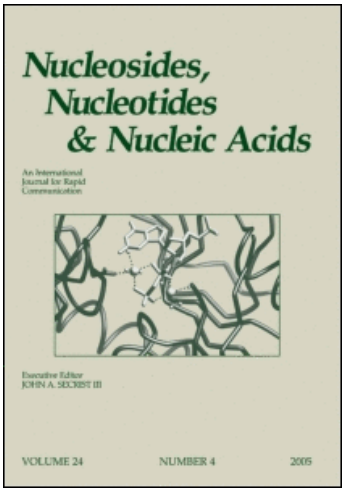

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Relationship Between Plasma Uridine and Insulin Resistance in Patients with Non-Insulin-Dependent Diabetes Mellitus

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RELATIONSHIP BETWEEN PLASMA URIDINE AND INSULIN RESISTANCE IN PATIENTS WITH NON-INSULIN-DEPENDENT DIABETES MELLITUS

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□ Objective*: It has been demonstrated that uridine infusion induces insulin resistance in rats. Furthermore, it was recently reported that plasma uridine is correlated with homeostasis model assessment of insulin resistance (HOMA-R) in hypertensive patients. Therefore, we investigated whether plasma uridine was correlated with HOMA-R in patients with non-insulin-dependent diabetes mellitus (NIDDM).* Subjects and Methods*: The subjects were 23 male patients with NIDDM (average age 63 years) and 18 healthy males (average age 60 years). Blood samples were drawn after an overnight fast, plasma uridine was then measured using high-performance liquid chromatography.* Results*: The average plasma uridine concentration in patients with NIDDM was higher than that in healthy subjects ($P < 0.05$). Furthermore, plasma uridine values were positively correlated with HOMA-R ($r = 0.48$, $P < 0.05$), serum insulin ($r = 0.46$, $P < 0.05$), and serum C-peptide radioimmunoreactivity (CPR) ($r = 0.44$, $P < 0.05$) values, whereas they were not significantly correlated with fasting blood glucose or hemoglobin A1c values.* Conclusion*: We found a positive relationship between plasma uridine value and HOMA-R, serum insulin, and CPR, suggesting that plasma uridine is a marker of insulin resistance in patients with NIDDM.*

Keywords Uridine; diabetes mellitus; insulin resistance

INTRODUCTION

The underlying cellular and molecular mechanisms of insulin resistance, a major feature of non-insulin-dependent diabetes mellitus (NIDDM), have not fully been elucidated. A previous study of rat adipocytes provided direct evidence that an increase in flux through the hexosamine biosynthetic

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pathway (HBP) leads to development of insulin resistance.[1] Approximately 2–5% of total intracellular glucose enters the HBP and is converted to uridine diphosphonate-N-acetylglucosamine (UDP-GlcNAc), a major end product. In addition, glucosamine can directly enter the HBP, where it is converted into glucosamine 6-phosphate by glucosamine kinase or hexokinase and then to UDP-GlcNAc, which is the immediate donor substrate of GlcNAcylation. Furthermore, in vitro and in vivo several studies have suggested that a relationship exists between elevated intra-cellular UDP-GlcNAc and the occurrence of insulin resistance.[2,3] In addition, infusions of uridine alone and glucosamine alone were found to increase skeletal muscle levels of both uridine diphosphonate (UDP)-glucose and UDP-GlcNAc, and also induced marked insulin resistance, suggesting that the marked reduction in insulin action induced by uridine and glucosamine is mediated by increased accumulation of muscle UDP-N-acetylhexosamine.[4] More recently, it was reported that plasma uridine is correlated with homeostasis model assessment of insulin resistance (HOMA-R) in hypertensive patients.[5] In the present study, we focused on the relationship between plasma uridine and insulin resistance, and investigated whether such a relationship exists in patients with NIDDM.

SUBJECTS AND MATERIALS

The subjects were 23 males with NIDDM (average age 63 years) and 18 healthy males (average age 60 years). Blood samples were drawn after an overnight fast, plasma uridine was then measured using high-performance liquid chromatography (HPLC), as described previously. In addition, immunoreactive insulin was measured using a YKO60 insulin ELISA kit (Yanaihara Institute Inc., Shizuoka, Japan) and connecting-peptide immunoreactivity (CPR) by our hospital laboratory. HOMA-R was calculated using the values for glucose and immunoreactive insulin with the following formula: HOMA-R = fasting insulin (ml/ml) × fasting plasma glucose (FPG) (mg/dl)/405.[6] Statistical analysis was performed by ANOVA. The relationships between the level of plasma uric acid and other variables were assessed using regression analysis with StatView (version 5.0 for Windows; Abacus Concepts, Berkeley, CA, USA). $P < 0.05$ was considered to indicate statistical significant and data are expressed as the mean ± SD.

RESULTS

The average plasma uridine concentration in patients with NIDDM was higher than that in healthy subjects ($P < 0.05$; Table 1). Furthermore, plasma uridine values were positively correlated with HOMA-R ($r = 0.48$, $P < 0.05$; Figure 1), serum insulin ($r = 0.46$, $P < 0.05$), and serum CPR ($r = 0.44$, $P < 0.05$) values, whereas they were not significantly correlated with fasting blood

TABLE 1 Characteristics of patients with NIDDM and healthy subjects

	Patients with NIDDM	Healthy subjects
Age (year)	63.4 ± 14.7	58 ± 18
BMI (kg/m^2)	25.3 ± 3.8	24.8 ± 3.3
Plasma uridine (μmol/l)	4.32 ± 0.64*	3.75 ± 1.04
Serum uric acid (μmol/l)	357 ± 89	342 ± 83
Serum creatinine (μmol/l)	71.7 ± 11.5	62.8 ± 13.3
Plasma glucose (μmol/l)	8.33 ± 2.89*	5.23 ± 0.50
IRI (μU/ml)	7.58 ± 5.83	
CPR (ng/ml)	2.27 ± 1.04	—
HOMA-R	3.18 ± 3.16	—
Urinary UN/BS (mmol/m^2)	140 ± 33	128 ± 47
Urinary uric acid/BS (mmol/m^2)	1.46 ± 0.44	1.49 ± 0.51
Urinary creatinine/BS (mmol/m^2)	5.04 ± 1.20	5.31 ± 1.85

BMI, body mass index; CPR, C-peptide immunoreactivity; HOMA-R, homeostasis model assessment insulin resistance; UN, urea nitrogen; BS, body surface; —, not determined.

*$P < 0.05$.

glucose or hemoglobin A1c (HbA1c) values. Stepwise multivariate regression analysis, which included HOMA-R, insulin, and CPR as explanatory variables, showed that HOMA-R was independently associated with plasma uridine level in the patients with NIDDM ($P < 0.05$).

DISCUSSION

A number of studies have demonstrated that ethanol, sucrose, fructose, xylitol, and rigorous exercise increases the concentration of uridine in plasma probably via pyrimidine degradation following enhanced ATP consumption as well as increased concentrations of purine bases (hypoxanthine, xanthine, and urate) via enhanced adenine nucleotide degradation.[7–10] In addition, another study found that plasma uridine concentration was high in overexcretion type gout patients, irrespective of whether purine degradation was induced by enhanced de novo purine synthesis or ATP consumption,

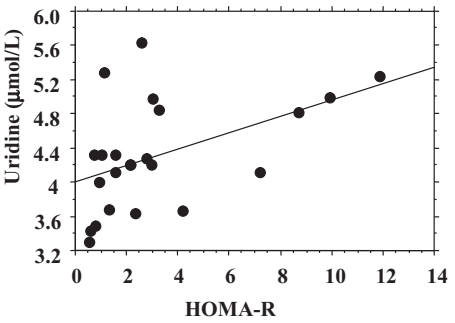

FIGURE 1 Relationship between plasma uridine and HOMA-R.

and may be a marker for uric acid production.[11] On the other hand, amino acid and glucagon have been shown to decrease uridine concentrations, presumably via the nucleoside transporter present in a variety of cells.[12,13] However, the physiological function of plasma uridine has not been explained in detail.

It is known that uridine increases glucose uptake and glycogen synthesis in skeletal muscles, while it also has an effect on lipolysis in adipose tissues, and stimulates the P2 receptor, leading to positive inotropic effects on both the heart and blood vessels via formation of uridine triphosphate (UTP), uridine diphosphate (UDP), and uridine monophosphate (UMP).[4,14] In addition, it was shown that uridine infusion increases UDP-glucose and glycogen, as well as UDP-GlcNAc, and also induces marked insulin resistance, suggesting that the marked reduction in insulin action induced by insulin resistance is mediated by increased accumulation of muscle UDP-N-acetylhexosamine.[2] In a recent study of hypertensive patients, plasma uridine levels were high and comparable to those observed in patients with NIDDM in the present study, and also found to be correlated with HOMA-R,[5] suggesting that plasma uridine is a marker of insulin resistance in hypertensive patients.

The present results suggest that plasma uridine may be a marker of insulin resistance in patients with NIDDM, but that plasma uridine is not related to the urinary excretion of uric acid in patients with NIDDM.

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