinan Zhang [a], Congrong Wang [a,c], Cheng Hu [a,c], Mingming Su [b], Guoxiang Xie [b], Aihua Zhao [a], Wei Jia [a,b,*], Weiping Jia [a,c,**]

[a] Shanghai Key Laboratory of Diabetes Mellitus and Center for Translational Medicine, Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Shanghai 200233, China
[b] University of Hawaii Cancer Center, Honolulu, HI 96813, USA
[c] Department of Endocrinology and Metabolism, Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Shanghai Diabetes Institute, Shanghai 200233, China

ARTICLE INFO

Article history:
Received 21 June 2015
Received in revised form 3 September 2015
Accepted 3 September 2015
Available online 6 September 2015

Keywords:
Free fatty acids
Metabolic syndrome
Obesity
Unsaturated fatty acids
Type 2 diabetes
Insulin resistance

ABSTRACT

Background: Obesity is not a homogeneous condition across individuals since about 25–40% of obese individuals can maintain healthy status with no apparent signs of metabolic complications. The simple anthropometric measure of body mass index does not always reflect the biological effects of excessive body fat on health, thus additional molecular characterizations of obese phenotypes are needed to assess the risk of developing subsequent metabolic conditions at an individual level.
Methods: To better understand the associations of free fatty acids (FFAs) with metabolic phenotypes of obesity, we applied a targeted metabolomics approach to measure 40 serum FFAs from 452 individuals who participated in four independent studies, using an ultra-performance liquid chromatograph coupled to a Xevo G2 quadruple time-of-flight mass spectrometer.
Findings: FFA levels were significantly elevated in overweight/obese subjects with diabetes compared to their healthy counterparts. We identified a group of unsaturated fatty acids (UFAs) that are closely correlated with metabolic status in two groups of obese individuals who underwent weight loss intervention and can predict the recurrence of diabetes at two years after metabolic surgery. Two UFAs, dihomo-gamma-linolenic acid and palmitoleic acid, were also able to predict the future development of metabolic syndrome (MS) in a group of obese subjects.
Interpretation: These findings underscore the potential role of UFAs in the MS pathogenesis and also as important markers in predicting the risk of developing diabetes in obese individuals or diabetes remission after a metabolic surgery.

1. Introduction

Obesity is closely associated with the risk of developing type 2 diabetes (T2D), nonalcoholic fatty liver disease (NAFLD), and cardiovascular disease (CVD). When the nutrient intake exceeds expenditure, tissues such as the adipose, liver, and skeletal become saturated with lipids and result in an increase in lipid export leading to elevated plasma free fatty acids (FFAs) (Kahn et al., 2006; Fabbrini et al., 2010). Previous results from epidemiologic studies have suggested that individuals with higher plasma concentrations of FFAs were at increased risk for T2D (Pankow et al., 2004a; Pankow et al., 2004b; Charles et al., 1997; Paolisso et al., 1995). Higher levels of FFAs have also been linked to peripheral (muscle) insulin resistance through inhibition of insulin-stimulated glucose uptake and glycogen synthesis (Boden, 2003). Plasma FFA levels are chronically elevated in obese individuals (Boden and Shulman, 2002) and therefore, it was hypothesized that increased FFA levels is an important feature of obesity-associated metabolic syndrome (MS) and CVD (Boden, 2011). Normalizing plasma FFA levels has been

Abbreviations: T2D, type 2 diabetes; NAFLD, nonalcoholic fatty liver disease; CVD, cardiovascular disease; MS, metabolic syndrome; FFA, free fatty acids; NW, normal weight; HO, metabolically healthy obese; UO, metabolically unhealthy obese; SFA, saturated fatty acid; UFA, unsaturated fatty acid; MUFA, monounsaturated acid; PUFA, polyunsaturated fatty acid; BMI, body mass index; SHOS, the Shanghai Obesity Study; SHDS, the Shanghai Diabetes Study; VLCD, very low carbohydrate diet; OGTT, oral glucose tolerance test; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TG, triglycerides; HDL, high-density lipoprotein; LDL, low-density lipoprotein; RSD, relative standard deviation; OPLS-DA, orthogonal partial least square discriminant analysis; HbA1c, glycated hemoglobin; DGLA, dihomo-gamma-linolenic acid; GLA, γ-linolenic acid; HA, heptadecanoic acid; PA, palmitoleic acid; AA, arachidonic acid; LA, linoleic acid; DNL, de novo lipogenesis; FATPs, fatty acid transport proteins; SCD, stearoyl-CoA desaturase; DAG, diacylglycerol.

* Correspondence to: W. Jia, Shanghai Key Laboratory of Diabetes Mellitus and Center for Translational Medicine, Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Shanghai 200233, China; University of Hawaii Cancer Center, Honolulu, HI 96813, USA.
** Correspondence to: W.P. Jia, Department of Endocrinology and Metabolism, Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Shanghai Diabetes Institute, Shanghai 200233, China.
E-mail addresses: wjia@cc.hawaii.edu (W. Jia), wpjia@sjtu.edu.cn (W. Jia).
[1] These authors contributed equally to this work.

http://dx.doi.org/10.1016/j.ebiom.2015.09.004

proposed as a novel therapeutic approach for obesity and metabolic diseases (Boden and Shulman, 2002; Kusunoki et al., 2006).

The metabolic abnormalities found in T2D, NAFLD, and CVD such as glucose intolerance, hypertension, dyslipidemia, and insulin resistance are not found in all obese or overweight individuals, and may also be found in normal-weight individuals (St-Onge et al., 2004). Several recent epidemiological studies reported that a subset of obese subjects (Stefan et al., 2013) can maintain healthy metabolic phenotypes. These metabolically healthy obese individuals were not found at increased risk of cardiovascular diseases (CVD) or all-cause mortality over seven years (Hamer and Stamatakis, 2012). These and other studies have led to a restructuring of the classification of obese individuals as either metabolically healthy (HO) or unhealthy (UO). However, the criteria for delineating obese populations into these two metabolic categories is controversial (Kramer et al., 2013). Because obese individuals are not homogeneous in health, simple anthropometric measure of body mass index (BMI) does not always translate excessive body fat into its biological effects on health (Karelis et al., 2004). Additional types of clinical and biochemical parameters including plasma FFA profiles of obese phenotypes may be useful in assessing future risk of subsequent medical problems. Although previous research has focused on some of the important roles of FFAs in obesity, strong evidence linking a single or a particular group of FFAs with the increased risk of MS is lacking (Boden, 2011).

The overall objective of this study was to assess the association of circulating fatty acid profiles with the metabolic status of obese individuals. We applied a targeted metabolomics approach to quantitatively measure blood concentrations of 40 different FFAs in four different groups of subjects. For each subject, 17 saturated FFAs (SFAs), 10 monounsaturated FFAs (MUFAs), and 13 polyunsaturated FFAs (PUFAs), including n−3 (omega−3) and n−6 (omega−6) PUFAs, were measured (Supplementary Table S1). Such a targeted metabolomics study was designed to address three specific questions related to FFAs and MS. First, are there significant differences in the FFA profiles among three groups, each with a different metabolic status, normal weight (NW), overweight/obese metabolically healthy (HO), and overweight/obese diabetic (UO) individuals? To answer this question, a cross-sectional study measured differences in FFA profiles and related them to BMI and other metabolic markers. Second, are any FFA profiles predictive for HO over a ten year evolution of health changes for their progression to UO? A longitudinal study was applied to compare baseline FFA profiles between individuals who remained healthy and those who developed MS ten years later. The last two studies involved therapeutic intervention and were used to address another question: do specific FFA patterns reflect significant changes in other metabolic markers related to therapeutic intervention over time? Serum FFA profiles were characterized in obese T2D patients before and after gastric bypass surgery and in obese patients before and after an 8 week dietary intervention utilizing a very low carbohydrate diet. The key result obtained from all four studies was a panel of UFAs, dihomo-gamma-linolenic acid (DGLA) and palmitoleic acid (PA) in particular, were predictive of the risk of developing MS or diabetes remission after metabolic surgery in a group of obese subjects, and were also potential markers for the inflammatory status of the subject.

2. Materials and Methods

2.1. Study Design and Population

Four independent studies were initiated by the Shanghai Jiao Tong University Affiliated Sixth People's Hospital (Fig. 1).

(1) A total of 312 subjects were selected from the Shanghai Obesity Study (SHOS) and enrolled in a cross-sectional study (Bao et al., 2013). The SHOS was a prospective study designed to investigate the occurrence and development of MS and its related diseases. Beginning in 2009, the SHOS recruited 5000 participants from four communities in Shanghai, China, which included a baseline study as well as, 1.5-, 3-, and 5-year follow-up studies. Of the 312 subjects in the cohort, 132 healthy subjects were normal weight, 107 subjects were either overweight or obese, and 73 subjects had been diagnosed with T2D complicated with hypertension, high cholesterol or hypertriglyceridemia.
(2) 10-year longitudinal study: 62 subjects were selected from the Shanghai Diabetes Study (SHDS) (Jia et al., 2007). The SHDS cohort was a multi-stage stratified epidemiological study designed to assess the prevalence of diabetes and associated metabolic disorders. It was initiated in 1998, when 5994 individuals were enrolled from two urban communities, Huayang and Caoyang Districts in Shanghai, China, and 1250 of them completed the follow-up examination in Huayang District between 2010 and 2011. Among 1250 eligible participants, we selected 62 subjects who were overweight/obese and metabolically healthy at baseline, of which, 50 became unhealthy overweight/obese and 12 remained healthy overweight/obese after ten years.
(3) Metabolic surgery intervention study: 40 obese patients with T2D were selected from the Department of Endocrinology and Metabolism outpatient clinic. They received Roux-en-Y gastric bypass surgery, a commonly performed operation for treating obesity-related T2D patients. They were required to complete

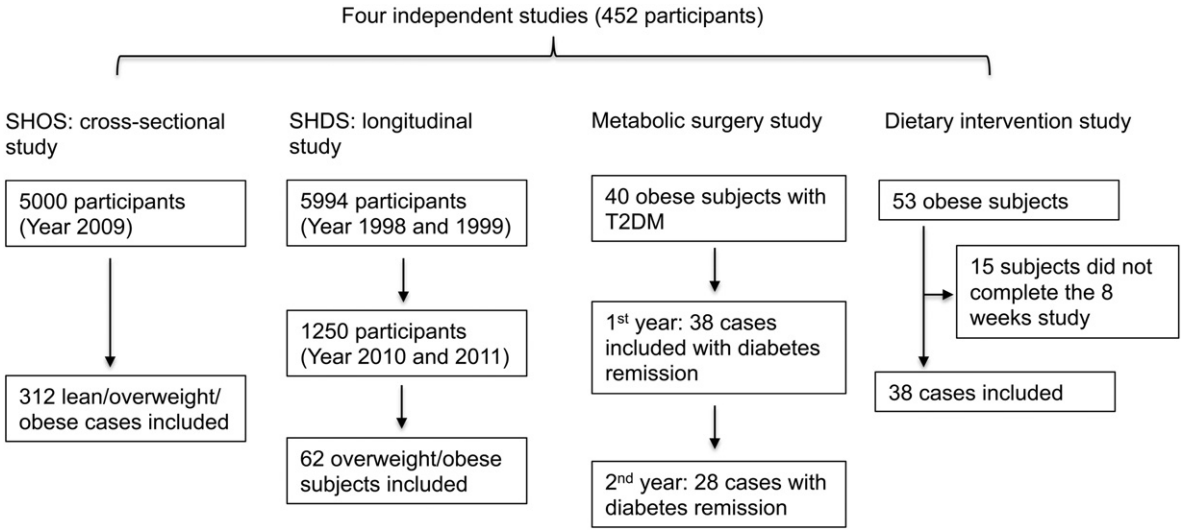

Fig. 1. Four independent studies used in this analysis.