DIFFERENTIAL PROFILE OF BODY FLUID CHANGE IN TYPE II DIABETIC PATIENTS AND HEALTHY VOLUNTEER SUBJECTS FOLLOWING PIOGLITAZONE TREATMENT

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Introduction

Pioglitazone, one of thiazolidinediones (TZD), activate peroxisome proliferator-activated receptor gamma and have insulin sensitizing effects that directly address the underlying pathology of diabetes [1]. However, individuals may not be able to tolerate TZD related side effects, including pulmonary and peripheral edema associated with body weight gain [2]. Identifying individuals sensitive to TZD-induced fluid retention non-invasively becomes clinically important for diabetic management. In the present study, we have evaluated the occurrence of edema and other side effects, during eight weeks of pioglitazone treatment in Type II diabetes mellitus (DM) patients and healthy control (HC) subjects using magnetic resonance imaging (MRI). We hypothesize that (1) ^{1}H T2 signal offer more sensitive detection of pioglitazone-induced edema than ^{1}H T1 signal or ^{23}Na MRI and are well consistent with the clinical and other laboratory data; (2) DM patients and HC subjects respond differently to pioglitazone treatment in terms of fluid retention.

Materials & Methods

Twelve DM patients with relatively well-controlled diabetes and six young HC subjects were treated with pioglitazone for 8 weeks (initial dose of 30mg on day 1-7 and 45mg on day 8-56), while three DM patients and two HC subjects received placebo. MRI technology was used to assess changes in calf fluid retention following postural change from sitting upright for 60 minutes to lying supine. This postural based change in calf fluid retention measured by MRI has been described as a postural delta signal (PDS) by Zuo et al [3, 4] (Figure 1). Changes in PDS index were assessed over the course of four individual scans [0 week (baseline), 2 weeks, 8 weeks, 10 weeks (washout)] using ^{1}H T1 weighted images, water ^{1}H T2 values, and ^{23}Na MRI. The ^{1}H MRI was performed on a 3T scanner (Trio, Siemens AG, Germany) using a volume coil with following parameters; (1) T2: spin-echo train n=12, TE step 15ms, TR/TE0 3600/15, slice thickness 10mm; (2) T1 weighted image (T1): Spin-echo, 2D, TR/TE/TI 880/22/160, slice thickness 10 mm, NEX 1, 130Hz/pt, FOV 270, matrix 160x256. The ^{23}Na MRI was conducted on a 4T scanner (INOVA, Varian Inc, CA) with a quadrature surface array. The parameters were as follows; GE 3D, TR/TE 20/2.5, slab 192, BW 42kHz, NEX 16, FOV 200, matrix 128x64x16, time gap between measures 10secs. The assessments of body fluid states were also made using deuterium oxide (total body water) and sodium bromide (extracellular water) dilution methods. Clinically, body weight and visual evaluation of pitting edema were performed at the time of each scan for the comparison. Finally, for parallel evaluation of edema and other side effects, both hematologic assays, including hemoglobin (HGB) and hematocrit (HCT), and blood chemistry measurements, including adiponectin, protein and albumin, were assessed.

Results

Both DM and HC subjects receiving pioglitazone experienced a rapid increase in serum adiponectin levels, consistent with the established efficacy of pioglitazone ($p<0.01$). However, it was observed that pioglitazone treatment induced fluid retention in DM patients, but not in HC subjects. Specific changes associated with fluid retention from baseline through week 8 in the DM subjects included significant increases in T2 PDS ($p=0.003$) and trend increases in Na PDS ($p=0.057$) by MRI (Figure 2); increases in extracellular water index by sodium bromide ($p=0.001$, Figure 2); decreases in HGB and HCT by hematologic assays ($p<0.01$, Figure 3); and decreases in serum protein and albumin by blood chemistry measurements ($p<0.01$, Figure 3). Correlation analysis indicate that T2 PDS measurements were well correlated with other measurements of body fluid changes such as HGB, HCT, serum protein, and albumin (all $p<0.05$). In contrast, total body water index by deuterium oxide and clinical assessments of body fluid retention such as changes of body weight and pitting edema did not exhibit consistent findings. Placebo-treated subjects also did not show any significant fluid changes.

Conclusion

The current study provides evidence that pioglitazone treatment induces edema in DM patients but not HC subjects. The significant correlation between T2 PDS and HGB, HCT, serum protein and albumin suggests that T2 measurement well reflects conventional laboratory data. The present data also highlight the potential advantages of using MRI methods of T2 PDS for the assessment and clinical follow-up of edema.

References

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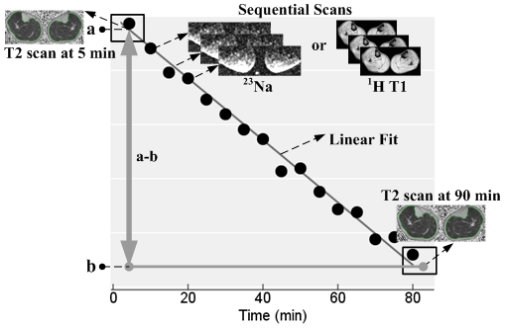

*Figure 1. Schematic illustration of calculation of postural delta signal (PDS). ^{1}H T2 PDS was calculated by subtraction (a– b) of two T2 signal intensity images at each scan; ^{23}Na PDS and ^{1}H T1 PDS (%) were calculated by [(a– b) / a]*100 for adjustment of MR coil loading and subject variation. The sequential images were acquired for approximately 80 minutes and then subsequent linear regression lines were fitted for the determination of the values from time points a and b in the ^{23}Na and ^{1}H T1 images.*

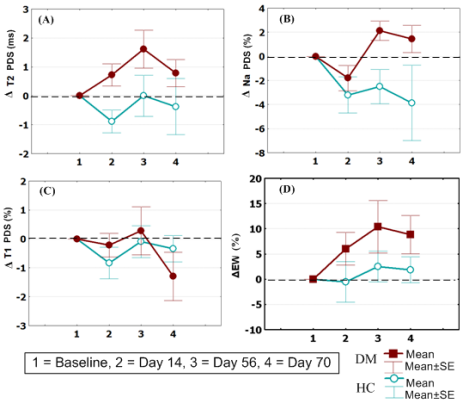

Figure 2. MRI signal detection of fluid shift after postural change from standing to supine. (A) Significant increase of T2 PDS following pioglitazone in DM, but not HC (GEE, coef=0.80, z=3.02, p=0.003; coef<0.001, z<0.001, p=0.998, respectively) from baseline through 8-week. (B) Trend increase of Na PDS following pioglitazone treatment in DM from baseline through 8-week (GEE, coef=1.07, z=1.9, p=0.057). (C) T1 PDS remained unchanged throughout the follow-ups in both DM and HC (GEE, coef=0.14, z=0.48, p=0.63; coef=-0.05, z=-0.17, p=0.86, respectively). (D) Extracellular water change by sodium bromide was statistically significant from baseline through 8-week in DM (GEE, coef=5.31, z=3.22, p=0.001). GEE, generalized estimating equation

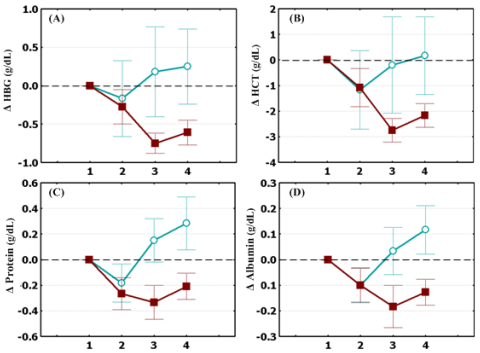

Figure 3. Laboratory changes following pioglitazone treatment. (A) Hemoglobin (HGB) significantly decreased in DM, but not HC (GEE, coef=-0.38, z=-4.14, p<0.001; coef=0.06, z=0.30, p=0.763, respectively) from baseline through 8-week (B) Hematocrit (HCT) significantly decreased following pioglitazone treatment in DM, but not HC (GEE, coef=-1.38, z=-4.41, p<0.001; coef=-0.17, z=-0.26, p=0.798, respectively) from baseline through 8-week. (C) Serum protein significantly decreased following pioglitazone treatment in DM, but not HC (GEE, coef=-0.17, z=-2.79, p=0.005; coef=0.08, z=0.89, p=0.374, respectively) from baseline through 8-week. (D) Serum albumin significantly decreased following pioglitazone treatment in DM, but not HC (GEE, coef=-0.09, z=-2.78, p=0.005; coef=0.17, z=0.41, p=0.685, respectively)