Original Article

Impact of Exercise on the Presence of Urinary Ketones Based on Korea National Health and Nutrition Examination Survey Data, 2014–2015

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Background: Ketone bodies are a well-known metabolite from the utilization of fatty acids in the fasting state. Some studies have demonstrated the metabolic benefits of urinary ketones in a specific population in whom ketone bodies were detected. However, other studies described the influence of associated factors on the presence of urinary ketone bodies. In the present study, we analyzed lifestyle factors that are hypothesized to be related to the presence of ketone bodies in urine.

Methods: Data from the Korea National Health and Nutrition Examination Survey (KNHANES, 2014–2015) were analyzed. The urinary ketone-positive group was defined as the population in whom urinary ketones were detected. We compared differences in metabolic characteristics as well as lifestyle characteristics such as smoking, alcohol intake, education levels, and exercise between the urine ketone-positive and -negative groups.

Results: Of the 9,379 identified eligible subjects, the urine-ketone group showed metabolic benefits with respect to several factors such as body mass index, waist circumference, triglyceride, and high density lipoprotein cholesterol after adjustment for sex and age. A higher proportion of urinary ketones was associated with current smoking ($P=0.050$), high education level ($P=0.008$), and aerobic exercise ($P=0.021$).

Conclusion: Aerobic exercise was identified as a factor associated with the presence of urinary ketones. It is also an important lifestyle intervention factor for the recovery of urinary ketones in patients with obesity.

Key words: Ketone bodies, Aerobic exercise, Life style, Obesity

INTRODUCTION

The three major causes of death in Korea are cancer, cardiovascular disease, and cerebrovascular disease.[1] In the United States, the leading causes of death and disability are chronic diseases, like cancer and diabetes.[2] A close relationship exists between chronic diseases and obesity, which is also a major global health problem.[3,4] Moreover, obesity can cause various comorbidities, including diabetes, hypertension, and dyslipidemia,[5,6] and, ultimately, considerable medical costs.[7] Ketone bodies are well-known metabolites used as fuel for energy generation when the human body has limitations with regards to glucose availability. They are water-soluble molecules produced from fatty acids[8] in the liver under the physiologic state of fasting or starvation, carbohydrate-restrictive diets, and intensive exercise,[9] and pathologic states of heavy alcohol use or untreated type 1 diabetes mellitus.[5] Ketone detection in urine can be useful as a biomarker for the ketogenic metabolic state. Previously, we reported that ketonuria after fasting is related not only to superiority in terms of basic metabolic parameters[10] but also with regard to weight loss intervention in obese people.[11] The aim of this study was to identify possible lifestyle-associated factors in relation to the presence of urinary ketone bodies in a healthy Korean population.

METHODS

Study subjects

Data for this study were collected from 2 years (2014–2015) of the Korea National Health and Nutrition Examination Survey (KNHANES). The KNHANES is a nationwide, population-based, cross-sectional, health and nutritional survey that has been performed by the Korea Centers for Disease Control and Prevention since 1998. The population sampling frame of the KNHANES is obtained from the Population and Housing Census of Korea, including the residents in Korea, aged 1 year or older. Our study subjects were from the second and third years (2014–2015) of the fifth KNHANES, accounting for 7,550 and 7,380 subjects, respectively (overall 14,930 subjects). The sex composition was 6,766 males (45%) and 8,164 females (55%). Of the 14,930 total subjects, 2,283 subjects were excluded due to lack of total weighing data, and 2,377 were excluded due to the absence of urinary ketone data, which is key to our research. In addition, 758 subjects with type 2 diabetes mellitus (T2DM) and 133 subjects with cancer, which could potentially account for the presence of urinary ketones, were excluded from the study. Finally, 9,379 subjects (4,077 males [43%] and 5,302 females [57%]) were included in the present study. Inclusion and exclusion criteria of this research are described in Fig. 1. The Institutional Review Board approved this study (IRB No. AJIRB-MED-EXP-19-046) and all subjects provided written informed consent.
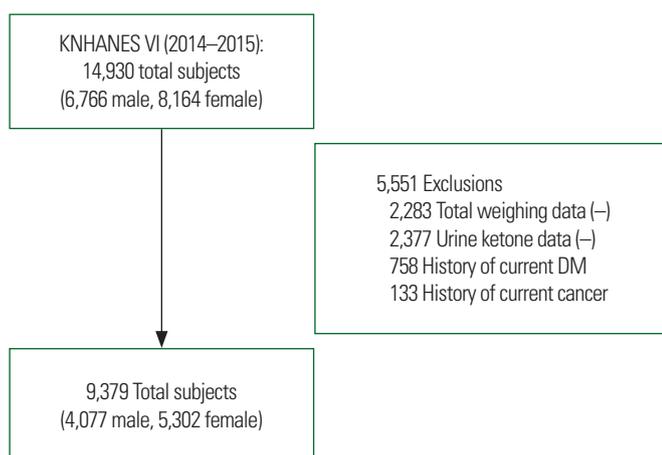
Figure 1. Flow diagram of subjects' inclusion and exclusion in this study. Participants in the Korea National Health and Nutrition Examination Survey (KNHANES), 2014–2015 were included. DM, diabetes mellitus.

Data collection

The KNHANES consists of three sections: health interview survey, health examination survey, and nutritional survey. Based on the health interview survey, we were able to exclude those with T2DM or cancer. From the health examination survey, we acquired data related to metabolic characteristics, including body mass index (BMI, kg/m^2), fasting glucose (mg/dL), total cholesterol (mg/dL), triglyceride (mg/dL), high-density lipoprotein (HDL) cholesterol (mg/dL), low-density lipoprotein (LDL) cholesterol (mg/dL), and aspartate aminotransferase (AST), and alanine aminotransferase (ALT, mg/dL). From the nutritional survey, we acquired data about calorie intake (kcal/day); protein and fat intake (g/day); and calcium, sodium, potassium, riboflavin, and niacin intake (mg/day). Individual data were recalculated from food intake frequency per day, which included 112 different foods commonly eaten by Koreans.

Presence of urinary ketones

The presence of urinary ketones was identified by urinalysis data from the health examination survey. Urinary ketone detection in urinalysis was classified into six different categories: negative (−), trace (+), and positive (1+ to 4+). The population with negative (−) urinary ketone detection was defined as the urinary ketone-negative group, and the trace (+) and positive (1+ to 4+) populations were defined as the urinary ketone-positive group.

Lifestyle data

We used data from four different lifestyle factors that could possibly affect the presence of ketone bodies in urine: current smoking status, alcohol drinking status, education level, and aerobic exercise. Smoking status defines non-smokers as those who have smoked less than 100 cigarettes in their lifetime, ex-smokers as those who quit smoking, and current-smokers are those who are currently smoking. Alcohol drinking status defined non-drinkers as those who do not consume alcohol, and current drinkers as those who drink more than one drink of alcohol per month each a year. Education level was divided into four groups: elementary school, middle school, high school, and more than university. As a lifestyle characteristic, the probability of exercising was also analyzed. The subjects in the group who exercised had more than 2 hours 30 minutes of moder-

ate-intensity physical aerobic activity, or 1 hour 15 minutes of high-intensity physical aerobic activity, or a mixture of moderate and high intensity of physical aerobic activity per week. All lifestyle characteristics data were obtained from the health interview survey, which contains direct responses by participants taking the questionnaire.

Statistical analysis

Complex sample analysis was used to weigh KNHANES data following the guidance on statistics from the Korea Centers for Disease Control and Prevention. General characteristics of the study subjects included age, BMI, waist circumference, and metabolic markers including total cholesterol, triglyceride, HDL cholesterol level, fasting blood glucose, LDL cholesterol level, AST, and ALT. In addition, daily calorie intake and macronutrients such as carbohydrate, fat, and protein, calcium, sodium, potassium intake, riboflavin, and niacin intake were described according to the ketone groups. The frequency of current smoking status, alcohol drinking status, educational level, and practice of aerobic exercise between the ketone groups were also compared using the chi-square test. The difference in the frequency of urinary ketones among different kinds of exercise such as walking frequency, duration of walking, anaerobic exercise, and aerobic exercise was also compared. Finally, the odds ratio of the presence of urinary ketones according to aerobic exercise level was calculated based on the logistic regression analysis before and after adjustments with some significant influencing factors to ketonuria. The P-values were used to assess the significance of all analyses. Data were analyzed using IBM SPSS version 23.0 (IBM Corp., Armonk, NY, USA) to account for the complex sampling design.

RESULTS

Basic metabolic and clinical characteristics of the study subjects are shown in Table 1. The characteristics were compared between the urinary ketone groups, and the analysis demonstrated metabolic superiority in subjects with urinary ketones. No significant difference in sex ratio was observed between groups; however, the mean age of the subjects was higher in the urinary ketone-negative group. Basic metabolic characteristics like BMI, waist circumference, total

Table 1. Comparison of metabolic characteristics between groups (n = 9,379)

Variable	U-ketone (−, n = 8,864)	U-ketone (+, n = 515)	P
Female sex	5,018 (56.6)	284 (55.1)	0.566
Age (yr)	42.5 ± 0.3	34.0 ± 0.8	< 0.001*
BMI (kg/m²)	23.5 ± 0.1	22.7 ± 0.2	< 0.001*
Waist circumference (cm)	80.6 ± 0.2	77.8 ± 0.6	< 0.001*
Fasting glucose (mg/dL)	96.1 ± 0.2	96.4 ± 1.8	0.862
Total cholesterol (mg/dL)	186.7 ± 0.5	178.0 ± 1.6	< 0.001*
Triglyceride (mg/dL)	132.7 ± 1.5	105.2 ± 6.3	< 0.001*
HDL cholesterol (mg/dL)	47.1 ± 0.4	51.1 ± 1.5	0.011*
LDL cholesterol (mg/dL)	113.6 ± 0.6	107.7 ± 2.2	0.008*
AST (mg/dL)	22.1 ± 0.2	21.6 ± 0.6	0.410
ALT (mg/dL)	21.8 ± 0.3	20.4 ± 1.0	0.189
Calorie intake (kcal/day)	2,168.5 ± 14.7	2,178.1 ± 56.3	0.869
Protein intake (g/day)	76.3 ± 0.8	76.5 ± 2.3	0.909
Fat intake (g/day)	50.7 ± 0.6	55.3 ± 2.0	0.028*
Carbohydrate intake (g/day)	323.3 ± 2.0	305.5 ± 7.3	0.020*
Calcium intake (mg/day)	510.2 ± 4.6	485.7 ± 14.2	0.089
Sodium intake (mg/day)	4,153.5 ± 50.6	3,935.3 ± 118.5	0.088
Potassium intake (mg/day)	3,133.3 ± 24.8	2,925.9 ± 80.7	0.014*
Riboflavin intake (mg/day)	1.46 ± 0.01	1.49 ± 0.04	0.488
Niacin intake (mg/day)	17.5 ± 0.2	17.1 ± 0.5	0.514

Values are presented as number (%) or mean ± standard error. P-values were calculated using general linear modeling without adjustment.
*P < 0.05 on general linear modeling after adjustment for sex and age.
U-ketone (−), urinary ketone negative; U-ketone (+), urinary ketone positive; BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

cholesterol, triglycerides, and HDL and LDL cholesterol were metabolically superior in the urinary ketone-positive group, with P-values of less than 0.05 in the general linear model after adjustment for sex and age. With regard to nutrition status, subjects in the urinary ketone-positive group consumed more fat but fewer carbohydrates and less potassium per day.

Differences in lifestyle characteristics, including smoking, alcohol consumption, education, and exercise were compared based on the presence of urinary ketones, as shown in Table 2. Comparison based on current alcohol drinking status was not statistically significant, with a P-value higher than 0.05. Individuals in the current smoker group showed a higher presence of urinary ketones than those in the non-smoker and ex-smoker groups. Differences were also seen with respect to education levels, indicating that highly educated groups had a tendency of higher prevalence of presence of urinary ketones, though the reverse effect was observed in the high-school group (higher ratio of urinary ketones than university-edu-

Table 2. Comparison of lifestyle characteristics between groups

Variable	U-ketone (–)	U-ketone (+)	P
Smoking status			0.050
Non-smoker*, ex-smoker (n=6,586)	6,261 (95.1)	325 (4.9)	
Current smoker (n=1,355)	1,262 (93.1)	93 (6.9)	
Alcohol drinking status			0.983
Non-drinker† (n=4,458)	4,227 (94.8)	231 (5.2)	
Current drinker (n=4,299)	4,041 (94.0)	258 (6.0)	
Education level (graduation level)			0.008
Below elementary school (n=2,395)	2,296 (95.9)	99 (4.1)	
Middle school (n=1,116)	1,059 (94.9)	57 (5.1)	
High school (n=2,587)	2,420 (93.5)	167 (6.5)	
More than university (n=2,529)	2,374 (93.9)	155 (6.1)	
Aerobic exercise‡			0.021
Yes (n=4,399)	4,130 (93.9)	269 (6.1)	
No (n=3,907)	3,713 (95.0)	194 (5.0)	

Values are presented as number (%).
*Population who had smoked less than 100 cigarettes in their lifetime; †Population who had consumed more than one alcoholic beverage in a month, within a year; ‡Engaging in more than 2 hours 30 minutes of moderate-intensity physical activity or 1 hour 15 minutes of high-intensity physical activity, or a mixture of moderate and high intensity of physical activity.
U-ketone (–), urinary ketone negative; U-ketone (+), urinary ketone positive.

Table 3. Comparison of urinary ketones according to the kinds of exercise

Variable	Chi-square	Adjusted F	P
Walking* (day/wk, n=5,892)	1.481	0.469	0.624
Duration of walking† (hr/day, n=6,967)	3.786	2.795	0.095
Anaerobic exercise‡ (day/wk, n=8,356)	1.823	1.281	0.259
Aerobic exercise§ (yes/no, n=8,306)	7.338	5.354	0.021

P-values represent chi-square.
*Numbers of walking days into below 1 day and above; †Numbers of walking hours into below 1 hour and above; ‡Numbers of anaerobic exercise days into below 1 day above; §Engaging in more than 2 hours 30 minutes of moderate-intensity physical activity or 1 hour 15 minutes of high-intensity physical activity or a mixture of moderate and high intensity of physical activity.

Table 4. Ketonuria according to exercise

Variable	Model 1	Model 2	Model 3
Aerobic exercise*	1.28 (1.04–1.58)	1.29 (1.04–1.60)	1.00 (0.80–1.27)

Values are presented as odds ratio (95% confidence interval) by logistic regression under complex sample analysis.
*Engaging in more than 2 hours 30 minutes of moderate-intensity physical activity or 1 hour 15 minutes of high-intensity physical activity or a mixture of moderate and high intensity of physical activity.
Model 1, without adjustment; Model 2, adjusted for body mass index, carbohydrate, and potassium consumption; Model 3, adjusted for age, sex, and triglycerides in addition to the factors listed in Model 2.

cated group).

As shown in Table 2, the group that engaged in regular aerobic exercise showed a higher prevalence of presence of urinary ketones (269/4,399 [6.1%]) than the group in which the subjects did not engage in regular aerobic exercise (194/3,907 [5.0%]). KNHANES data includes three other types of exercise, the number of days of walking per week, duration of walking hours per day, and the days of anaerobic exercise per week. The details of the three types of exercise are shown in Table 3. Our aim was to analyze trends in the presence of urinary ketones based on data from the other three exercise groups. However, as shown in Table 3, when a chi-square test was performed for each group of exercises, statistical significance was verified only for the group practicing aerobic exercise. Adjustments were made in basic metabolic characteristics by logistic regression, and some significant differences were observed (Table 1). Three different odds ratios obtained with different adjustment factors are presented in Table 4. The odds ratios and 95% confidence intervals were 1.28 (1.04–1.58) and 1.29 (1.04–1.60) before adjustment and after adjustment for BMI, carbohydrate intake, and potassium intake, respectively, showing statistical significance; the odds ratio was 1.00 (0.80–1.27) when age, sex, and triglyceride lev-

el were additionally adjusted.

DISCUSSION

In the present study, data from KNHANES 2014–2015 were analyzed and a cross-sectional study for the presence of ketonuria was performed by comparing basic metabolic characteristics between the ketonuria groups and four different lifestyle factors that were hypothesized to affect the presence of ketonuria. As demonstrated in our previous study, the group demonstrating the presence of urinary ketones was superior in terms of metabolism, such as BMI, waist circumference, total cholesterol, triglyceride, and HDL and LDL cholesterol concentration. Although alcohol consumption was not statistically significant, a minor correlation was observed between lifestyle characteristics like smoking, education, and aerobic exercise and the presence of urinary ketones.

The relationship between urinary ketone bodies and metabolic indicators including obesity has not been proven, but some studies have demonstrated a possible connection. A study by Mohammadiha[12] showed that metabolism in obese people has a lower tendency toward ketosis and ketonuria, indicating difficulties in utilization of

fatty acids and higher levels of free fatty acids or low levels of ketones in the blood during the fasting state.[13,14] Based on such differences in metabolic state, a low-carbohydrate, ketogenic diet can be helpful for weight loss in obese people,[15] which is of clinical importance for physicians in treating obese patients. Some studies have also shown improvements in metabolic markers, such as blood pressure, lipid profile, insulin resistance, and glucose or insulin levels, while consuming ketogenic, low-carbohydrate diets,[10,16,17] thus demonstrating that the ketogenic state can be related to an overall metabolic benefit that includes more than just weight loss in obesity. While several reported studies have shown a relationship between ketogenic state, especially ketonuria, and metabolic state, few studies have discussed factors that affect the presence of urinary ketone bodies, which can be useful biomarkers for the ketogenic state. As a biomarker for the ketogenic metabolic state, ketone detection in urine can be helpful. As a screening tool, ketonuria, which can be easily measured by urinalysis, can be a useful tool to estimate the ketogenic state of the body. We have already reported that ketonuria after fasting can be related to superiority not only with regard to basic metabolic parameters[18] but also in terms of weight loss intervention in obese people.[19]

In the present study, the urinary ketones group showed metabolic superiority in terms of several factors, including BMI, waist circumference, total cholesterol, and triglycerides compared with the nonketones group. This result is consistent with the results of our previous study[18] in which we demonstrated metabolic superiority in weight, BMI, waist circumference, lipid, and blood pressure in individuals with urinary ketones. The present results imply that the presence of urinary ketones can be employed as a metabolic biomarker associated with a patient's current metabolic status and response to obesity treatment. In addition, basic metabolic characteristics were compared, and data about calorie, fat, and carbohydrate intake, which are the main concerns related to the low-carbohydrate and high/low-fat diet for weight reduction and metabolism, were included. Some studies have suggested a low-carbohydrate diet as an alternative to a low-fat diet for weight loss,[20,21] and one study on low-carbohydrate, high-protein, and high-fat diets suggested that more significant weight loss was achieved in 1 year compared with conventional diets, although the significance did not extend past the first year.[22] In this study, individuals in the urinary ketones group tended to have lower carbohydrate intake and higher fat intake, which is consistent with the ketogenic diet presented in previous studies and can be considered an effective diet for obese patients.

Four different lifestyle factors that can influence the presence of urinary ketones, smoking, alcohol, education, and exercise, were analyzed. The effect of alcohol on urinary ketones was not statistically significant, although the effects of the three other factors were significant. With regard to smoking status, those in the current smoker group showed a higher presence of urinary ketones than those in the non-smoker and ex-smoker groups. Our results suggest that smoking can lead to a ketogenic state in the body, and these ketones can be measured by urinalysis. Existing studies about smoking and obesity have shown that smoking cessation can lead to body weight gain based on the fact that nicotine is both an appetite suppressant and metabolic stimulant.[23-25] Collectively, it can be concluded that smoking can be beneficial for obese patients for weight loss; however, the benefits of smoking for weight loss do not outweigh its cardiovascular risks.[26] In addition, highly educated groups exhibited a tendency of higher prevalence of presence of urinary ketones, though the reversal was observed in the high-school group with the presence of a higher ratio of urinary ketones than the university-educated group. Previous studies about the relationship between education and obesity have shown that those in the highly-educated group have a higher socioeconomic status and a lower tendency of becoming obese.[27,28] An Organisation for Economic Co-operation and Development (OECD) health report also documented that education provides individuals with better access to information and improved critical thinking skills, which suggests that non-obese individuals in the lower social class group have better knowledge about food than obese individuals in the same group.[29] The present study also indicates that individuals in the highly educated group exhibited a higher prevalence of the presence of urinary ketones, a higher ketogenic status of the body, and a lower tendency toward obesity possibly due to their better knowledge about food intake.

We also analyzed the effect of exercise and found that the group that practiced aerobic exercise showed a higher tendency for the presence of urinary ketones. The positive effect of increased physical activity or exercise on metabolic syndrome, obesity, and insulin

sensitivity has already been mentioned in many previous studies.[29] In our study, only the effects of aerobic exercise were analyzed, which can be a limitation, based on recent information suggesting anaerobic exercise may also be effective in reducing fat mass. After adjusting for confounding factors like BMI, carbohydrate intake, and potassium intake, statistical significance for aerobic exercise was observed, but this significance was lost when age, sex, and triglyceride level were adjusted for. This result suggests that age, sex, and triglycerides influence the presence of ketonuria.

To the best of our knowledge, this is the first study to evaluate the relationship between the presence of ketonuria and various lifestyle factors. Although we have already demonstrated the relevance of ketonuria in metabolic superiority, there was no evidence about the possible factors influencing the presence of ketonuria. The associated lifestyle factors demonstrated in our study could be employed when providing education about treatment for obese patients, as well as used as basic data for future research. In addition, this research is based on the KNHANES study, which is a major public health survey in Korea. The KNHANES study offers objective and standardized data on average and distribution, as well as a large number of physiologic measurements that were useful for our study. It is hypothesized that based on the results of the present study, the majority of appropriate data for Korean health can be obtained.

This study has several limitations; first of all, KNHANES is a cross-sectional study; its data are inadequate for prospective observation of study subjects. For example, the presence of urinary ketones can vary depending on changes in lifestyle such as exercise or diets, which are not included in our study. Further cohort studies are necessary to complete the limitations of the present study. There were some confounding factors, including age, sex, and triglyceride levels for which statistical significance could not be achieved when the factors were adjusted. Further study on the presence of urinary ketones by adjusting possible factors is essential. Our results also suggested that age, sex, and triglyceride are important factors determining the presence of urinary ketones. We can assume that ketone body formation when fasting may vary according to subject's age, sex, and fat mass, which is represented by triglyceride concentration. Therefore, adjusting for these factors will significantly affect P-values. Further analysis including age, sex, and triglyceride concentration is needed in the future.

In conclusion, exercise is a clinically important factor determining the presence of urinary ketones and may be a useful education tool for the treatment of obese patients.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Study concept and design: all authors; acquisition of data: JMH; analysis and interpretation of data: all authors; drafting of the manuscript: JMH; critical revision of the manuscript: NSJ; statistical analysis: all authors; administrative, technical, or material support: all authors; and study supervision: NSJ.

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