

Insulin resistance induced by maximal exercise correlates with a post-exercise increase in uridine concentration in the blood of healthy young men.

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SUMMARY

Uridine is postulated to participate in the development of insulin resistance. Since exercise is an effective tool in the treatment of insulin resistance it appeared justified to assess the impact of maximal exercise on plasma uridine and insulin sensitivity indices (e.g. insulin and HOMA-IR) in healthy subjects.

The study included forty-four healthy males (18.5 ± 2.92 yrs, VO_{2max} 50.2 ± 6.26 ml kg^{-1} min^{-1}). Subjects performed a single maximal exercise on a bicycle ergometer. Blood samples were taken three times: immediately before exercise, immediately after exercise and at the 30th minute of rest. Uridine concentrations were determined in the whole blood using high-performance liquid chromatography. Serum insulin levels were measured by a specific ELISA method. Insulin sensitivity was assessed by homeostasis model assessment method (HOMA-IR)

A maximal exercise-induced increase in the concentration of uridine correlated with post-exercise increases in insulin levels and HOMA-IR.

Our results indicate a relationship between the concentration of uridine in the blood and indicators of insulin sensitivity in healthy subjects. We are the first to demonstrate that a maximal exercise-induced increase in the concentration of uridine is correlated with post-exercise increases in insulin levels and HOMA-IR in healthy subjects. It appears that uridine may be an indicator of insulin resistance.

Key words: uridine, HOMA-IR, exercise

INTRODUCTION

Uridine is a pyrimidine nucleoside that forms a part of RNA, and is not only necessary for the endogenous synthesis of nucleic acids but also plays an important role in the synthesis of glycogen via UDP-glucose. In addition, it contributes to the synthesis of bio-membranes through formation of pyrimidine nucleotide-lipid conjugates (Yamamoto et al. 2011).

Uridine is known to increase the production of uridylated end products of the hexosamine biosynthetic pathway and results in substantial resistance to the metabolic effects of insulin (Hawkins et al.1997). It was also found that plasma uridine is correlated with HOMA-IR in patients with type 2 diabetes mellitus (Yamamoto et al. 2010) as well as in patients with essential hypertension (Hamada et al. 2007). In addition, increased concentrations of uridine in blood have been reported in children with newly diagnosed type 1 diabetes and there have been reports of a relationship with concentrations of fructosamine and HbA1c levels (Dudzinska 2011). It is therefore possible that high blood plasma uridine concentrations play some role in the development of insulin resistance.

In assessing the impact of exercise on the concentration of uridine we have previously shown that maximal exercise in young healthy men leads to a significant increase in blood concentration of uridine (Dudzinska et al. 2010). Similarly, Yamamoto et al. (1997) showed a significant increase in the concentration of this nucleoside using effort with much less intensity. The results of these studies show that exercise-induced ATP consumption not only increases the degradation of purine nucleotides but also pyrimidine nucleotides (UTP → UDP → UMP → Uridine), leading to a significant increase in uridine concentration in blood.

Available literature does not provide information on post-exercise uridine concentration changes in relation to peripheral insulin sensitivity in healthy people. The only information indicating a link between uridine and insulin resistance comes from in vitro studies (Hawkins et al. 1997, Hawkins et al. 1997a) and two clinical studies (Hamada et al. 2007, Yamamoto et al. 2010). Since exercise is an effective tool in the treatment of insulin resistance it seems justified to assess the impact of exercise on the maximum concentration of uridine and insulin sensitivity indices (e.g. insulin and HOMA-IR).

METHODS

Subjects

Forty-four healthy male subjects volunteered to participate in his study. Subjects were studied in the morning after an overnight fast. Their age, height, weight, and peak oxygen consumption were 18.5 ± 2.92 yrs, 189.3 ± 5.99 cm, 75.9 ± 9.45 kg and 50.2 ± 6.26 ml · kg⁻¹ · min⁻¹, respectively.

Participants' anthropometrical and physiological characteristics are shown in Table 1. They had no history of any metabolic and cardiovascular diseases. Participants were nonsmokers and refrained from taking any medications or supplements known to affect metabolism.

The subjects were fully informed of any risks and discomfort associated with the experimental procedures before giving their consent to participate. The study was approved by the local ethics committee in accordance with the Helsinki Declaration.

Anthropometric Measurements

Body height (cm) was measured to the nearest centimetre using a rigid stadiometer.

Body mass (kg) was measured in underwear to the nearest 0.1 kg using an electronic scale.

Body mass index (BMI) was calculated by dividing weight in kilograms by height in square metres (kg/m²). Systolic and diastolic blood pressure (SBP and DBP) were measured according to guidelines at the right arm after a 10-minute rest by using a calibrated sphygmomanometer.

Exercise Protocol

The examined individuals were subjected to a continuous effort test with progressively increasing intensity (up to a refusal) on a cycloergometer (Kettler X-7, Germany). The test was preceded by a 5 minute warm-up on the cycloergometer (25 W). The test proper began at a resistance of 70 W while maintaining 70 revolutions per minute. The effort continued with

an increasing load (20 W every 3 minutes) until refusal, or until the tested individual was not able to maintain the required frequency of rotation. A heart rate monitor (Polar S610, Finland) was used to record resting heart rate and changes during exercise. The uptake of oxygen during exercise was examined using an Oxycon gas analyzer (Jaeger, Germany).

Blood Analysis

The blood samples were obtained from an antecubital forearm vein immediately before exercise, immediately after exercise, and 30 minutes after exercise testing.

Serum was separated at 800 x g. Samples were immediately stored at -80 C. All assays were performed within 5 days of serum collection.

Serum glucose was measured by the glucose oxidase method on a Beckman Glucose Analyzer (Fullerton, CA).

Serum insulin was measured by an enzyme immunosorbent assay (ELISA) kit (Mercodia AB, Uppsala, Sweden). Detection limits for insulin was 1 mU/L. Insulin resistance (homeostasis model assessment - HOMA-IR) was derived using the HOMA equation (Matthews et al. 1985).

Concentrations of uridine was determined in whole blood using high-performance liquid chromatography. The samples (500 µL) of heparinized blood were deproteinized with an equal volume of 1.3 M HClO₄, mixed, and then centrifuged at 20,000 G for 5 min at 4⁰C. The supernatant (400 µL) was neutralized with 130-160 µL of 1M K₃PO₄ (to pH 5-7). The neutralized extract was again centrifuged as above, and the supernatant was stored at -80⁰C until analysis.

Chromatographic analysis was performed using a Hewlett-Packard series 1100 chromatograph according to the method used by Smolenski et al. (1990). The concentrations of uridine, which are present in both erythrocytes and plasma, are expressed as µmol/l whole blood. They are not directly comparable to concentrations measured in separated erythrocytes or plasma.

Statistical Analysis

All values are reported as mean \pm SD. ANOVA with repeated measurements was used to compare data over time. When the ANOVA was significant, (RIR) Tukey's post hoc tests were used to localize the difference. The correlations between variables were examined using Pearson correlation. The accepted level of significance was defined as $P < 0.05$.

RESULTS

The characteristics of several anthropometrical and physiological parameters are shown in Table 1. The study included 44 healthy young men aged 18.5 ± 2.92 years, with normal body mass assessed using the BMI scale (World Health Organization 1998). In the examined group of people the duration of exercise was 21.0 ± 4.97 minutes, and the oxygen consumption at maximum load was 50.2 ± 6.26 ml/min/kg, indicating that subjects had good oxygen capacity for this age group in comparison with reference data (Astrand et al. 1986) (Table 1).

The plasma concentration of uridine in humans ranges from 3 to 8 μ M. Therefore the rest uridine concentration of men in the study group was within the ranges reported by other authors (Yamamoto et al. 2011). The maximum physical effort led to a significant ($P < 0.001$) increase in the concentration of uridine in relation to the values observed before exercise. Significantly increased ($P < 0.001$) uridine concentrations were still observed at 30 minutes of rest, which indicates that the maximal physical exercise induced a uridine increase not only immediately after exercise but also sustained for some time (Table 2).

Plasma glucose concentrations were significantly higher ($P < 0.001$) immediately after exercise in relation to resting values. At 30 minutes of rest we observed a significant decrease ($P < 0.001$) in glucose concentrations in relation to the post-exercise level, and it had returned to the baseline level (Table 2).

Physiological responses to increased glucose concentration immediately after exercise included a simultaneous and significant ($P < 0.001$) increase in insulin levels. At 30 minutes of rest we observed a significant ($P < 0.001$) decrease in insulin levels compared to post-exercise levels. Although during restitution we observed lower insulin concentrations in relation to resting values, the decline was not confirmed statistically (Table 2).

In order to assess insulin sensitivity, we used the HOMA-IR. Immediately after a single intense physical exercise we observed a deterioration of insulin sensitivity in a significant increase ($P < 0.05$), HOMA-IR. Although at 30 minutes of rest we observed a significant improvement in insulin sensitivity, both in relation to resting and post-exercise value, this change which was only confirmed statistically ($P < 0.001$) when compared to post-exercise values (Table 2).

Our results show significant correlations between a post-exercise increase in uridine and (i) glucose ($r = 0.32$, $P < 0.03$) (Fig. 1), (ii) insulin ($r = 0.36$, $P < 0.01$) (Fig. 2) and (iii) HOMA-IR ($r = 0.31$ $P < 0.04$) (Fig. 3).

DISCUSSION

Our results show that a maximal exercise-induced increase in blood uridine correlates with post-exercise increases in insulin levels and HOMA-IR. This is the first study on healthy humans that assesses a post-exercise relationship between the concentration of uridine and indicators of insulin sensitivity.

We show that intense exercise leads to a transient post-exercise hyperglycaemia. Higher plasma glucose concentrations have been reported after an anaerobic Wingate test (Moussa et al. 2003, Vincent et al. 2004), exhaustive high-intensity exercise (Marliss et al. 1992, MacDougall et al. 1997, Higaki et al. 1996, Zouhal et al. 2009) and moderate circuit resistance exercise (Kraemer et al. 2004).

The increase in blood glucose is caused by a positive balance between the production and consumption of glucose associated with the strong anti-regulatory response accompanying high loads (Wasserman et al. 1989, Kjaer et al. 1991, Marliss and Vranic 2002, Howlett et al. 2003). The increase in endogenous glucose production is much higher than the increase in its consumption during intense exercise and shows a significant dependence on increased plasma catecholamines (Purdon et al. 1993, Marliss and Vranic 2002). In our experiment, the response to increased glucose concentrations after exercise included increased insulin secretion; hyperinsulinemia in response to high-intensity exercise was also observed in a number of studies (Marliss et al. 1992, Purdon et al. 1993, Sigal et al. 1994, Marliss and Vranic 2002, Wojtaszewski et al. 2003, Ghanbari-Niaki et al. 2010). Thus, transient post-exercise insulin resistance observed in our studies, may be due to rigorous exercise-induced

secretion of catecholamines. We additionally showed that a post-exercise rise in insulin and glucose levels is correlated with a post-exercise increase in uridine concentrations.

Already in our previous studies we have shown that maximal exercise leads to increased blood concentrations of uridine (Dudzinska et al. 2010). This increase is caused by intensified degradation of pyrimidine nucleotides (UTP→UDP→UMP→uridine) induced by a decrease in ATP levels in contracting muscles (Dudzinska et al. 2010). Because skeletal muscle plays an important role in regulating the insulin-mediated uptake of glucose, and glucose disposal is markedly increased by a single bout of exercise (Brun et al. 1995, Hayashi et al. 2005), we think that the increase in uridine, correlated with increasing concentrations of glucose and insulin, creates favorable conditions for the saturation of muscle with glycogen mobilized in the contracting muscle.

There is considerable evidence that the phosphorylation of uridine by the salvage pathway is a process affected by insulin. Peck and Messinger (1971) first showed that insulin stimulates the incorporation of uridine into RNA and uracil nucleotides in isolated bone cells. Similar observations were made by Rillema et al. (1975) in experiments on mammary gland explants. Haugaard et al. (1977) showed that insulin stimulates the phosphorylation of uridine in skeletal muscle. It has been reported that the tissue content of UTP and rate of glycogen synthesis in the absence of exogenous uridine decreased with time. Uridine added to the medium increased cellular UTP and UDP-glucose and stimulated glycogen synthesis. Insulin significantly increased the synthesis of UTP from extracellular uridine. This action of insulin appeared to be due to a stimulation of phosphorylation of the nucleoside (Haugaard et al. 1997). Uridine has been reported to stimulate glucose uptake and glycogen synthesis in isolated rat skeletal muscle (Kypson and Hait, 1976, 1977), also that the pyrimidine nucleotide metabolism is regulated by insulin, and that insulin activates uridine kinase (EC 2.7.1.48), the enzyme transforming uridine to UTP, which is the rate-limiting component in glycogen biosynthesis and in several metabolic systems leading to the synthesis of essential cell components (Haugaard et al. 1990, 1997).

Based on HOMA-IR measurements, subjects in our study were in an insulin-resistant state immediately after exercise. Although exercise seems to be key in improving glucose homeostasis, our research shows that it may cause temporary deterioration in post-exercise insulin sensitivity. Similarly, Ghanbari-Niaki et al. (2010) showed that high-intensity anaerobic exercise leads to exercise-induced deterioration in insulin sensitivity. In our study, a

positive correlation between the measured indices of insulin sensitivity (e.g. insulin and HOMA-IR) and the concentration of uridine, indicates a relationship between post-exercise insulin resistance and uridine concentration.

This observed dependence is of particular importance in relation to the results presented by Hawkins et al. (1997, 1997a), who demonstrated that uridine induces insulin resistance. In an experiment designed to demonstrate the effects of UDP-N-acetylglucosamine (UDP-GlcNAc) on the insulin-stimulated glucose uptake in skeletal muscle, an infusion of uridine lead to increased levels of UDP-glucose and UDP-GlcNAc and significantly induced insulin resistance.

The decrease in insulin action on peripheral glucose uptake was highly correlated with the increase in skeletal muscle UDP-GlcNAc levels. This suggests that a significant reduction in insulin action induced by uridine is mediated by increased accumulation of muscle UDP-GlcNAc (Hawkins et al. 1997). Also, further studies confirmed the participation of UDP-GlcNAc in glucose toxicity and hyperglycemia-induced insulin-resistance (Dias and Hart 2007, Copelan et al., 2008).

The view that uridine promotes insulin resistance is also based on studies in which an increase in plasma uridine concentration was correlated with indicators of insulin resistance (insulin and HOMA-IR) in patients with essential hypertension (average age 59 years, SBP/DBP; $155 \pm 9/91 \pm 11$ mmHg), who have never been treated with antihypertensive, antidiabetic, antidyslipidemic or antihyperuricemic agents (Hamada et al. 2007) and in patients with non-insulin-dependent diabetes mellitus (average age 63 years, plasma glucose 8.33 ± 2.89 μ M) (Yamamoto et. al. 2010). Hamada et al. (2007) have reported that plasma uridine levels positively correlated with both, plasma insulin ($r=0.379$; $P=0.01$) and HOMA-IR ($r=0.395$; $P=0.007$) in the hypertensive patients, but not with body mass index, serum levels of uric acid, triglyceride, low-density and high-density lipoprotein cholesterol. Also Yamamoto et al. (2010) have reported that plasma uridine values were positively correlated with serum insulin ($r=0.46$; $P\leq 0.05$) and HOMA-IR ($r=0.48$; $P\leq 0.05$) in patients with non-insulin-dependent diabetes mellitus, suggesting that plasma uridine is a marker of insulin resistance. Elevated levels of uridine can be observed in previously published studies on children with newly diagnosed type 1 diabetes (Dudzinska 2011). Importantly, the concentration of uridine positively correlated with serum fructosamine and HbA1c, which indicates the relationship between persistent hyperglycemia and the concentration of uridine.

In our study, a positive correlation between the measured indices of insulin sensitivity (e.g. insulin and HOMA-IR) and the concentration of uridine indicates the possible involvement of this nucleoside in the pathogenesis of post-exercise insulin-resistance. Thus, it is possible that the sustained increase in plasma uridine may play a significant role in the induction of insulin resistance.

Increasing concentrations of uridine after maximal exercise confirms our previous observations (Dudzinska et al. 2010). Also, Yamamoto et al. (1997) showed that exercise, albeit at lower intensity (65% VO₂ max), is associated with a significant increase in exercise-induced concentrations of uridine. Interestingly, we showed that a post-exercise increase in the concentration of uridine is maintained even at 30 minutes of rest, and thus after the normalization of blood glucose, insulin and HOMA-IR in healthy subjects. Thus, exercise stimulates a sustained increase in concentrations of uridine, and thus may create favorable conditions for the induction of insulin resistance through the mechanisms we have discussed above.

It is not known how quickly the concentration of uridine returns to resting values, and the effect of exercise on the concentration of uridine not only in patients with diabetes, but also in other diseases accompanied by reduced insulin sensitivity (obesity, metabolic syndrome, cardiovascular diseases). We believe that further research is needed on this subject; perhaps it could bring new and important information about the pathogenesis of insulin resistance.

In summary, our findings indicate a relationship between blood uridine and indicators of insulin sensitivity in healthy subjects. We demonstrate for the first time that a maximal exercise-induced increase in blood uridine is correlated with post-exercise increases in insulin levels and HOMA-IR in healthy subjects. It therefore seems that uridine may be used as a marker of insulin resistance.

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REFERENCES

ASTRAND PO, RODHAL K (1986) Textbook of Work Physiology: Physiological Bases of Exercise. *New York, McGraw-Hill Company*.

BRUN JF, GUIINTRAND-HUGER R, BOEGNER C, BOUIX O, ORSETTI A: Influence of short-term submaximal exercise on parameters of glucose assimilation analyzed with the minimal model. *Metabolism* **44**: 833–840, 1995.

COPELAND RJ, BULLEN JW, HART GW: Cross-talk between GlcNAcylation and phosphorylation: roles in insulin resistance and glucose toxicity. *Am J Physiol Endocrinol Metab* **295**: 17-28, 2008.

DIAS WB, HART GW: O-GlcNAc modification in diabetes and Alzheimer's disease. *Mol Biosyst* **3**: 766–772, 2007.

DUDZINSKA W, LUBKOWSKA A, DOLEGOWSKA B, SAFRANOW K: Blood uridine concentration may be an indicator of the degradation of pyrimidine nucleotides during physical exercise with increasing intensity. *J Physiol Biochem* **66**:189-196, 2010.

DUDZINSKA W: Uridine correlates with the concentration of fructosamine and HbA1c in children with type 1 diabetes. *Acta Paediatr* **100**: 712-716, 2011.

GHANBARI-NIAKI A, SAGHEBJOO M, SOLTANI R, KIRWAN JP: Plasma visfatin is increased after high-intensity exercise. *Ann Nutr Metab* **57**: 3-8, 2010.

HAMADA T, MIZUTA E, YANAGIHARA K, KAETSU Y, SUGIHARA S, SONOYAMA K, YAMAMOTO Y, KATO M, IGAWA O, SHIGEMASA C, INOKUCHI T, YAMAMOTO T, SHIMADA T, OHTAHARA A, NINOMIYA H, HISATOME I: Plasma levels of uridine correlate with blood pressure and indicators of myogenic purine degradation and insulin resistance in hypertensive patients. *Circ J* **71**: 354-356, 2007.

HAUGAARD ES, FRANTZ KB, HAUGAARD N.: Effect of uridine on cellular UTP and glycogen synthesis in skeletal muscle: stimulation of UTP formation by insulin. *Proc Natl Acad Sci U S A* **74**: 2339-2342, 1977.

HAUGAARD N, TORBATI A, SMITHGALL T, WILDEY G: Stimulation of the phosphorylation of uridine in skeletal muscle by insulin and vanadate. *Mol Cell Biochem* **93**: 13-19, 1990.

HAWKINS M, ANGELOV I, LIU R, BARZILAI N, ROSSETTI L: The tissue concentration of UDP-N-acetylglucosamine modulates the stimulatory effect of insulin on skeletal muscle glucose uptake. *J Biol Chem* **272**: 4889–4895, 1997.

HAWKINS M, BARZILLAI N, LIU R, HU M, CHEN W, ROSSETTI L: Role of the glucosamine pathway in fat-induced insulin resistance. *J Clin Invest* **99**: 2173-2182, 1997(a).

HAYASHI Y, NAGASAKA S, TAKAHASHI N, KUSAKA I, ISHIBASHI S: A single bout of exercise at higher intensity enhances glucose effectiveness in sedentary men. *J Clin Endocrinol Metabol* **90**: 4035–4040, 2005.

HIGAKI Y, KAGAWA T, FUJITANI J, KIYONAGA A, SHINDO M, TANIGUCHI A, NAKAI Y, TOKUYAMA K, SUZUKI M, TANAKA H: Effects of a single bout of exercise on glucose effectiveness. *J Appl Physiol* **80**: 754-759, 1996.

HOWLETT KF, WATT MJ, HARGREAVES M, FEBBRAIO MA: Regulation of glucose kinetics during intense exercise in humans: effects of alpha- and beta-adrenergic blockade. *Metabolism* **52**: 1615–1620, 2003.

KJAER M, KIENS B, HARGREAVES M, RICHTER EA: Influence of active muscle mass on glucose homeostasis during exercise in humans. *J Appl Physiol* **71**: 552–557, 1991.

KRAEMER RR, DURAND RJ, HOLLANDER DB, TRYNIECKI JL, HEBERT EP, CASTRACANE VD: Ghrelin and other glucoregulatory hormone responses to eccentric and concentric muscle contractions. *Endocrine* **24**: 93-98, 2004.

KYPSON J, HAIT G: Effects of uridine and inosine on glucose metabolism in skeletal muscle and activated lipolysis in adipose tissue. *J Pharmacol Exp Ther* **199**: 565-574, 1976.

KYPSON J, HAIT G: Metabolic effects of inosine and uridine in rabbit hearts and rat skeletal muscles. *Biochem Pharmacol* **26**: 1585-1591, 1997.

MAC DOUGALL JD, WARD GR, SUTTON JR: Muscle glycogen repletion after high-intensity intermittent exercise. *J Appl Physiol* **42**: 129-32, 1997.

MARLISS EB, SIMANTIRAKIS E, MILES PDG, HUNT R, GOUGEON R, PURDON C, HALTER JB, VRANIC M: Glucose turnover and its regulation during intense exercise and recovery in normal male subjects. *Clin Invest Med* **15**: 406-419, 1992.

MARLISS EB, VRANIC M: Intense exercise has unique effects on both insulin release and its roles in glucoregulation. Implications for diabetes. *Diabetes* **57**: 271-283, 2002.

MATTHEWS DR, HOSKER JP, RUDENSKI AS, NAYLOR BA, TREACHER DF, TURNER RC: Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* **28**: 412-419, 1985.

MOUSSA E, ZOUHAL H, VINCENT S, PROIUX J, DELAMARCHE P, GRATAS-DELAMARCHE A: Effect of sprint duration (6 s or 30 s) on plasma glucose regulation in untrained male subjects. *J Sports Med Phys Fitness* **43**: 546-553, 2003.

PECK WA, MESSINGER K, CARPENTER J.: Regulation of pyrimidine ribonucleoside incorporation in isolated bone cells. Stimulation by insulin and by 2,3-dihydroxy-1,4-dithiobutane (dithiothreitol). *J Biol Chem* **246**: 4439-4446, 1971.

PURDON C, BROUSSON M, NYVEEN SL, MILES PD, HALTER JB, VRANIC M, MARLISS EB: The roles of insulin and catecholamines in the glucoregulatory response during intense exercise and early recovery in insulin-dependent diabetic and control subjects. *J Clin Endocrinol Metab* **76**: 566-573, 1993.

RILEMMA JA.: Rapid effects of insulin on uridine metabolism in mammary gland explants. *Am J Physiol* **228**: 1531-1534, 1975.

SIGAL RJ, PURDON C, FISHER SJ, HALTER JB, VRANIC M, MARLISS EB: Hyperinsulinemia prevents prolonged hyperglycemia following intense exercise in insulin-dependent diabetic subjects. *J Clin Endocrinol Metab* **79**: 1049–1057, 1994.

SMOLENSKI RT, LACHNO DR, LEDINGHAM SJM, YACOUB MH: Determination of sixteen nucleotides, nucleosides and bases using high-performance liquid chromatography and its application to the study of purine metabolism in heart for transplantation. *J Chromatogr* **527**: 414-420, 1990.

VINCENT S, BERTHON P, ZOUHAL H, MOUSSA E, CATHELINE M, BENTUE-FERRER D, GRATAS-DELAMARCHE A: Plasma glucose, insulin and catecholamine responses to a Wingate test in physically active women and men. *Eur J Appl Physiol* **91**: 15-21, 2004.

WASSERMAN DH, SPALDING JA, LACY DB, COLBURN CA, GOLDSTEIN RE, CHERRINGTON AD: Glucagon is a primary controller of hepatic glycogenolysis and gluconeogenesis during muscular work. *Am J Physiol Endocrinol Metab* **257**: 108-117, 1989.

WOJTASZEWSKI JF, JORGENSEN SB, FROSIG C, MACDONALD C, BIRK JB, RICHTWR EA: Insulin signaling: effects of prior exercise. *Acta Physiol Scand* **178**: 321-328, 2003.

WORD HEALTH ORGANIZATION. Obesity: preventing and managing the global epidemic. Report of a WHO consultation on obesity. *WHO, Geneva 1998*.

YAMAMOTO T, INOKUCHI T, KA T, YAMAMOTO A, TAKAHASHI S, TSUTSUMI Z, TAMADA D, OKUDA C, MORIWAKI Y: Relationship between plasma uridine and insulin resistance in patients with non-insulin-dependent diabetes mellitus. *Nucleos Nucleot Nucl* **29**: 504-508, 2010.

YAMAMOTO T, KOYAMA H, KURAJOH M, SHOJI T, TSUTSUMI Z, MORIWAKI Y: Biochemistry of uridine in plasma. *Clinica Chim Acta* **412**: 1712-1724, 2011.

YAMAMOTO T, MORIWAKI Y, TAKAHASHI S, TSUTSUMI Z, YAMAKITA J, HIGASHINO K: Effect of muscular exercise on the concentration of uridine and purine bases in plasma - adenosine triphosphate consumption-induced pyrimidine degradation. *Metabolism* **46**: 1339-1342, 1997.

ZOUHAL H, VINCENT S, MOUSSA E, BOTCAZOU M, DELAMARCHE P, GRATAS-DELAMARCHE A: Early advancing age alters plasma glucose and glucoregulatory hormones in response to supramaximal exercise. *J Sci Med Sport* **12**: 652-656, 2009.

Table 1. Anthropometrical and physiological characteristics of subjects.

Parameters	Mean \pm SD
Age (years)	18.5 \pm 2.92
Body height (cm)	189.3 \pm 5.99
Body mass (kg)	75.9 \pm 9.45
BMI (kg m ⁻²)	23.1 \pm 2.07
HRrest (bpm)	68.1 \pm 7.45
SBP (mmHg)	130.0 \pm 9.72
DBP (mmHg)	72.3 \pm 7.24
VO ₂ max (ml kg ⁻¹ min ⁻¹)	50.2 \pm 6.26

Values are given as means \pm SD; n = 44; BMI – body mass index; HR- heart rate; SBP – systolic blood pressure; DBP – diastolic blood pressure; VO₂max – maximum of oxygen uptake.

Table 2. The effect of exercise on concentrations of blood and serum metabolic variables.

	Pre-exercise	Post-exercise	Rest 30 min
Uridine(μ M/L)	3.3 \pm 1.08	4.3 \pm 1.21** (vs.Pre)	4.3 \pm 1.14** (vs.Pre)
Glucose (mM)	5.2 \pm 0.99	6.1 \pm 1.15** (vs.Pre)	5.2 \pm 0.73** (vs.Post)
Insulin (μ U/mL)	11.9 \pm 7.20	17.2 \pm 9.82* (vs.Pre)	8.2 \pm 4.77** (vs.Post)
HOMA-IR	2.3 \pm 1.29	5.1 \pm 4.51** (vs.Pre)	2.1 \pm 1.21** (vs.Post)

Values are given as means \pm SD; n = 44; HOMA-IR– homeostasis model assessment insulin resistance.

*P <0.05; **P <0.001

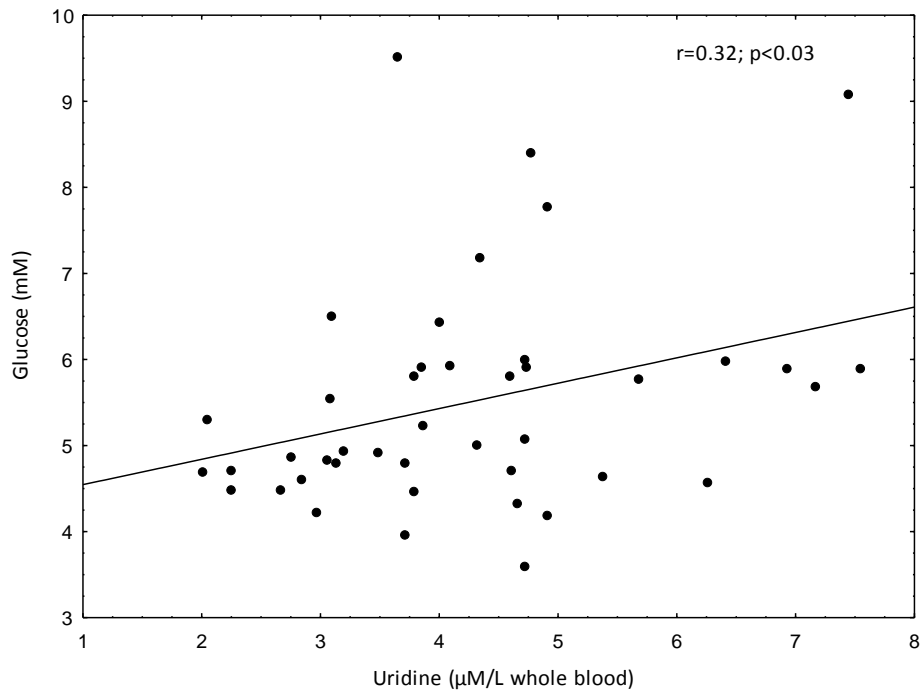


Figure 1

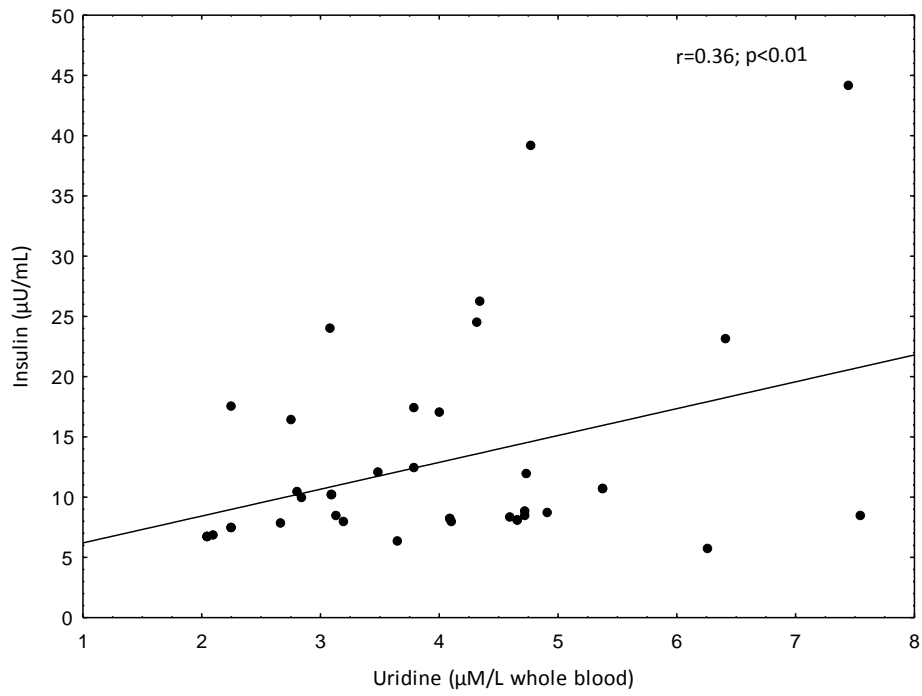


Figure 2

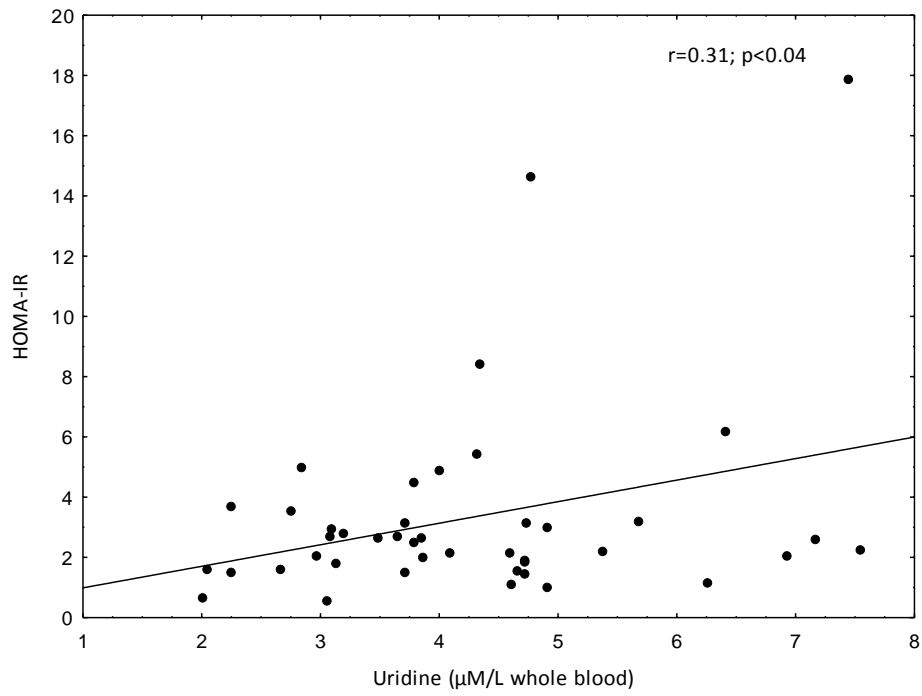


Figure 3

FIGURE LEGENDS

Figure 1

Relationship between blood uridine and serum glucose.

Figure 2

Relationship between blood uridine and serum insulin.

Figure 3

Relationship between blood uridine and HOMA-IR.