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Effects of nucleos(t)ide analogs on body composition in HBV-infected men: An age- and BMI-matched, cross-sectional study

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ABSTRACT

Objective: Chronic hepatitis B (CHB) requires long-term treatment with nucleos(t)ide analogs (NAs). The goal of the present study was to evaluate the effects of long-term treatment with NAs on body composition in men with CHB.

Method: We performed a cross-sectional study of men infected with hepatitis B virus (HBV) who have never been on NAs with high HBV-DNA (naïve group; n = 30), those on NAs for 7 y with virologic suppression (NA-treated group; n = 50), and healthy men (control group; n = 30) matched by age and body mass index (BMI) to evaluate whether body composition differed. Body composition was assessed by multiple-frequency bioelectrical impedance analysis. All patients and healthy controls underwent anthropometric measures, dietary intake, and physical activity level survey.

Results: Body fat mass (BFM) and visceral fat area (VFA) were significantly lower in HBV-infected men naïve to NAs than in controls ($P < 0.05$). With virology suppression after treatment with NAs, BFM, VFA, and waist-to-hip ratio (WHR) were significantly increased in the NA-treated group compared with the naïve group ($P < 0.05$). Although there were no significant differences in BFM, VFA, and WHR between NA-treated men and controls ($P > 0.05$), WHR in the NA-treated group was 0.94 ± 0.06, indicating central obesity. Liver function, liver stiffness measurement, dietary intake, and physical activity level were the same between NA-treated and naïve men with CHB.

Conclusions: BFM and VFA is elevated in CHB men on NAs with virologic suppression compared with age and BMI-matched NA-naïve CHB men, which suggests that NAs may increase BFM and VFA of CHB men by virologic suppression. Further study is needed to clarify the adverse effects related to metabolic complications of lipid metabolism due to NA therapy.

Introduction

Hepatitis B is a serious and common infectious disease of the liver, affecting millions of people worldwide. More than 2 billion people alive today have been infected with hepatitis B virus (HBV) at some time in their lives. Chronically, HBV patients could progress to liver cirrhosis, hepatocellular carcinoma, and chronic hepatic insufficiency. Additionally, HBV carriers can transmit the disease for long periods [1]. Since the licensing of lamivudine (LAM) in 1999, the treatment of chronic hepatitis B (CHB) has been revolutionized by the inception of oral nucleos(t)ide analogs (NAs), which act as inhibitors of the HBV polymerase. At present, treatment strategies for HBV infection, including nucleosides (LAM, telbivudine [LdT], entecavir [ETV]) and nucleotide analogs (adefovir dipivoxil [ADV] or tenofovir disoproxil fumarate [TDF]), are highly effective in inhibiting HBV replication and have been approved worldwide for the treatment of chronic HBV infection [2].

Although NAs effectively suppress HBV replication and reduce the risk for disease progression, they cannot clear the replication

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template of covalently closed circular DNA (cccDNA) [3]. Hepatitis B surface antigen (HBsAg) seroclearance also rarely occurs. As a result, long-term treatment with NAs is necessary for patients who are not expected or fail to achieve a sustained off-treatment virologic response and who require extended NA treatment [4–6]. In HIV-infected patients receiving long-term highly active antiretroviral therapy (HAART), fat redistribution has a prevalence ranging from 18% to 83% [7,8]. Laboratory and clinical experience has shown that HAART can induce severe and considerable adverse effects related to metabolic complications of lipid metabolism, characterized by signs of lipodystrophy, insulin resistance, central adiposity, dyslipidemia, increased risk for cardiovascular disease, and even an increased risk for atherosclerosis [9,10]. This raises concerns about whether long-term treatment with NAs may affect body composition in patients with CHB. Results from one study warned that body fat changes seem related to long-term anti-HBV therapy in HBV-infected patients [11].

To our knowledge, there are few studies that evaluated the effects of long-term treatment with NAs on body composition in patients with CHB. The purpose of the present study was to evaluate whether there was any evidence of body composition changes in HBV-infected men, both naïve and those on NA therapy compared with healthy controls.

Methods

Study design

We performed a cross-sectional study of HBV-infected men who have never been on NAs with high HBV DNA levels (naïve group; n = 30), those on NAs with virologic suppression (NA-treated group; n = 50), and healthy men (control group; n = 30) matched by age and body mass index (BMI) to evaluate whether body composition differed. Data collection was conducted from December 2014 to March 2015.

Each participant signed the informed consent at the beginning of the study. The study protocol was conducted in accordance with the provisions of the Declaration of Helsinki and approved by the Institutional Review Board of Beijing YouAn Hospital, Capital Medical University (Beijing, China).

Patient selection

The inclusion criteria for HBV-infected patients were adopted in accordance with the American Association for the Study of Liver Diseases guideline [6]. Chronic HBV infection was established by the positive for HBsAg or HBV DNA using polymerase chain reaction assays for >6 mo before enrollment.

Clinical exclusion criteria included presence of other chronic liver diseases, including hepatitis C, Wilson's disease, hemochromatosis, autoimmune liver disease, liver cirrhosis, and hepatocellular carcinoma. Patients with HIV infection, those with active thyroid disease, and those with alcohol abuse also were excluded. Additionally, patients with previous NA treatment failure were excluded.

Eligible men from the NA-treated group were selected from a cohort of 108 patients with HBV who were consecutively enrolled from June 2007 to July 2008 in Beijing YouAn, Capital Medical University, China. Of this cohort, 55 were NA naïve and the other 53 were treated with LAM. These patients were treated with 10 mg of ADV or with 0.5 mg of ETV once daily. The details of patients were previously described [12]. Patients from the NA-treated group had been treated with NAs (ETV or ADV) for 7 y and had repeatedly normal (or minimally raised) liver enzymes and negative tests for HBV DNA before enrolling. Of this NA-treated group, 28 were ADV-treated patients and the other 53 were ETV-treated patients. The patients from the naïve group were in the immune-tolerant phase and were not treated according to the current standard [6]. Controls were recruited from healthy volunteers, most of who were hospital employees. No patients had any clinical evidence of ascites or fluid retention.

Anthropometric measurements

Anthropometric measurements were carried out by the same investigator and included body weight, height, midarm circumference (MAC), and triceps skinfold thickness (TSF). All measurements were taken in the morning, under fasting conditions. Weight was obtained with the individual wearing lightweight clothing and measured to the nearest 0.1 kg. Height was obtained without shoes and measured to the nearest 0.1 cm. MAC and TSF measurements were performed three times on the left arm by using intertape and adipometer. Mid-arm muscle circumference (MAMC) was calculated following the formula: $\text{MAMC} = \text{MAC (mm)} - \pi \times \text{TSF (mm)}$.

Body composition measurements

Body composition, which for this study included total body water (TBW), intracellular water (ICW), extracellular water (ECW), total body protein (TBP), mineral, body fat mass (BFM), fat-free mass (FFM), skeletal muscle mass (SMM), percent body fat (PBF), waist-to-hip ratio (WHR), visceral fat area (VFA), and body cell mass (BCM), was estimated by means of multiple-frequency bioelectrical impedance analysis (MFBIA) with body composition analyzer InBody 720 (Biospace Co., Ltd., Seoul, Korea; 1–1000 kHz). MFBIA is noninvasive and applies the body's electrical properties and changing opposition to the flow of an electrical current through particular body tissues to distinguish components of individual variation in body composition [13]. It may be applied to measure the body composition of middle-aged or older individuals [14]. The participants were examined in the standing position, lightly dressed with the use of eight electrodes. The examination took <2 min and required only a standing position [15]. Calculation of body composition was performed as previously described [16,17].

Dietary intake and physical activity survey

A dietitian, using a 24-h dietary recall, assessed each patient's dietary energy and macronutrient intakes. Nutrient intakes (energy, fat, protein, and carbohydrate) were calculated using standardized Chinese Food Composition Tables [18].

Physical activity was assessed using the Modifiable Activity Questionnaire (MAQ) [19]. We categorized total physical activities into three levels: low activity/physical inactivity, moderate activity, and high activity.

Clinical, laboratory, and imaging technique/method/modality

Liver stiffness measurement (LSM) using transient elastography (FibroScan®) is a useful tool to assess fibrosis in Chinese patients with CHB. LSM was performed using FibroScan® (Echosens, Paris, France) according to the manufacturer's recommendations. Only LSM with ≥10 valid measurements, success rate ≥60% and interquartile range (IQR) over median ratio ≤30% were considered reliable. The patients with LSM <7.4 kPa were considered to have no or minimal fibrosis, according to Chinese recommendations for the clinical application of transient elastography in liver fibrosis assessment [20].

Serum biochemical profiles including the concentrations of alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TBIL), albumin, creatinine, prothrombin activity (PTA), triacylglycerols (TGs), cholesterol, high-density lipoprotein, and low-density lipoprotein were measured using an Olympus Automatic Biochemical Analyzer AU5400 (Olympus, Tokyo, Japan). The cutoff value of ALT was 50 IU/L. The normal range of albumin was 40–55 g/L. Serum HBV DNA level was determined using the Cobas HBV Amplicor Monitor assay (Roche Diagnostics, Pleasanton, CA, USA).

Statistical analysis

Demographic characteristics, anthropometric, and laboratory values are described by mean and SD for continuous variables and by frequency and percent for categorical variables by group. Differences in continuous variables between two groups were analyzed using the two independent sample t tests. One-way analyses of variance were used to test for the comparison among the three groups. Post hoc multiple comparisons using Bonferroni corrections were performed for pairwise comparisons of these measured parameters between the three groups. Pearson χ^2 test or Fisher's exact tests were applied to categorical variables as appropriate. The statistical analysis was performed using IBM SPSS Statistics for Windows, version 19.0 (IBM Corp., Armonk, NY, USA); a two-sided $P < 0.05$ was considered statistically significant and $P = 0.017$ for Bonferroni corrected multiple comparisons.

Results

Characteristics of the participants

All three groups were well matched by age and BMI, and there were no statistically significant differences in other variables (Table 1). Additionally, to further analyze the influence of different BMI distributions on body composition, we compared the percentage of BMI distributions, which showed no significant differences among the three groups (Table 2). The median LSM values were 6.65 kPa (range, 5.2–7.5) and 6.87 kPa (range, 4.9–7.6) in the NA-treated and naïve groups, respectively. The