

# **Effects of honey on the urinary total nitrite and prostaglandins concentration**

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## **Abstract**

**Objectives:** To evaluate effects of natural and artificial honey solutions on urinary nitrite content, prostaglandin excretion and urinary variables in healthy individuals.

**Methods:** The study comprised 12 individuals, 9 males and 3 females; age range 25 to 45 years. Urinary total nitrite, prostaglandin E2 (PGE2), prostaglandin F2 alpha (PGF2 alpha) and thromboxane B2 (TXB2) were assessed in spot morning sample and 1 h, 2 h, and 3 h after ingestion of 80 g of natural honey dissolved in 250 ml water. Honey solution was given at night; urine volume, urinary osmolality and electrolytes, and serum osmolality and electrolytes, were assayed 10 h after drinking honey. Same procedure was repeated after drinking artificial honey (30 g glucose plus 38 g fructose) and compared with control (drinking 250 ml of water).

**Results:** The mean (SD) of total urinary nitrite excretion was  $103 \pm 43.5$   $\mu\text{mol/L}$  which was increased by 40%, 55% and 74% at 1, 2, and 3 h after drinking honey solution respectively. The mean urinary PGE2 was  $1.323 \pm 0.8$  ng/ml that was decreased by 31% 3 h after honey ingestion. The mean urinary PGF2 alpha was  $1.554 \pm 1.2$  ng/ml and that of TXB2 was  $0.35 \pm 0.4$  ng/ml. Forty-four percent reductions in urinary PGF2 alpha and 67% reduction in TXB2 were obtained 3 h after drinking honey. Honey increased insignificantly free water clearance, filtered sodium and creatinine clearance. It decreased insignificantly urinary osmolality, urinary calcium, urinary sodium, and fasting blood sugar (FBS). Little changes were obtained in urine volume and urinary urea, glucose and creatinine concentration. Artificial honey decreased urinary nitrite and increased urinary prostaglandins concentration. It increased insignificantly free water clearance, filtered sodium, urinary urea, urinary creatinine and creatinine clearance. It decreased insignificantly urinary osmolality, urinary calcium, urinary sodium, and fractional excretion of sodium (FENa). Artificial honey increased FBS by 14% and urinary glucose by 76.5%, and decreased serum sodium and plasma osmolality.

**Conclusion:** Honey solution decreased urinary prostaglandins concentration and increased total urinary nitrite content whilst artificial honey decreased urinary nitrite and increased urinary prostaglandins.

**Key words:**

Nitric oxide, prostaglandin, honey, artificial honey, osmolality, electrolytes.

**Introduction**

Honey is an ancient remedy for management of wounds. It was mentioned in The Holy Quran as cure for human illness (Surat Al-Nahl (The Bees), Aya 69). It has been used for treatment of respiratory diseases, urinary diseases, gastrointestinal diseases, and skin diseases including ulcers, wounds, eczema, psoriasis and dandruff (1-2). In healthy and diabetics, honey could stimulate insulin secretion and decrease blood glucose levels (3-5). Honey elevated serum iron and hemoglobin concentration (6). Honey improved lipid profile and decrease triglyceride in patients with hypertriglyceremia (7). Recently we have found that honey lowers plasma prostaglandins in healthy subjects and increases NO in saliva collected from normal individuals (8,9). Various honey contained high amount of NO metabolites and intravenous honey could increase urinary nitrite excretion in the animals (10).

Prostaglandins and NO have important role in physiology and pathology of urinary system. Endothelium derived NO synthesized in the kidney inhibits sodium reabsorption, mediating pressure natriuresis and diuresis (11). NO decreases ADH and inhibits fluid reabsorption (12). Prostaglandins inhibit sodium tubular reabsorption and ADH; decrease aldosterone secretion and cause glomerular vasodilatation, natriuresis and diuresis (13). Prostaglandin overproduction is associated with enuresis, frequency of micturition and renal colic (14-16). Prostaglandin increased in glomerulonephritis and thromboxane plays

an important role as an exaggerating factor in the development of chronic glomerulonephritis and glomerular microvascular lesion in patients with nephrotic syndrome, lupus nephritis and purpura nephritis (17,18). Inhibition of thromboxane could ameliorate renal diseases (19). The main objectives of this study were: 1- to investigate the effect of honey or artificial honey on urinary excretion of prostaglandins and total nitrite content, and 2- to investigate the effect of honey, artificial honey, and water on urinary variables in healthy individuals.

## **Materials and Methods**

### **Patients and honey selection**

The study included 9 men and 3 women (mean age 37 years, range 25 to 45); the criteria for inclusion were: normal healthy volunteer, no symptoms of any urological or metabolic diseases. A complete clinical examination and laboratory investigations showed that all had normal complete blood and renal function. The volunteers gave their written consent to participate in the study after being informed of the purpose and steps of trial. Unprocessed honey, dark yellow in color, multifloral origin, was used for experimentation. Honey was collected from UAE. It was stored in dark containers at room temperature for using in the study. Biochemical tests were performed. Honey composition included fructose 38 g%, glucose 30 g%, acidity 13%, moisture 20%, vitamin C 2.3 mg%, copper 0.098 mg%, zinc 0.6 mg%, and glutathione reductase 0.52 mg%. Its pH was 3.4. Artificial honey was prepared from 38 g of fructose and 30 g of glucose.

### **Prostaglandin and nitric oxide assay**

Nitrate and nitrite concentration were measured in the nitrite assay kit using Griess Reagents (Assay Design, Ann Arbor, MI, USA). The quantitative analysis of prostaglandins level was performed with use of ELISA test (Neogen Corp. USA).

## **Experiment 1**

Spot MSU specimens after 12 h of fasting was collected from all participants and the total nitrite content and PGE<sub>2</sub>, PGF<sub>2</sub> alpha and TXB<sub>2</sub> levels estimated. After assaying urinary nitrite and prostaglandins level the volunteers were given honey (80 g of honey dissolved in 250 ml of water). The composition of water included calcium 0.5 mg/L, magnesium 2.5 mg/L, sodium 22.4 mg/L, potassium 0.35 mg/L, fluoride 0.2 mg/L, chloride 21.1 mg/L, nitrate 1.8 mg/L, sulphate 10.2 mg/L, pH 8.1 and TDS 135 mg/L. Urine specimens were collected from all the participant 1, 2, and 3 h after drinking honey for total nitrite and prostaglandin assay. Same procedure was repeated after one week when volunteers were given artificial honey dissolved in 250 ml water.

## **Experiment 2**

Volunteers were instructed to take their dinner at 6.00 p.m, stop drinking water at 8.00 p.m and empty their bladder at 10.00 p.m. Each participant drunk honey solution. The overnight urine was collected from 22.00 p.m to 8.00 a.m. Blood samples were withdrawn at 08.00 a.m to assay glucose, sodium, potassium, chloride, blood urea nitrogen (BUN), creatinine, calcium, magnesium and phosphorus. All the individuals completed the investigations, including the nocturnal measurement of urine volume, serum osmolality, creatinine clearance, and total night urine osmolality. Creatinine clearance was calculated from a standard formula based on height, weight, serum creatinine and 10-h urinary creatinine. Plasma and urinary sodium and potassium were assayed by flame photometry, and other test by routine methods. Plasma and urinary osmolality were measured by freezing-point depression. The osmotic clearance was calculated as (urine volume x urine osmolality) / plasma osmolality and free water clearance as (osmotic clearance – urine volume). FENa was estimated as the clearance of sodium times creatinine clearance times 100. The procedure of urine collection and blood sampling was repeated after one-week

with drinking of 250 ml of water instead of honey and after 2 weeks with drinking of artificial honey.

### **Statistical analysis**

The comparison was made between the natural pure honey, the artificial honey and the control. Urine samples were compared to the control and to the artificial honey. All the values were expressed as the mean (SD) and ANOVA was used to compare between the means.  $P < 0.05$  was significant. GraphPad Prism software was used for statistical analysis.

### **Results**

Urinary PGE<sub>2</sub> was decreased by 4%, 6% and 31 % at 1, 2 and 3 h after drinking honey. Urinary PGF<sub>2</sub> alpha decreased by 15%, 28 % and 44% at the same time intervals. Greater reduction was obtained in urinary TXB<sub>2</sub> after drinking honey; it was decreased by 15%, 36% and 67% at each time intervals (Table 1). Artificial honey increased PGF<sub>2</sub> alpha and TXB<sub>2</sub> at each time intervals while PGE<sub>2</sub> was increased by 16% at 2 h after ingestion. Honey increased total urinary nitrite by 40%, 55% and 74% at 1, 2 and 3 h after ingestion. Artificial honey decreased urinary nitrite content by 22%, 17% and 17% at the same time intervals (Table 2).

Honey decreased insignificantly urine osmolality, osmolar clearance, FENa, urinary concentration of sodium, calcium and urea, and absolute amount of urinary glucose, urea and sodium. Very little changes were obtained in urine volume, urinary concentration of glucose, creatinine and phosphorus and absolute amount of potassium and phosphate. Honey increased serum phosphate (24%) and decreased serum creatinine (14%), BUN (33%) and FBS (17%) (Table 3).

Artificial honey increased insignificantly creatinine clearance, filtered sodium, osmolar clearance and free water clearance. It decreased urinary osmolality, and FENa. Artificial honey decreased insignificantly urinary concentration of sodium, potassium, calcium and increased urinary concentration of glucose and urea . Urine volume and absolute amount of

glucose, urea, creatinine, chloride, calcium and phosphorus were insignificantly increased after artificial honey.

Artificial honey increased FBS by 14%, serum magnesium by 6%, serum phosphorus by 28% whilst it decreased BUN by 38%, and serum creatinine by 17% (Table 3).

## **Discussion**

The present study shows that honey decreases urinary prostaglandins during 3 hours after ingestion. Highest reduction was obtained at hour three. TXB2 was reduced more than other prostaglandins. The basal values (0-time value) of prostaglandin before honey administration compared to basal values before artificial honey administration seem to be different; the time between two measurements was one week. This difference could not be explained by the results of present study as the study was scheduled to investigate effect of honey or artificial honey on basal prostaglandin values during a period of 3 hours after drinking. Honey increased total urinary nitrite content. It was found that glucose increase TXA2, and reduced prostacyclin (PGI<sub>2</sub>) and NO release (20). On the contrary, honey reduced prostaglandin excretion. This effect might be due to unidentified substances in the honey that affect cyclooxygenase pathway.

Honey decreased plasma and urinary glucose concentration while artificial honey increased them. This reduction in plasma glucose and consequently in urinary glucose could be attributed to the stimulatory effects of honey on insulin production (5). With reduction of urinary prostaglandin and sodium excretion by honey, it was expected to obtain a significant reduction in the urine volume. The little changes in the urine volume obtained after honey drinking might be ascribed to the increase in the urinary NO production. The statistically insignificant differences between the urinary variables measured after natural and artificial honey could be ascribed to the small number of the patients recruited.

The effects of natural honey on the urinary excretion of glucose, urea, creatinine, calcium, phosphorus, and sodium, FENa, osmolar clearance, and urinary osmolality, are similar to

the effects of indomethacin though pronounced effects are obtained with indomethacin (14). In addition, indomethacin decreased urine volume, frequency of micturition, free water clearance, creatinine clearance and filtered sodium. These differences between indomethacin and honey are probably due to ability of indomethacin to decrease both NO and prostaglandin (14). It seems that honey reduced urinary prostaglandins without harmful effects on renal blood flow or glomerular filtration rate that was increased by honey. It is important to inhibit prostaglandin synthesis in inflammatory conditions of renal tissues to subside signs and symptoms of inflammations. Such inhibition might contribute to side effects, as prostaglandins are important mediators of diuresis and renal perfusion. Increasing NO production could ameliorate such side effects. Honey did the job, inhibiting prostaglandins and elevating NO production. Higher or repeated doses or using various honeys might demonstrate pronounced effects. However, the mechanism of action of honey is not known. Honey might inhibit COX1, COX2 or both. Regarding NO, honey contains NO metabolites and it might stimulate NO synthase. The properties of honey make it a suitable candidate for further experimentation to explore its possible place in the management of urological diseases.

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