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Original Article

Statistical study of the relationship between hyperuricemia, dyslipidemia and type 2 diabetes in rural population of Tizi-Ouzou, Algeria

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Abstract

Aim : The main objective of our work was to assess the relationship between type 2 diabetes, hyperuricemia and dyslipidemia in the population of Tizi-Ouzou. By evaluating the relationship between hyperuricemia and some blood lipid parameters, we thus establish, in type 2 diabetes, the correlation between uremia and these lipid parameters. **Subjects and methods:** The survey was carried out by means of an individual questionnaire. We excluded from our study pregnant women, patients with cancer, patients with end-stage renal disease and subjects who did not respond to the questionnaire. **Results**: Serum uric acid level increased with age (p = 0.025). Hyperuricemia was associated with heart disease (p = 0.0007). All patients with gout presented an elevated serum uric acid (p = 0.000001). Dyslipidemia was more common in patients with elevated serum uric acid levels (p = 0.0008). Triglyceridemia was significantly associated with hyperuricemia (p = 0.025). The relationship between type 2 diabetes and glomerular filtration rate was not significant, while the latter was decreased in patients with elevated serum uric acid levels (p = 0.0001). In, stratified analysis, age was effect modifier, the age-dependent results make us understand that resistance to insulin constitutes a significant factor of hyperuricemia. **Conclusion:** The association between hyperuricemia and dyslipidemia in type 2 diabetes emphasizes that insulin resistance acts on both lipid parameters and uricemia. A diet correcting dyslipidemia may also correct the uricemia.

Keywords: Hyperuricemia, diabetes type 2, dyslipidemia, lipoproteins.

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1 Introduction

Diabetes is considered a veritable global epidemic. Type 2 diabetes (DT2) is by far the most frequent, accounting for around 90% of diabetes cases[1]. The incidence of this chronic metabolic disease, linked to changes in lifestyle and eating habits, over the past 30 years, has seen increasing exponentially [2]. The WHO estimates to 629 million diabetics worldwide by 2045, 90% of them will be type 2 diabetics. In Algeria, the number of diabetics is around 4.4 million [3].

Serum uric acid is constantly present in reduced quantities, where it proves to be a powerful antioxidant, displaying a protective role. The total pool of uric acid in the body varies between 1000 and 1200 mg. It depends on the relationship between its formation from different sources and its excretion. This component is renewed at a rate of 65% per day coming exclusively from de novo purino-synthesis pathway [4]. However, if the concentration of uric acid is elevated in the blood plasma (hyperuricemia), >60mg/L in women or >70 mg/L in men, beyond such values, the patient presents significant risk of developing metabolic disorders [5].

In DT2, hyperuricemia appears to be associated with insulin resistance syndrome [6]. Studies have shown that high uric acid levels are often associated with DT2, high blood pressure, cardiovascular disease, and obesity. High concentrations of VLDL (very-low-density lipoprotein) inhibit the renal uric acid excretion. In long term, dyslipidemia can cause insulin resistance and hyper-insulinemia. However, high insulin levels inhibit renal elimination of uric acid and increase liver production of VLDL cholesterol. Thus, diet constitutes one of the major causes leading to hyperuricémie [5]. Numerous epidemiological studies indicate that lipid abnormalities, in DT2, appear to play a key role in the greater frequency and severity of cardiovascular accidents [7].

The main objective of our work was to assess the relationship between DT2 and hyperuricemia in the population of Tizi-Ouzou. The secondary objective was to highlight the relationship between hyperuricemia and some serum lipid parameters, such as triglycerides (TG), total cholesterol, HDL cholesterol (HDL-c) and LDL cholesterol (LDL-c), thus establishing, in DT2, the correlation between uremia and these different lipid parameters.

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2 Subjects and Methods

2.1 Population and data collection

The current study was carried out on 80 adult patients aged 20-year-old and over, including both sexes, admitted to the polyclinics of Mdouha and Ouagnoun in Tizi-Ouzou. Concerning DT2, a patient is classified as suffering from this disease if he/she is followed for this disease (patient under treatment) or an adult patient, for whom the biochemical results meet the definition of this disease (chronic hyperglycemia). Concerning the group of controls, as hyperuricemia is a purely biochemical diagnosis, the only way to classify a patient as a control (subjects free from the disease) is the fact that he has normal uricemia on the day of inclusion in the study.

Eighteen (18) patients with hyperuricemia and 62 controls, with normal uricemia were then recruited. The selection of the study population was randomly performed, limited by the time and availability of the subjects. We excluded from our study pregnant women, patients with any type of cancer, patients with end-stage renal disease, patients who have undergone ablation and subjects who did not respond to the questionnaire.

The present study is an unpaired case-control type study. The survey was carried out by means of an individual questionnaire.

2.2 Anthropometric measurements

Body weight, height, waist and hip circumferences were measured. Body weight was measured using a mechanical scale. The individuals were weighed standing, immobile, without support, and dressed lightly. Height was measured in a standing position. The waist circumference was carried out using a non-stretchy measuring tape, graduated to the millimeter, carried out in a standing and relaxed position, on the horizontal plane which corresponds to the thinnest part of the torso. Anthropometric equipment was regularly checked and calibrated. The size of each individual and the degree of overweight were assessed by calculating the Body Mass Index or BMI according to equation 1:

$$\mathrm{BMI} = \frac{\mathrm{weight}}{\mathrm{Hight}^2}, in\ kg/m^2 \qquad (\mathrm{eq.}\,1)$$

We thus assessed the health risk on the basis of the waist-to-hip ratio (WHR) according to equation 2:

$$\mathrm{WHR} = \frac{\mathrm{waist\ size}}{\mathrm{hip\ circumference}}, in\ cm/cm \qquad (\mathrm{eq.}\,2)$$

2.3 Blood samples

Blood samples were taken by venipuncture at the elbow crease in the morning on an empty stomach. All samples were taken with a medical tourniquet and the subjects in semi-sitting position. The blood was collected in heparin tubes (4ml), for the diabetic population an EDTA tube (4ml) was added. The blood was collected on heparin tubes was centrifuged for 5 min at 4000 rpm to obtain serum used for the assay of the different biological parameters; total cholesterol, HDL-$_C$, LDL-$_C$, TG, fasting blood glucose, urea, creatinine and the assay uric acid. As for the determination of HbA1c, was carried out on total blood.

2.4 Biochemical assays

Total cholesterol test

This assay was performed using the cholesterol esterase method. The reagent containing cholesterol esterase (CE), cholesterol oxidase (CO), peroxidase (POD), 4-aminoantipyrine (4-AAP) and phenol, was used to measure the concentration of cholesterol in the sample. During the reaction, the cholesterol esters (EC) are enzymatically hydrolyzed by cholesterol esterase to cholesterol and free fatty acids (reaction1). Free cholesterol, including that originally present, is then oxidized by cholesterol oxidase to cholestene-3-one and hydrogen peroxide (reaction2). Peroxidase catalyzes the reaction of hydrogen peroxide with 4-AAP and phenol to give quinonimine (product colored red) (reaction3). This assay is carried out according to the reactions below:

$$\mathrm{Cholesterol\ esters} \xrightarrow{CE} \mathrm{Cholesterol} + \mathrm{fatty\ acid} \quad (1)$$

$$\mathrm{Cholesterol} + \mathrm{O_2} \xrightarrow{CO} \mathrm{Cholesten-3-one} + \mathrm{H_2O_2} \quad (2)$$

$$2\,\mathrm{H_2O_2} + 4-\mathrm{AAP} + \mathrm{Phenol} \xrightarrow{POD} \mathrm{Quinonimine} + \mathrm{H_2O} \quad (3)$$

The ARCHITECT PLUS ci4100 system monitors the variation in absorption at 520nm. This variation is directly proportional to the concentration of cholesterol in the sample and is used by the system to calculate and express the total cholesterol concentration.

Serum triglycerides assay

This assay was carried out using the glycerol oxidase method. During the reaction, the TGs in the sample are rapidly and completely hydrolyzed to glycerol and free fatty acids by the lipase (reaction 4). A series of three coupled enzymatic steps using glycerol kinase (GK) (reaction 5), the glycerol phosphate oxidase (GPO) (reaction 6) and horseradish peroxidase (HPO) (reaction 7) allows oxidation coupling of 3,5-dichloro-2-hydroxybenzene sulfonic acid (DHBS) with 4-aminoantipyrine to form a red quinoneimine dye.

This assay was carried out according to the reactions below:

$$TGs \xrightarrow{Lipase} Glycerol + Free\ fatty\ acids \quad (4)$$

$$Glycerol + ATP \xrightarrow{GK} Glycérol-3-phosphate + ADP \quad (5)$$

$$Glycérol-3-phosphate + O_2 \xrightarrow{GPO} Dihydroxyacetone + H_2O_2 \quad (6)$$

$$2H_2O_2 + 4-aminoantipyrine + DHBS \xrightarrow{HPO} Quinonimine \quad (7)$$

The ARCHITECT PLUS ci4100 system doses TG using the same principle as that used for the determination of total cholesterol.

HDL-c and LDL-c assays

These assays were carried out by the HDL direct cholesterol method. The reagent containing (detergent, poly-anion, CE, CO, 4AAP, phenol and POD) is used to measure the concentration of cholesterol. This method is based on a unique detergent which solubilizes only the HDL lipoprotein particles and releases HDL cholesterol (reaction 8) which reacts with EC and CO (reaction 9) in the presence of chromogenic (DSBmT: N, N-bis (4 sulfobutyl)–m-toluidine-disodium)to produce stable red substance (reaction 10).

$$LDL, VLDL, CM \xrightarrow{Detergent,\ poly-anion} stable\ complexes \quad (8)$$

$$HDL-c \xrightarrow{CE,\ CO} \Delta^4 Cholesterol + H_2O_2 \quad (9)$$

$$H_2O_2 + DSBmT + 4-AAP \xrightarrow{POD} \Delta^4 Cholesterol + H_2O_2 \quad (10)$$

This change in absorbance at 560nm is directly proportional to the concentration of HDL-c in the sample, and is used by the system to express the concentration of HDL-c. The LDL-c content is determined by a deduction using the Friedwald formula (equation 3).

$$LDL-c = Total\ Cholestérol - (HDL-c + TG/5) \quad (eq.3)$$

Uric acid assay

This assay was carried out using the uricase method. The uric acid reagent containing (4-AAP, TBHB, uricase, peroxidase and Tris buffer) is used to measure the concentration of uric acid in the sample. Uric acid is oxidized to allantoin by uricase with production of hydrogen peroxide (H2O2) (reaction 11). H_2O_2 reacts with 4-AAP and TBHB in the presence of peroxidase to give a quinoneimine dye (reaction 12).

$$Uric\ acid + O_2 \xrightarrow{Uricase} Allantoin + CO_2 + H_2O_2 \quad (11)$$

$$H_2O_2 + 4-AAP + TBHB \xrightarrow{Peroxydase} Quinoneimine \quad (12)$$

The resulting change in absorbance at 548nm is proportional to the concentration of uric acid in the sample.

Creatinine assay

This assay was carried out using the alkaline picrate method. The creatinine reagent containing (picric acid and sodium hydroxide) is used to measure the creatinine concentration in the sample. At alkaline pH, the creatinine in the sample reacts with the picrate to form a creatinine-picrate complex (reaction 13).

$$Creatinine + Picric\ acid \xrightarrow{Alcalin\ pH} Creatinine-Picrate\ complex \quad (13)$$

The rate of increase in absorbance at 500nm due to the formation of this complex is directly proportional to the concentration of creatinine in the sample.

Serum urea assay

This assay was carried out by the urease method; the reagent containing (urease, glutamate dehydrogenase 'GD', oxoglutarate and NADH) is used to measure the urea concentration in the sample. The urea in the sample is hydrolyzed by urease to ammonia and carbon dioxide (reaction14). The second reaction, catalyzed by GLD, converts ammonia and oxoglutarate to glutamate and water with the simultaneous oxidation of nicotinamide adenine dinucleotide (NADH) reduced to nicotinamide adenine dinucleotide (NAD) (reaction15). Two moles of NADH are oxidized for each mole of urea present. The initial rate of decrease in absorbance to 340nm is proportional to the urea concentration in the sample.

$$Urea + H_2O \xrightarrow{Urease} 2\,NH_3 + CO_2 \quad (14)$$

$$NH_3 + Oxoglutarate + NADH + H^+ \xrightarrow{GD} Glutamate + NAD^+ + H_2O \quad (15)$$

Hb1Ac assay

The determination of Hb1Ac is carried out via the Biorad D-10 automated system. It is based on the separation of the molecules by Ion Exchange HPLC. The samples are automatically diluted in the system, and then injected into the analytical cartridge. The system sends a programmed buffer gradient of increasing ionic strength into the cartridge, the hemoglobin molecules are then separated according to their ionic interactions with the material contained in the cartridge. The separated hemoglobin molecules then pass through the spectrophotometer cell where changes in absorbance at 415nm are measured. The result is obtained in 3 minutes.

2.5 Statistical analysis

All collected data were analyzed using IBM SPSS Statistics version 20 software. In terms of statistical tests, to assess the relationship between two qualitative variables we used the Chi2 test, while to assess the relationship between a qualitative

variable and a continuous quantitative variable we used Student's *t*-test. To assess the relationship between two continuous quantitative variables we used Pearson's correlation test and established, if the relationship is statistically significant, the regression line equation.

Concerning the epidemiological association between DT2 and hyperuricemia, we calculated the odds ratio (OR), which is equal to the exposure rating in the cases that divides the exposure rating among controls. We calculated the 95% odds ratio confidence interval (95% CI) according to the Miettinen method (equation 4):

$$\text{CI at } 95\% = \text{OR}^{1\pm\frac{1.96}{\sqrt{\chi^2}}} \qquad (\text{eq. } 4)$$

$\chi 2$ is the value of the Chi2 test

Definition of statistical variables

Hyperuricemia

We classified as cases patients with hyperuricemia and as controls those with normal uremia. Hyperuricemia is defined in women by uricemia greater than 60mg/L and in men by uricemia greater than 70mg/L.

Health risk

We defined health risk based on the waist-to-hip ratio as described by World Health Organization (WHO). The health risk can be low, moderate or high. The values corresponding to these three risk levels depend on sex as explained in Table 1:

Table 1: Effect of sprouting on enzyme activity (n=3)

Waist/Hip Ratio		
In men	In Women	Health Risk
<0.95	<0.80	Weak
[0.96-1.0]	[0.81-0.85]	Moderate
>1.0	>0.85	High

Type 2 diabetes

With regard to DT2, we referred to the medical history to classify patients. So, if a patient says they have it, we ask the nature of their diabetes treatment and at what age, did they discover their illness.

Dyslipidemia

Concerning dyslipidemia, we classified our patients on the basis of the results of their lipid profile. Dyslipidemia is present if there is an increase in triglycerides, total cholesterol, or both. The normal values used in our study are recommended by NCEP (2001). Normal triglycerides level (≤ 1.5g / l) and High (> 2.0g/L). Normal total cholesterol (<2g/L) and High (≥ 2.40g/L).

Glomerular filtration rate

We calculated the glomerular filtration rate (GFR) according to the MDRD (Modification of the Diet in Renal Disease) formula (equation 5) [8].

$$\text{GFR} = 186 \times ([\text{serum creatinine}] / 88.4)^{-1.154} \times \text{age}^{-0.203} \quad (\text{eq. } 5)$$

GFR: mL/min/1.73m²;[serum creatinine]: µmol/L; Age: years.

Bias

Selection bias may affect our study. To make our sample representative of the general population, we selected two different polyclinics for patients' recruitment, one located in the city and the other in the rural areas. The investigated participants can be of a medium socio-economic level. The size of the sample is dictated by the number of patients admitted to the hospital and who have accepted to answer the questionnaire and this for a limited period of time.

Confusion bias is another bias that could affect our study. Indeed, lipid and carbohydrate metabolism, and uric acid metabolism are complex, intricate and have many risk factors in common, including diet and physical activity, therefore, a statistically significant relationship between two variables may not be real and may be explained by further factors, and an insignificant relationship may not be due to a lack of statistical power but rather be a relationship masked by other factors.

3 Results and Discussion

3.1 Uricemia and socio-demographic factors

In terms of sex distribution (Figure 1.A), there was a predominance of women in both patients and controls. Women represented 61.1% of the cases and 83.9% of the controls. However, this difference is not statistically significant (p = 0.09).

By inhibiting the organic anion transporter, estrogen blocks the reabsorption of uric acid and promotes its elimination in the urine. The uricosuric action of estrogens explains on the one hand, the fact that uricemia is lower in women compared to men, and on the other hand, the increase in uricemia with age in women [9]. In our study, there was a predominance of women in both; the hyperuricemia group and the normal uremia one, more pronounced in this latter. Although the relationship between sex and hyperuricemia was not significant, the fact that there were more women than men in the normal uricemia group. This could be linked to the uricosuric action of estrogens.

The distributions of cases and controls by place of residence did not differ significantly (p = 0.21). Patients living in rural areas represented 66.7% of cases and 50% of controls (Figure 1.B).

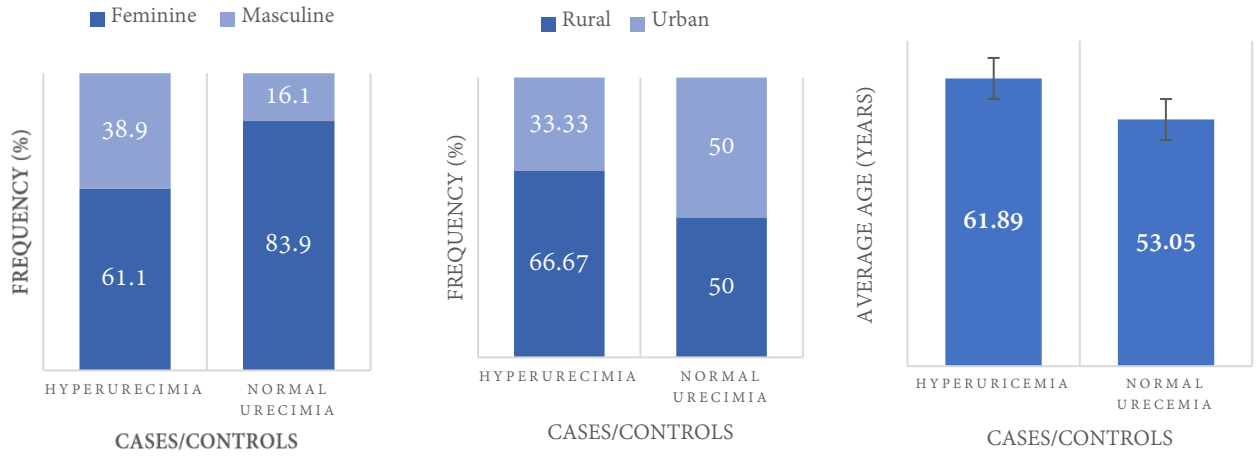

Figure 1: Uricemia and socio-demographic factors. **A**: Gender; **B**: place of residence; **C**: age

The relationship between hyperuricemia and place of residence is not significant, this may be due to the fact that the lifestyles of rural and urban areas have tended to be similar in recent decades due to the urbanization of the countryside. Therefore, the frequency of environmental factors associated with serum uric acid was identical.

The relationship between age and hyperuricemia was statistically significant (p = 0.025). The average age of the cases, 61.89 ± 14.74 years, was higher than that of the controls: 53.05 ± 14.42 years (Figure 1.C).

The mean age of the hyperuricemia group was significantly higher than that of the normal uremia group, since female patients were much more numerous than male (approximately 4 women for 1 man). This difference can also be explained by the uricosuric action of estrogens that disappears after menopause.

3.2 Uricemia and behavioral factors

The distributions of cases and controls according to physical activity did not differ significantly (p = 0.53). Patients who consider their physical activity to be insignificant represent 22.2% and 12.9% of cases and controls respectively (Figure 2.A).

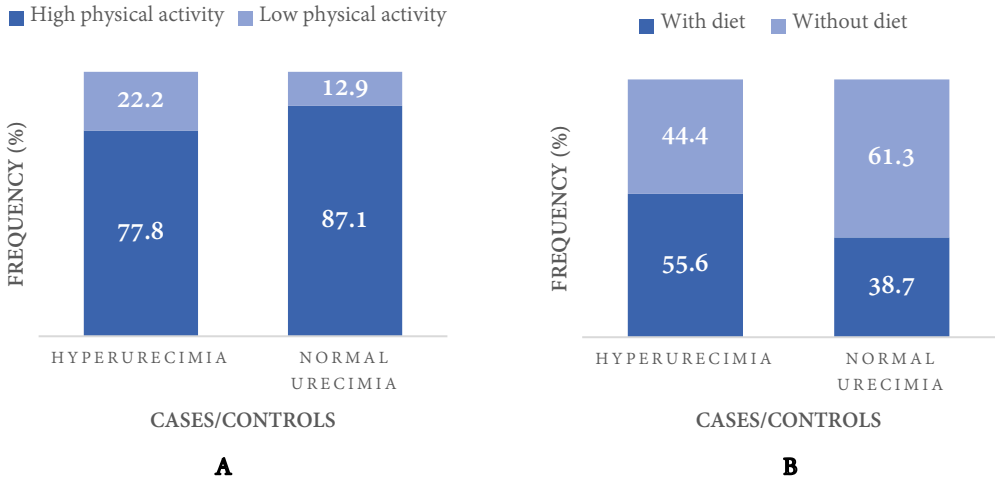

Figure 2: Uricemia and behavioral factors. **A**: physical activity and **B**: diet

The distributions of cases and controls according to diet did not differ significantly (p = 0.2). Patients following no diet represented 44.4% and 61.3% of cases and controls respectively (Figure 2.B).

We did not record any significant relationship between physical activity and hyperuricemia, or between diet and hyperuricemia. It is difficult to explain this given the subjectivity that characterizes patient responses regarding these two factors. Indeed, the perception of the importance of physical activity differs from one patient to another. In patients who claim to be on a diet, it was impossible to determine the nature of their diet, or compliance with it. Consequently, an information bias linked to the patient is most likely present.

3.3 Uricemia and anthropometric parameters

The relationship between body size and hyperuricemia was statistically insignificant (p = 0.087). The average body mass index was 29.53 ± 3.67 Kg/m^2 and 27.24 ± 5.23 kg/m^2 in the cases and controls, respectively (Figure 3.A). The distributions of cases and controls according to health risk, based on the waist-to-hip ratio, did not differ significantly (p = 0.51). Patients with high health risk represent 55.6% and 46.8% of cases and controls respectively (Figure 3.B).

In their prospective study, with a follow-up period of seven years, Zhu and collaborators found that a loss of 10 kg or more of body weight would reduce the uricemia by 6.22 mg/L and that a weight gain exceeding 10kg would increase it by 4.37mg/L [12]. In our study, the relationship between body size and hyperuricemia was not significant, but the average BMI of patients with hyperuricemia was equal to the threshold defining obesity.

3.4 Uricemia and medical history

The distributions of cases and controls according to arterial hypertension did not differ significantly (p = 0.28). Hypertensive patients represented 38.9% and 25.8% of cases and controls respectively (Figure 4.A). The results of a meta-analysis that included 18 prospective studies suggest that high blood pressure increases the risk of developing hyperuricemia [13]. Theoretically, this relationship between high blood pressure and hyperuricemia can be explained in two ways. On the one hand, the decrease in renal plasma flow, characteristic of the hypertensive patient, which promotes the reabsorption of uric acid coupled to sodium. On the other hand, the development of arteriolosclerosis leading to tissue ischemia which in turn increases the activity of xanthine oxidase, an enzyme involved in the formation of uric acid [9].

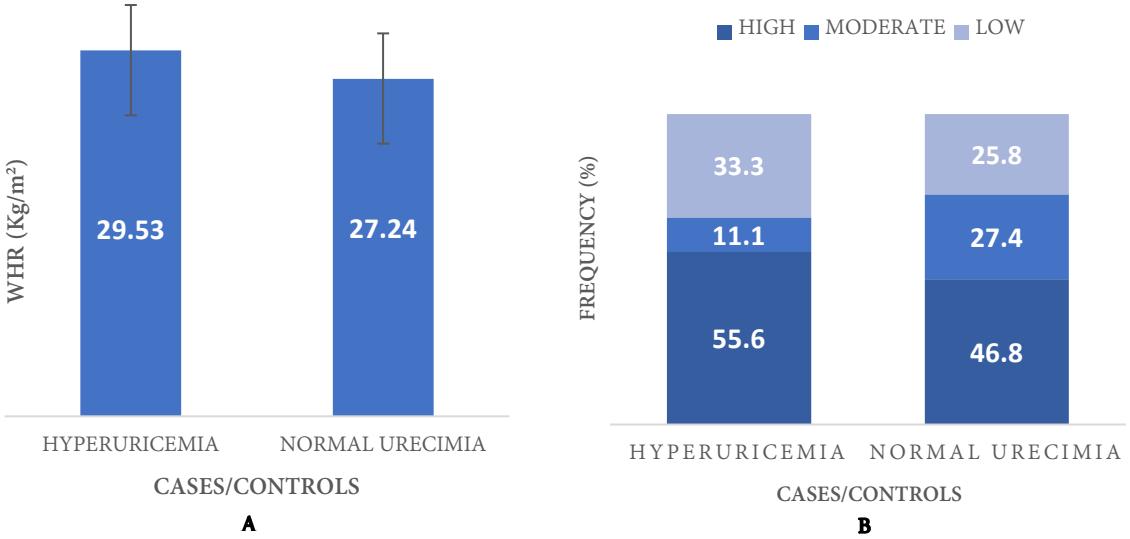

Figure 3: Uricemia and anthropometric parameters. **A**: WHR; **B**: Risk for health

The increase in the prevalence of obesity is one of the factors explaining the increase in the prevalence of hyperuricemia and gout [10]. The association between obesity and uricemia is well established. In the Coronary Artery Risk Development in Young Adults (CARDIA) study, the frequency of hyperuricemia in women with a body mass index greater than 23.5 kg/m2 is multiplied by 5.7 compared to that in women whose body mass index is less than 20.8 kg/m^2 [11].

In our study, the relationship between high blood pressure and hyperuricemia was not statistically significant. It is true that the lack of statistical power cannot be ruled out, but an information bias can also be at the origin of this non-significant difference. In the case of hypertension, we did not measure the blood pressure of the patients, to classify them we based on anamnestic data, therefore, some patients, ignoring that they are hypertensive can be classified as normotensive.

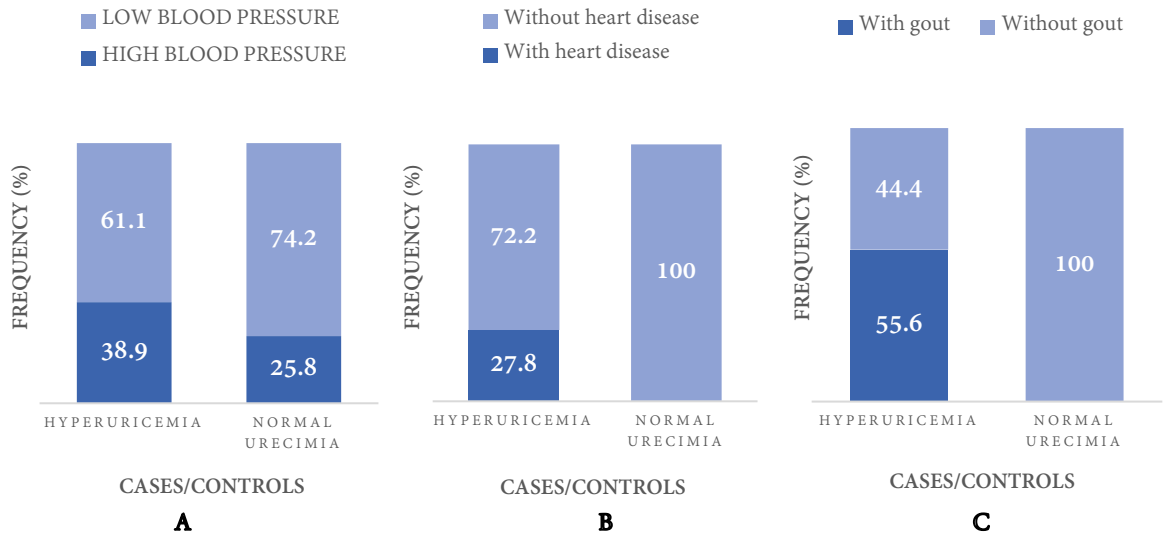

Figure 4: Uricemia and medical history. A: Blood pressure; B: Heart disease and C: gout

The distributions of cases and controls according to heart disease differed significantly (p = 0.0007). All patients with heart disease were in the case group (Figure 4.B). The relationship between uricemia and cardiovascular risk has aroused much interest in recent decades. Although studies have found a relationship between hyperuricemia, cardiovascular disease and mortality, especially in chronic kidney disease, the scientific community is not unanimous on the nature of this relationship. For many, hyperuricemia is not really an independent risk factor for cardiovascular disease. In their cohort study in Taiwan where nearly 500,000 people are followed for eight years, Wen and his collaborators found that after adjustment of glomerular filtration level, the association between uricemia and the risk of cardiovascular mortality strongly attenuated [14].

The distributions of cases and controls according to gout differed significantly (p = 0.000001). All of the gout patients were in the cases group (Figure 4.C). Hyperuricemia is considered a necessary but not sufficient precondition for gout[15]. Although gouty arthritis characteristically occurs in patients with hyperuricemia, it is incorrect to equate hyperuricemia with clinical gout. Hyperuricemia predisposes patients to both gout and nephrolithiasis, but therapy is generally not warranted in the asymptomatic patient. Recognizing hyperuricemia in the asymptomatic patient, however, provides the physician with an opportunity to modify or correct underlying acquired causes of hyperuricemia [16].

3.5 Uricemia and serum lipids profiles

The distributions of cases and controls according to dyslipidemia differ significantly (p = 0.0008). Dyslipidemia occurred in 83.3% of cases, while it was solely present in 38.7% of controls (Figure 5).

In our study the relationship between hyperuricemia and dyslipidemia was significant; the frequency of dyslipidemia was higher in the hyperuricemia group. An analysis of blood uric acid levels in a dyslipidemic Arab population showed that hyperuricemia is common in dyslipidemic patients in Kuwait, where its important determinants are male sex, obesity, diabetes and statin treatment [17].

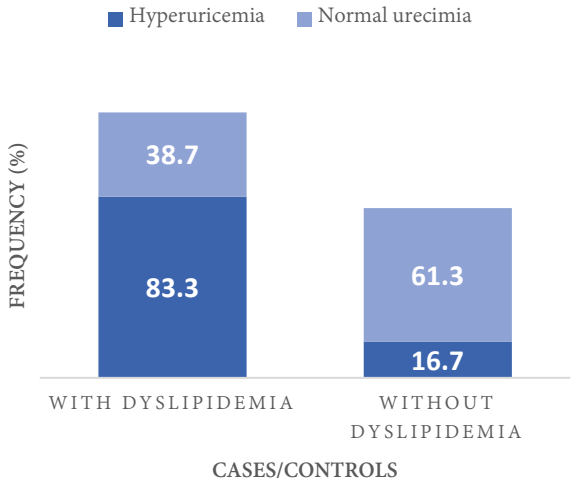

Figure 5: Uricemia and Uricemia and dyslipidemia

Table 2 summarizes the relationship between lipid parameters and hyperuricemia. The relationship between triglyceridemia and hyperuricemia was statistically significant (p = 0.025). The average triglyceridemia of the cases, of 2.59 ± 2.09 g/L, was higher than that of the controls: 1.37 ± 0.64 g/L. The relationship between TC and hyperuricemia was not statistically significant (p = 0.15). Average TC was 1.96 ± 0.38 g/L and 1.8

± 0.42 g/L in cases and controls respectively. The relationship between HDL-c and hyperuricemia was not statistically significant (p = 0.054). The average HDL-c was 0.42 ± 0.12 g/L and 0.48 ± 0.1 g/L in the cases and the controls respectively. The relationship between LDL-c and hyperuricemia was not statistically significant (p = 0.74). The mean LDL-c displayed 1.01 ± 0.4 g/L and 1.04 ± 0.35 g/L in the cases and the controls, respectively. Our results join those of a study carried out in India where triglyceridemia was elevated in 60.3% of the patients with hyperuricemia, the LDL cholesterolemia elevated in 80% of these patients [18]. However, in a Bangladeshi study evaluating the correlations between uricemia and lipid parameters, the authors found that they were all significant. Uricemia evolves in the same direction as triglyceridemia, total cholesterolemia and LDL cholesterolemia, on the other hand, it evolves in the opposite direction from HDL cholesterolemia, when the uricemia increases, HDL cholesterolemia decreases and vice versa [19]. In our study, only the relationship between hyperuricemia and triglyceridemia was statistically significant, mean triglyceridemia was higher in the hyperuricemia group. Regarding the other lipid parameters, the relationship was not significant. Although a lack of statistical power that could be the cause, several factors may also explain the difference between our results and those of the Bangladeshi study, in particular ethnic origin and all the genetic characteristics which may be associated with it, and behavioral factors particularly nutrition and physical activity.

It is established that dyslipidemia, in DT2 patients, usually shows hypertriglyceridemia and hyper HDL-cholesterolemia, while LDL-cholesterolemia is slightly different from that of the general population [20]. In our investigation, 44 patients were followed for DT2, a frequency of 55%. This high frequency may explain the absence of a significant relationship between uricemia and LDL-c.

Table 2: Uricemia and serum lipids profiles

	Hyperuricemia (g/L) ± SD	Normal uricemia (g/L) ± SD	*p-value*
Serum TGs	2.59 ± 2.09	1.37 ± 0.64	0.025
Serum TC	1.96 ± 0.38	1.8 ± 0.42	0.015
HDL-c	0.42 ± 0.12	0.48 ± 0.1	0.054
LDL-c	1.01 ± 0.4	1.04 ± 0.35	0.74

SD: Standard deviation; TGs: Triglycerides; TC: Total cholesterol; HDL-c: High-density lipoprotein cholesterol; LDL-c: Low-density lipoprotein cholesterol

3.6 Uricemia and glomerular filtration rate

The relationship between glomerular filtration rate and hyperuricemia was statistically significant (p = 0.0001). The average flow rate of the cases was 77.29 ± 23.64 ml/min/1.73m²; it was lower than that of the controls which was equal to 98.53 ± 18.14 mL/min/1.73m² (Table 3).

In their prospective study including patients with a priori normal renal function, followed for eight years, Weiner and his collaborators found that the risk of developing renal disease increases in proportion to the uricemia [21].

Table 3: Patients distribution according to glomerular filtration rate and type 2 diabetes

Type 2 diabetes	Glomerular filtration rate (mL/min/1.73m²) Sum	Mean ± SD	*p*-value
With	44	92.15 ± 23.22	0.46
Without	36	95.71 ± 18.85	

SD: Standard deviation.

In another prospective study, including healthy patients, followed for seven years, it was shown that when the blood sugar level exceeds 90 mg/L, the risk of developing renal failure is tripled [22]. In our study, the average glomerular filtration rate of the hyperuricemia group was significantly lower than that of the normal uremia group. Unlike the two studies that are prospective, the one we conducted is retrospective, therefore we cannot state whether hyperuricemia is a cause or a consequence. Nevertheless, we confirm that uricemia and kidney function are intimately associated.

3.7 DT2 and uricemia

DT2 and factors associated with hyperuricemia

All non-diabetic type 2 patients are exempted from heart disease; only 11.4% of heart disease cases were recorded among type 2 diabetics (Figure 6A). Insulin resistance and compensatory hyperinsulinemia have been shown to predict coronary heart disease in non-diabetics [23], although it is not clear if this is a direct effect or secondary to the risk factors present in these individuals [24].

The distributions of patients with DT2 and gout did not differ significantly (p = 0.99). Gout was present in 13.6% and 11.1% of patients with DT2 and those without diabetes respectively (Figure 6B). In meantime, the relationship between glomerular filtration rate and DT2 was statistically insignificant (p = 0.46) (Figure 6D). The average flow rate was 92.15 ± 23.22 mL/min/1.73m² in patients with DT2 and 95.71 ± 18.85 mL/min/1.73m² in non-diabetics. Our results are in contrast with data from two generations of the Framingham Heart Study that provided evidence that individuals with higher serum uric acid are at a higher future risk of DT2 independent of other known risk factors [25]. Because insulin resistance, characteristic of the metabolic syndrome and DT2, results in lower urine pH through impaired kidney ammonia genesis [26]. In addition, insulin has been shown to enhance a parallel UA and sodium reabsorption in the proximal convoluted tubule, resulting in hyperuricemia and decreased uric acid and sodium excretion. Hyperinsulinemia seems to induce hyperuricemia, and by influencing proximal tubular reabsorption of glucose and sodium, may alter the tubular transport of uric acid [27].

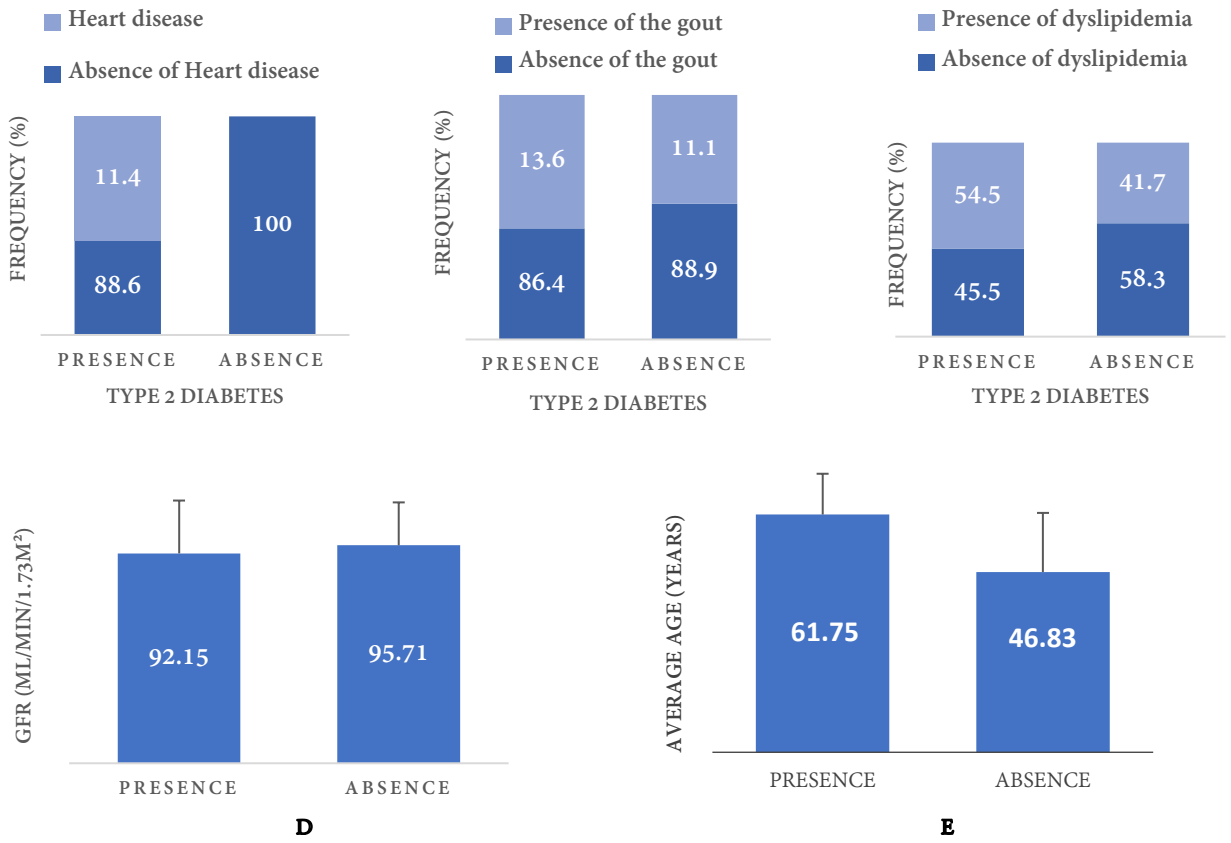

Figure 6: Type 2 diabetes and factors associated with hyperuricemia. A: Heart disease; B: Gout; C: Dyslipidemia; D: Age and E: GFR

The distributions of patients according to DT2 and dyslipidemia did not differ significantly (p = 0.34); dyslipidemia was present in 54.5% and 41.7% of patients with DT2 and those without diabetes respectively (Figure 6C).

The relationship between age and DT2 was statistically significant (p = 0.0001). The average age of patients with DT2, 61.75 ± 10.6 years, was higher than that of non-diabetic patients which was 46.83 ± 15.35 years (Figure 6E).

Prior the age of 65, although the relationship is not significant, our results are similar to those found in a prospective study where it is found that DT2 was associated with hyperuricemia [28]. After the age of 65, DT2 significantly decreases uricemia; of course, no one would dare to conclude that DT2 is a protective factor for hyperuricemia after the age of 65, but this rather suggests that DT2 is not an independent factor for hyperuricemia. Indeed, we know that diet is directly related to serum uric acid [29].

Table 4: Stratified analysis of DT2 and hyperuricemia by age

Age (year)	Uricemia	Sum	Type 2 Diabetes		Odd Ratio	*p*-value
			Number	Odds of exposure		
≤65	Hyperuricemia	10	06	1.50	2.03	0.51
	Normal uricemia	47	20	0.74		
>65	Hyperuricemia	8	4	1	0.07	0.03
	Normal uricemia	15	14	14		

In terms of glycemic control, 52.4% of patients with DT2 presented optimal results. In 14.3% of patients, the anti-diabetic treatment must be readjusted (Figure 7). In the stratified analysis (Table 4), we found that the nature of the relationship between DT2 and hyperuricemia varied with age.

After the age of 65, patients with DT2, especially if they are more or less well balanced and have no other chronic illnesses, show little importance to dietary advice. The diet rich in purines and fructose, combined with insulin resistance increases uricemia. After age 65, on the other hand, due to the presence of other diseases, patients with DT2 may have an adequate diet,

unlike non-diabetic patients who may be consumers of products susceptible to increase uricemia, especially meats. In this case, there is a distortion in the relationship between DT2 and blood sugar levels through food, especially since the latter is closely linked to blood sugar levels.

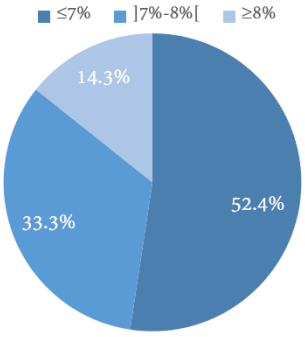

Figure 7: Distribution of patients with type 2 diabetes, according to glycated hemoglobin

The glycemic balance reflects therapeutic compliance, but also can reflect the quality of consumed food. Given the satisfactory results of glycated hemoglobin in patients with DT2, the hypothesis of an adequate diet compared to non-diabetic patients is, therefore, more plausible to explain the biased relationship between DT2 and hyperuricemia after the age of 65.

Uricemia and some lipid parameters in DT2

There was a statistically weak positive linear relationship (R^2 = 0.1352) between uricemia and triglyceridemia (Figure 8.A); The relationship between uricemia and total cholesterolemia was too weak to be considered (R^2 = 0.0075) (Figure 8.B); There was a statistically non-significant negative linear relationship between uricemia and HDL-c and LDL-c R^2 = 0.013 and R^2= 0.0244 (Figure 8.C-D).

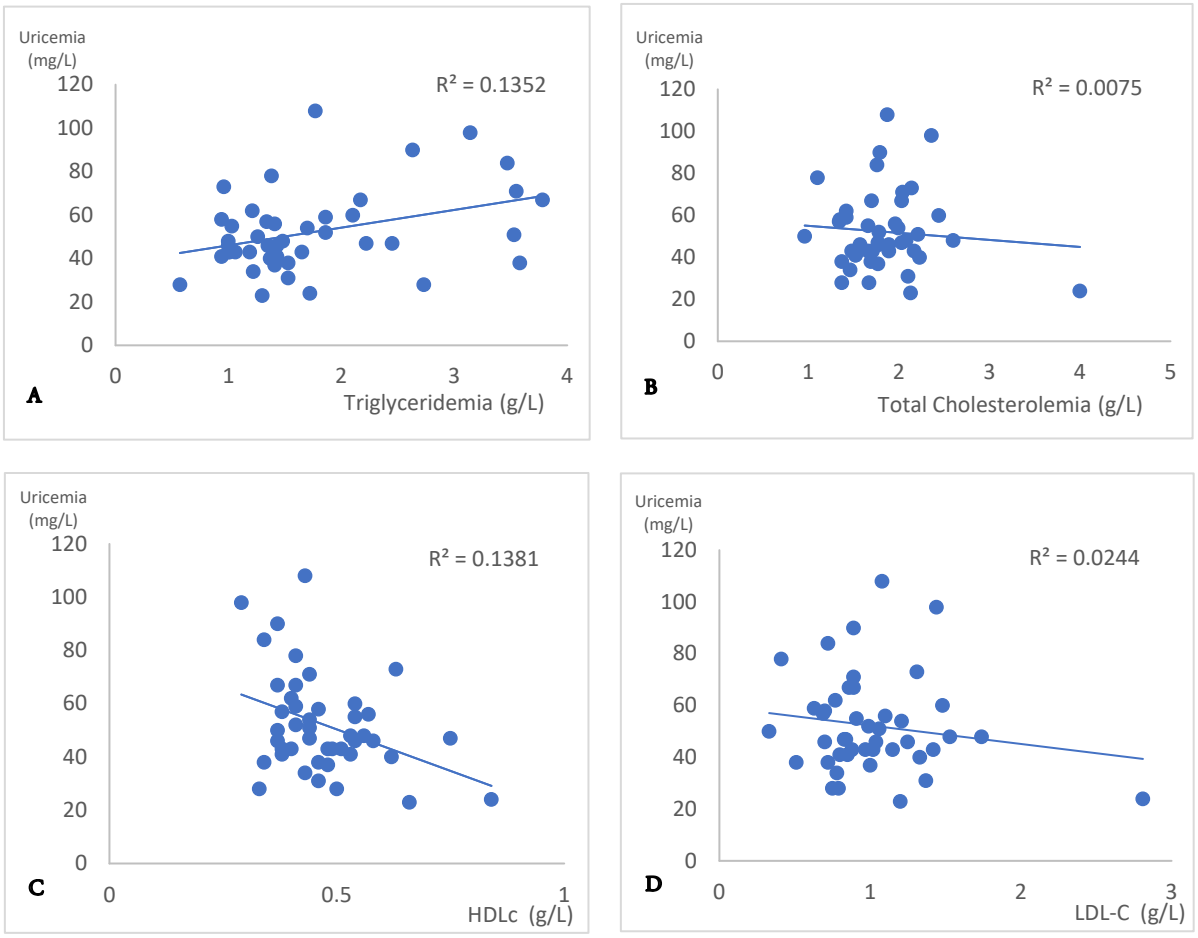

Figure 8: Uricemia and lipid parameters in diabetes type 2. A: Correlation between Uricemia and Triglyceridemia; B: Correlation between Uricemia and total cholesterolemia; C: Correlation between Uricemia and HDL-c; D: Correlation between Uricemia and LDL-c

In our study, on the other hand, in patients with DT2, we highlighted a weak positive linear relationship between uricemia and triglyceridemia and a weak negative linear relationship between uricemia and HDL-c. Indeed, the uricemia evolves in the same direction as the triglyceridemia, whereas with HDL-c it evolves in the opposite direction. In other words, when the lipid balance is disturbed, so is uricemia. Although theoretically the relationship between lipid metabolism and uric acid metabolism is complex, we can explain this relationship by the fact that these two metabolisms have in common an important behavioral factor, nutrition. A diet correcting dyslipidemia is also likely to correct uricemia.

4 Conclusion

Much has been drafted about the relationship between hyperuricemia and metabolic syndrome in general, and DT2 in particular. In fact, numerous epidemiological studies have been carried out. Some suggest that insulin resistance promotes elevation of uricemia, for others hyperuricemia increases the risk of DT2, but all are unanimous that hyperuricemia and DT2 are associated.

Through the relationship between age and hyperuricemia, we assume that the protective effect of these hormones, well established theoretically, also concerns the population of Tizi-Ouzou. All gout patients in our study have high uric acid levels. This can be linked to the non-optimal effectiveness of the type of treatment prescribed, to the insufficient dosage or to the non-observance of the hygieno-dietetic rules.

The relationship between hyperuricemia and dyslipidemia in our study assumes that nutrition constitutes a key common element in both metabolisms. The association between hyperuricemia and dyslipidemia in DT2 acts on both lipid parameters and uricemia.

Concerning the glomerular filtration rate, the association is significant with hyperuricemia and not significant in DT2. This makes us think that in DT2, in order to preserve the renal function of patients, the optimal glycemic balance is not sufficient. Uricemia must be included in the follow-up biological assessment.

Finally, the relationship between lipid metabolism and uric acid metabolism is complex; these two metabolisms have in common an important behavioral factor which is nutrition. A diet correcting dyslipidemia may also correct the uricemia.

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Author contribution: K.L., D.D., and R.C. conceived and designed the study. All authors undertook the literature research. D.D., S.L., S.A. and R.C. participated in the experiment and data acquisition. S.J. and H.D. Data analysis was achieved by all authors. K.L., R.C., S.L., and S.A. carried out the statistical analysis. K.L., S.L., and S.A. prepared and drafted the manuscript. K.L., D.D., and R.C. reviewed the manuscript. All authors have read and agreed to the published version of the manuscript.

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References

1. Nolan, J., O'Halloran, D., McKenna, T., Firth, R., & Redmond, S. (2006), The cost of treating type 2 diabetes (CODEIRE). Irish Medical Journal, 99 (10), 307-310
2. Hu, F. B., Liu, Y., & Willett, W. C. (2011). Preventing chronic diseases by promoting healthy diet and lifestyle: Public policy implications for China. Obesity Reviews, 12(7), 552-559. https://doi.org/10.1111/j.1467-789x.2011.00863.x
3. Lamri, L., Gripiotis, E., & Ferrario, A. (2014). Diabetes in Algeria and challenges for health policy: A literature review of prevalence, cost, management and outcomes of diabetes and its complications. Globalization and Health, 10(1), 11. https://doi.org/10.1186/1744-8603-10-11
4. Bennesser, A.H., Tazi, M.Z., Harmouche, H., Aouni, M., & Maaouni, A. (2010), La goutte: Nouvelles recommandations. Espérance Médicale, 17 (166), 119-133
5. De Oliveira, E. P., & Burini, R. C. (2012). High plasma uric acid concentration: Causes and consequences. *Diabetology & Metabolic Syndrome*, 4(1). https://doi.org/10.1186/1758-5996-4-12
6. Bo, S., Cavallo-Perin, P., Gentile, L., Repetti, E., & Pagano, G. (2001). Hypouricemia and hyperuricemia in type 2 diabetes: Two different phenotypes. *European Journal of Clinical Investigation*, 31(4), 318-321. https://doi.org/10.1046/j.1365-2362.2001.00812.x
7. McEwen, L. N., Karter, A. J., Waitzfelder, B. E., Crosson, J. C., Marrero, D. G., Mangione, C. M., & Herman, W. H. (2012). Predictors of mortality over 8 years in type 2 diabetic patients: Translating research into action for diabetes (TRIAD). Diabetes Care, 35(6), 1301-1309. https://doi.org/10.2337/dc11-2281
8. Levey, A. S. (1999). A more accurate method to estimate glomerular filtration rate from serum creatinine: A new prediction equation. *Annals of Internal Medicine*, 130(6), 461. https://doi.org/10.7326/0003-4819-130-6-199903160-00002
9. Schils, R.; & Krzesinski, J. M. (2016), Hyperuricémie et risque potentiel de pathologie cardiovasculiare et rénale. *Revue Médicale de Liège*. 71(5), 262-268.
10. Roddy, E., & Choi, H. K. (2014). Epidemiology of gout. *Rheumatic Disease Clinics of North America*, 40(2), 155-175. https://doi.org/10.1016/j.rdc.2014.01.001
11. Rathmann, W., Funkhouser, E., Dyer, A. R., & Roseman, J. M. (1998). Relations of hyperuricemia with the various components of the insulin resistance syndrome in young black and white adults: The CARDIA study. *Annals of Epidemiology*, 8(4), 250-261. https://doi.org/10.1016/s1047-2797(97)00204-4

12. Zhu, Y., Zhang, Y., & Choi, H. K. (2010). The serum urate-lowering impact of weight loss among men with a high cardiovascular risk profile: The multiple risk factor intervention trial. *Rheumatology*, 49(12), 2391-2399. https://doi.org/10.1093/rheumatology/keq256
13. Grayson, P. C., Kim, S. Y., LaValley, M., & Choi, H. K. (2010). Hyperuricemia and incident hypertension: A systematic review and meta-analysis. *Arthritis Care & Research*, 63(1), 102-110. https://doi.org/10.1002/acr.20344
14. Wen, C. P., David Cheng, T., Chan, H. T., Tsai, M. K., Chung, W. I., Tsai, S. P., Wahlqvist, M. L., Yang, Y. C., Wu, S. B., Chiang, P. H., & Wen, S. F. (2010). Is high serum uric acid a risk marker or a target for treatment? Examination of its independent effect in a large cohort with low cardiovascular risk. *American Journal of Kidney Diseases*, 56(2), 273-288. https://doi.org/10.1053/j.ajkd.2010.01.024
15. Roubenoff, R. (1990), Gout and hyperuricemia. *Rheumatic Diseases Clinics of North America*, 16 (3), 539-550.
16. Harris, M. D.; Siegel, L. B.; Alloway, J. A. (1999), Gout and hyperuricemia. *American Family Physician,* 59 (4), 925-934.
17. Al-Meshaweh, A. F., Jafar, Y., Asem, M., & Akanji, A. O. (2012). Determinants of blood uric acid levels in a Dyslipidemic Arab population. *Medical Principles and Practice*, 21(3), 209-216. https://doi.org/10.1159/000333483
18. Lokanath, D., & Sharada, A. (2014), Association of hyperuricemia and dyslipidemia-A potent cardiovascular risk factor. *Journal of Medical Science and Clinical Research*, 2(6), 1261-1269.
19. Ali, N., Rahman, S., Islam, S., Haque, T., Molla, N. H., Sumon, A. H., Kathak, R. R., Asaduzzaman, M., Islam, F., Mohanto, N. C., Hasnat, M. A., Nurunnabi, S. M., & Ahmed, S. (2019). The relationship between serum uric acid and lipid profile in Bangladeshi adults. *BMC Cardiovascular Disorders*, *19*(1). https://doi.org/10.1186/s12872-019-1026-2
20. Farnier, M. (2011), la dyslipidémie chez le diabétique. *Diabète et Obésité*, 6 (49), 170-175.
21. Weiner, D. E., Tighiouart, H., Elsayed, E. F., Griffith, J. L., Salem, D. N., & Levey, A. S. (2008). Uric acid and incident kidney disease in the community. *Journal of the American Society of Nephrology*, 19(6), 1204-1211. https://doi.org/10.1681/asn.2007101075
22. Obermayr, R. P., Temml, C., Gutjahr, G., Knechtelsdorfer, M., Oberbauer, R., & Klauser-Braun, R. (2008). Elevated uric acid increases the risk for kidney disease. *Journal of the American Society of Nephrology*, 19(12), 2407-2413. https://doi.org/10.1681/asn.2008010080
23. Zavaroni, I., Bonini, L., Gasparini, P., Barilli, A., Zuccarelli, A., Dall'Aglio, E., Delsignore, R., & Reaven, G. (1999). Hyperinsulinemia in a normal population as a predictor of non—insulin-dependent diabetes mellitus, hypertension, and coronary heart disease: The Barilla factory revisited. *Metabolism*, 48(8), 989-994. https://doi.org/10.1016/s0026-0495(99)90195-6
24. Abbasi, F., Brown, B. W., Lamendola, C., McLaughlin, T., & Reaven, G. M. (2002). Relationship between obesity, insulin resistance, and coronary heart disease risk. *Journal of the American College of Cardiology*, 40(5), 937-943. https://doi.org/10.1016/s0735-1097(02)02051-x
25. Bhole, V., Choi, J. W., Woo Kim, S., De Vera, M., & Choi, H. (2010). Serum uric acid levels and the risk of type 2 diabetes: A prospective study. *The American Journal of Medicine*, 123(10), 957-961. https://doi.org/10.1016/j.amjmed.2010.03.027
26. Abate, N., Chandalia, M., Cabo-Chan, A. V., Moe, O. W., & Sakhaee, K. (2004). The metabolic syndrome and uric acid nephrolithiasis: Novel features of renal manifestation of insulin resistance. *Kidney International*, 65(2), 386-392. https://doi.org/10.1111/j.1523-1755.2004.00386.x
27. Daudon, M., Traxer, O., Conort, P., Lacour, B., & Jungers, P. (2006). Type 2 diabetes increases the risk for uric acid stones. *Journal of the American Society of Nephrology*, 17(7), 2026-2033. https://doi.org/10.1681/asn.2006030262
28. Li, C., Hsieh, M., & Chang, S. (2013). Metabolic syndrome, diabetes, and hyperuricemia. *Current Opinion in Rheumatology*, 25(2), 210-216. https://doi.org/10.1097/bor.0b013e32835d951e
29. Johnson, R. J., Nakagawa, T., Sanchez-Lozada, L. G., Shafiu, M., Sundaram, S., Le, M., Ishimoto, T., Sautin, Y. Y., & Lanaspa, M. A. (2013). Sugar, uric acid, and the etiology of diabetes and obesity. *Diabetes*, 62(10), 3307-3315. https://doi.org/10.2337/db12-1814

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