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Population Attributed Risk (PAR) of Hyperuricemia for Diabetes Mellitus in 20-74-Year-Old Population of Yazd during a 10-Year Longitudinal Cohort: Yazd Healthy Heart Cohort (YHHC), Iran

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ABSTRACT

Introduction: Regarding the high impact of Diabetes Mellitus type II (DM II) on human's health, it seems that identifying DM II risk factors is important to prevent its development. Further studies are needed to ensure the positive role of uric acid in the onset of diabetes. This study targeted at investigating the attributed risk of hyperuricemia for the onset of DM II.

Methods: In the present study, 1641 non-diabetic people, selected through multi-stage random cluster sampling, were followed up for 10 years (2006 - 2016). During the study, data on the variables of the study were collected and entered in SPSS 16 which was used to analyze the data. To calculate the attributions of hyperuricemia in the risk of developing diabetes, Levin's formulas and attributed risk related to the prevalence of exposure during these ten years were used.

Results: Findings showed DM II was developed in 54.8% of people with hyperuricemia, whereas 28.2% of people with normal uric acid level developed diabetes. The Population Attributed Risk (PAR) of hyperuricemia and uric acid over than 75th percentile of serum uric acid for DM II incidence were calculated by the weighted attributed risk formula was 3.6 % and 24.2 %, respectively. With the treatment of hyperuricemia or serum uric acid over than 75th percetile, the incidence of diabetes in population was reduced up to 3.6% or 24.2% over a 10-year period respectively.

Conclusion: In this study, there was a significant correlation between high uric acid level and the risk of diabetes. Therefore, necessary measurements should be taken to treat the hyperuricemia patients in order to prevent the incidence of diabetes caused by high blood acid uric.

Keywords: Risk, Diabetes Mellitus, Hyperuricemia, Incidence

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Introduction

Considering the high impact of Diabetes Mellitus type II (DM II) on human's health, recently it is one of the most important challenges of public health [1]. Diabetes mellitus, as a global epidemic is a challenging issue throughout the world [1]. Regarding the high burden of diabetes, comprehensive identification of its risk factors is necessary for its prevention.

Uric Acid (UA) is the most important product of food purine metabolism and the purine produced in the human body. Naturally, two-thirds of urate is excreted through the urine, and the rest is excreted through the digestive system [2].

The literature showed that hyperuricemia increases the risk of hypertension, cardiovascular diseases, as well as kidney diseases, and is considered as a risk factor for metabolic syndrome [3, 4].

In people with type 2 diabetes, hyperuricemia was related to peripheral arterial diseases, high blood pressure, high blood cholesterol, high hemoglobin A1C, increased albuminuria, low glomerular filtration, and early onset or rapid progression of kidney disease caused by diabetes. Hyperuricemia was reported to cause hypertrophy of glomeruli in a study [5-7].

In obese people, insulin resistance status, blood lipid disorders, an increase in uric acid are common due to stimulation of proximal kidney tubules by insulin to retrieve urate [8-10].

In a study carried out on 1449 diabetic patients with normal kidney functioning and without overt proteinuria for 5 years, the cumulative incidence of CKD was significantly greater in patients with hyperuricemia than in those without hyperuricemia (29.5 vs. 11.4%, $P < 0.001$) [11].

High concentration of uric acid is one of the most important findings in people with risk factors for heart diseases. However, its empress in the development of diabetes is still not clear [13].

Although high concentrations of uric acid are known due to diabetes, more studies are needed [12].

In some studies, uric acid was cited as one of the causative factors of diabetes [13], but in some other studies, this relationship was not confirmed [14].

Since the increase of serum uric acid level is usually related to risk factors for diabetes, such as alcoholism and metabolic syndrome, it is not confirmed that uric acid is just a risk determinant for diabetes or an independent risk factor [15].

This study aimed to determine the causality effect of hyperuricemia for DM II and also the attributed diabetes risk associated with hyperuricemia among the 20-74-year-old population of Yazd.

Methods

This Yazd Healthy Heart Cohort (YHHC) longitudinal study was carried out based on the research Yazd Healthy Heart Project (YHHP) [16].

In this project, 2000 people were selected from the 20-74-year-old population through multi-stage random clustering sampling. The selected population was examined, and people with a history of diabetes or diagnosed diabetes in base phase of YHHP were excluded from the basic phase. Finally, information of 1641 participants was filed to conduct the study.

Then, the selected individuals were classified into five age groups of 20-34, 35-44, 45-54, 55-64, and 65-74 years old. The study lasted 10 years from 2006 to 2016. During the study period, laboratory data including fasting blood glucose and blood urine were collected and recorded in the patients' profiles [17].

In the first five years of the study, the participants were evaluated annually according to the studied factors, but in the second five years, these evaluations were just conducted in the eighth and the 10th years of the study.

The diabetes was defined based on the American Diabetes Association benchmark; individuals with a history of taking anti-diabetes drugs or fasting blood glucose levels ≥ 126 mg /dl were considered diabetic, patients with glucose levels of 100 to 125 were classified as pre-diabetic(having impaired

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glucose tolerance), and those with glucose levels of less than 100 were categorized as healthy [18].

Patients who took medications in the last year of the study or had a fasting blood sugar level of 126 or higher were categorized as diabetic and entered the study.

Hyperuricemia was defined both on the basis of uric acid indices of greater than 7 mg /dl in males and greater than 6 mg / dl in females and according to the percentile of 75 (blood uric acid of higher than 5.7 mg / dl in males and higher than 4.5 mg / dl in females) [19].

Ethical approval

The present study was ethically approved by the Shahid Sadoughi University of Medical Sciences ethics committee (code of ethics: IR.SSU.SPH.REC.1396.37). Informed consents were obtained from participants at the initial and follow-up phases.

Statistical analysis method

At the end of the study, the required data were extracted from the questionnaire archive according to the study variables. In order to analyze the data, Chi-square, independent t-test and logistic regression statistical models were used through the SPSS Version 16. A level of 0.05 was considered significant. All variables with a significant correlation in the univariate analysis were included in the logistic regression model backward methods in order to eliminate their confounding effect.

Population Attributed Risk (PAR) is an estimate of a proportion of the total number of diabetic patients in a specific population that is caused by a particular factor such as hyperuricemia. Population attributed risk of a definite risk factor is influenced by its prevalence and relative risk, which was calculated in this study based on the Levin formulas and the attributed population risk which was weighted by the exposure prevalence:

Levin formulae =PAR = PF (RR-1) / [PF (RR-1)+1] [20]. In this formula, PF is the fraction of the population exposed to a risk factor.

Table 1. Population Attributed Risk

	Case	Control	Total
Exposed	a	b	a+b
Not Exposed	c	d	c+d
Total	a+c	b+d	a+b+c+d

$$PAR = \frac{[(b/(b+d)(OR-1)]}{[((b/(b+d)(OR-1)+1]}$$

PAR estimate weighted with the exposure prevalence = $\frac{(ITP*PPS+IUP*PPW)-IUP}{(ITP*PPS+IUP*PPW)}$

In this formula, ITP is Incidence of diabetes in the total population, PPS is the prevalence of population suffered from hyperuricemia, IUP is the incidence of diabetes in the unexposed population and PPW is the prevalence of population without hyperuricemia.

Results

In this study, 1641 people were enrolled and followed up for 12226 person-years over a period of 10 years (Person-time is an estimate of the actual time at risk – in years, months, or days – that all participants contributed to a study). During the study, 1076 lived people (65.56% of participants) completed the study till the end, 140 people died, and 425(25.9%) participants refused to continue cooperation. Firstly, the variables of age, gender, BMI, waist, systolic and diastolic blood pressure, blood cholesterol and triglyceride levels, obesity, and uric acid levels were tested as the univariate analysis factor with the incidence of diabetes.

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Table 2. Univariate analysis of demographic and cardiovascular risk factors of people with diabetes and healthy people

Variables	Diabetic	Non-diabetic	P-value
Age (Begin the study)	51.2 ± 11	43.7 ±14	<0.0001
BMI	28.3 ±5.8	26 ±8.9	<0.0001
Waist	98.6 ±10.5	91.1 ±12	0.001
SBP	130 ±15	124 ±14	<0.0001
DBP	83.5 ±9	81.3 ±8.8	<0.0001
Cholesterol	204 ±41	191.6 ±42	<0.0001
TG	200 ±108	159 ±97	<0.0001
Uric acid	4.9 ±1.2	4.3 ±1.2	<0.0001

According to Table 2, all variables with a significant correlation in the univariate analysis were included in the logistic regression model backward methods in order to eliminate their confounding effect. After adjusting for confounding factors; the age, increased waist circumference, triglyceride values greater than 150 and uric acid more than the 75th percentile were recognized as independent risk factors of diabetes.

Table 3. Results of fitting the logistic regression model

Variable	B	SE	RR	95%CI	P-value
Age(At the base)	0.039	0.007	1.018	1.02-1.05	<0.0001
Uric acid	0.843	0.402	1.691	1.05-5.10	0.036
Waist	0.653	0.176	1.274	1.36-2.71	<0.0001
TG	0.751	0.178	1.883	1.49-3.00	<0.0001

At the beginning of the study, 91 (5.5%) patients had hyperuricemia, at the end of the study, 49 (54.8%) of patients with hyperuricemia were suffering from diabetes. However, the incidence of diabetes in individuals with normal uric acid was 28.2% (437 people). By calculating the hyperuricemia attributed risk in the incidence of diabetes based on the definition of hyperuricemia (the uric acid threshold of greater than 7 mg for males and 6 mg for females), it was found that in the case of removing hyperuricemia, the occurrence of diabetes can be reduced by 3.6%. By treating hyperuricemia, the risk of developing diabetes in people with hyperuricemia decreased by 24.2% over ten years.

Table4. The AR and PAR based on incidence of diabetes in the study population according to two definition; HU and uric acid level of 75th and over

Indices	HU	UA 75th percentile for DM risk
Incidence of DM	54.8%	49%
Incidence of DM in normal range of uric acid	28.2%	22%
Relative Risk for DM incidence	1.94	1.68
Attributed Risk	26.6%	27%
Attributed Risk percent	48.5%	51%
PAR using weighted by HU prevalence	3.6%	22.5%
PAR using Levien Formula and RR	3.74%	24.2%
PAR using Levien Formula and OR	8.28%	36.2%

DM: Diabetes Mellitus, HU: Hyper-Uricemia, UA: Uric Acid

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Based on the definition of hyperuricemia as the uric acid level of more than 75th percentile, the prevalence of hyperuricemia in the whole population was 23.8%. With elimination of hyperuricemia more than 75th percentile, the occurrence of 24.2% of diabetes can be prevented over a period of 10 years. There was no significant difference in age and sex groups.

Therefore, the attributed risk according to the definition of hyperuricemia (threshold of 7 mg /dl for men and 6 mg /dl for women) was compared with hyperuricemia definition based on the 75th percentile in both genders (threshold of 5.7 mg /dl in males and 4.5 mg /dl in females). Then, it was discovered that if the threshold of hyperuricemia changes from 6 mg /dl to 4.5 mg /dl in females and from 7 mg /dl to 5.7 mg /dl in males, the diabetes mellitus can be decreased by 24.2%, instead of 3.6%. (Table4)

The attributed risk of hyperuricemia in the incidence of DM II was 3.73% according to Levin formula. By replacing the odds ratio with the relative risk in the Levin formula, the attributed risk was estimated at 8.28%. The calculated PAR by the Levin formula using relative risk was much closer to the PAR calculated using the weighted incidence formula with the prevalence of exposure in the community.

Discussion

Findings of the current research demonstrated that the incidence of diabetes is significantly correlated with the level of serum uric acid. In this study, 54.8% of people with hyperuricemia suffered from DM incidence, whereas this rate was 28.2% in participants with normal uric acid. Thus, by treating patients with hyperuricemia with definition of 7 mg /dl for men and 6 mg /dl for women, we can prevent diabetes incidence by 3.6% in the community. By treating hyperuricemia, the risk of developing diabetes in people with hyperuricemia decreased 26.6% over ten years.48.5% of DM incidence is due to HU.

We calculated AR PA percent and PAR in various methods and various hyperuricemia definitions. As seen in this study we use two different hyperuricemia definitions and three methods of calculation of PAR.

According to previous studies, the increase in blood uric acid has been known as one of the consequences of insulin resistance and diabetes. However, other researches have reported that the increased amount of uric acid in the blood can be a causative factor for the spread of obesity-independent type 2 diabetes, dyslipidemia, and hypertension [(21)].

In a study carried out by SudhindraRao et al. in India, the means of uric acid level in patients with diabetes and healthy participants were 3.84 mg /dl and 3.78 mg /dl, respectively and no significant difference was observed between these two groups [(22)]. However, we found a significant relationship between blood uric acid and diabetes risk in the present study; the probability of diabetes increased with the rise in uric acid levels (OR=1.26, 95% CI= 1.1-1.4).

Furthermore, Safi et al. evaluated 100 diabetic persons and 100 healthy individuals. The means of uric acid measured in individuals with diabetes and healthy individuals were 6.07 mg /dl and 5.01 mg /dl, respectively. This indicated that serum uric acid levels were much more in diabetic people than healthy individuals [(23)]. In the current study, the relationship between blood uric acid and diabetes was also significant (uric acid level 4.9$\pm$1.2 vs. 4.3$\pm$1.2).

In a meta-analysis, Oinlv et al. investigated eight cohort papers and concluded that high quantity of serum uric acid is germane to an increase in the risk of type 2 diabetes so that with 1 mg /dl increase in serum uric acid levels, the risk of type 2 diabetes increases by 6%. This finding is in the same line with the present study [(15)].

E. Krishnan et al. studied the diabetes risk associated with hyperuricemia in American peoples with gout. In this study, it has been proven that increased uric acid levels significantly increase the risk of diabetes after justifying confounding factors (hazard ratio: 1.19 95% CI: 1.01-1.41) [(24)]. In the present study, the

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relationship between hyperuricemia and diabetes was also significant (OR: 1.26 95% CI: 1.1-1.4).

Another meta-analysis conducted on cohort studies revealed that hyperuricemia increases the chance of getting diabetes; with 1 mg /dl increase in serum uric acid levels, the risk of type 2 diabetes has increased by 17%. These results also confirm the findings of our study [12].

Mirzapur et al. reported an inverse relationship between the serum uric acid and the fasting blood glucose levels in diabetic patients. However, in the present study, we found a significant association between serum uric acid and diabetes [25]. It was further observed that treating high uric acid in patients with hyperuricemia; diabetes can be prevented up to 3.6%.

Limitation: Among the problems and weaknesses of the current study, the irregular visits and lack of cooperation of some participants can be mentioned. In this case, we tried to minimize the lost data by making phone calls and inviting people to continue their cooperation.

Conclusion

In this study, we observed a significant relationship between the level of blood uric acid and the risk of DM II. Consequently, necessary measurements should be taken to treat hyperuricemia in order to prevent the development of diabetes caused by high levels of uric acid. Considering the fact that Iran has encountered significant epidemic of diabetes, similar studies should be undertaken regarding the attributed diabetes risk associated with other risk factors.

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Conflict of Interest

The authors declare that they have no conflicts of interest.

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