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PIOGLITAZONE STIMULATES RENIN AND FAVORS SODIUM RETENTION AND WEIGHT GAIN IN HEALTHY SUBJECTS

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Glitazones induce peripheral edema through an unknown mechanism in up to 20% of cases. This study examines the effects of pioglitazone (PIO) on renal sodium handling and renal hemodynamics in healthy male volunteers (HV) exposed to a high (HS) and low (LS) sodium diet. The influence of PIO on plasma renin activity (PRA), aldosterone and atrial natriuretic peptide (ANP) was examined.

Nine HV aged 22-28 y were enrolled. BMI, blood pressure and glucose tolerance were normal. The study had a double-blind, randomized, placebo controlled, twofold cross-over design. Each subject received either PIO 45 mg qd or placebo qd, for 6 weeks, with 2 weeks wash-out. From weeks 1-4, subjects were on their usual diet. During weeks 5 and 6, subjects were either on a LS or a HS diet for a week which was followed by ambulatory blood pressure measurements, hormonal measurements and renal function studies. The differences between PIO and placebo effects were examined (median, *range among all subjects*). No subject developed edema. Insulin sensitivity, systolic and diastolic blood pressure, glomerular filtration rate, renal plasma flow or filtration fraction did not change significantly with PIO. Weight increased with PIO in 7/9 subjects while on a LS diet (0.7kg; *-1-2.9*) and in 6/9 while on a HS diet (1.1kg; *-1.5-3.4*). Median sodium (Na) excretion with placebo was of 21.2mmol/24h and 239.7mmol/24h respectively while on a LS and HS diet. Urinary Na excretion decreased with PIO in 6/9 subjects on a LS diet (-12.2mmol/24h; *-21-8.7*, $p=0.05$), and in 5/9 subjects on a HS diet (-30mmol/24h; *-344-69*). Na clearance decreased in 6/9 subjects on a LS diet (-0.05 ml/min; *-0.11-0.05*) and in 6/9 subjects on a HS diet (-0.15 mmol/ml; *-2.7-0.4*). Na clearance at the proximal level decreased with PIO in 8/9 subjects on a LS diet (-4.9 ml/min; *-14.4-1.5*, $p=0.01$) and in 5/9 subjects on a HS diet (-2 ml/min; *-43-8.5*). PRA increased with PIO in 8/9 subjects on a LS diet (0.16 ng/ml/h; *-0.07-0.8*, $p=0.02$) and on a HS diet (0.09 ng/ml/h; *-0.1-0.21*, $p=0.03$). Aldosterone increased in 5/9 subjects on a LS diet (6 pg/ml; *-19-144*) and in 6/9 subjects on a HS diet (5 pg/ml; *-20-74*). ANP levels did not change.

In conclusion, pioglitazone increases PRA, independently from Na intake and favors Na retention in healthy volunteers. This mechanism could contribute to the development of edema in subjects treated with glitazones.

Key Words: Proximal Sodium Reabsorption, Epidemiology, Women

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METABOLIC DETERMINANTS OF PROXIMAL SODIUM REABSORPTION IN HEALTHY WOMEN

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Increased reabsorption of sodium (Na) in the proximal segments of the nephron is present in hypertensive patients. Studies performed in men reported an association between proximal Na reabsorption and features of the metabolic syndrome. This study explores the relationship between metabolic variables and proximal Na reabsorption in healthy women.

This study is population-based and cross-sectional examining 661 healthy women aged 40-75y. After 15 minutes rest, blood pressure was measured 3 times, blood was drawn and urine was collected. Fractional excretion of endogenous lithium (FELi) was used as an indirect marker of proximal sodium reabsorption, lithium being only reabsorbed in the proximal tubule. All women receiving blood pressure, blood glucose or lipid lowering therapy were excluded.

Correlations: FELi was positively correlated with the fractional excretion of sodium (FENa, $r=0.3$, $p<0.001$). FELi was negatively associated with total cholesterol ($r=-0.14$, $P<0.0001$), LDL-cholesterol ($r=-0.16$, $P<0.0001$), BMI ($r=-0.08$, $P<0.05$) and weight ($r=-0.09$, $P<0.05$). Menopausal status or a family history of hypertension did not affect the associations.

Simple linear regression analysis: age, waist circumference, waist/hip ratio, systolic blood pressure, diastolic blood pressure, Hdl cholesterol, triglycerides, serum uric acid or a family history of hypertension were not significant predictors of FELi. BMI was a significant predictor but the strongest relationships were found between FELi and total cholesterol, LDL-cholesterol and FENa.

Multivariate linear regression model: When significant predictors of FELi were examined in a multivariate linear regression model also controlling for age, weight, systolic blood pressure and FENa, total cholesterol ($p=0.003$) or LDL-cholesterol ($p=0.001$) significantly and independently predicted FELi.

In conclusion, these data suggest that metabolic parameters, in particular total cholesterol and LDL-cholesterol and to a lesser extent weight and BMI, are associated with increased proximal Na reabsorption in a healthy untreated women population. Considering the possible link between increased reabsorption of sodium and the development of hypertension, a major cardiovascular risk factor, this association may provide an additional hypothesis for the increased cardiovascular risk of subjects with the metabolic syndrome.

Key Words: proximal sodium reabsorption, epidemiology, women