Subcortical physiological abnormalities in type 2 diabetes detected using magnetization transfer

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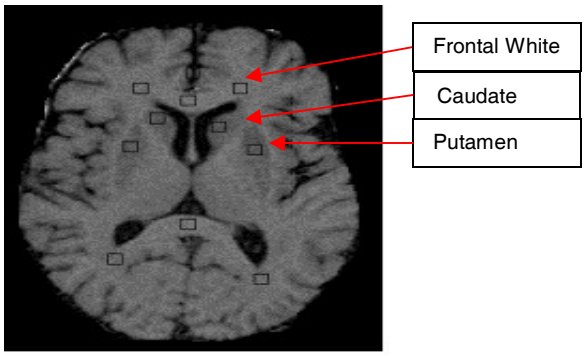
Type 2 diabetes is a common metabolic disorder that is associated with considerable morbidity and mortality. Clinical depression is frequently encountered in patients with type 2 diabetes and is associated with poor quality of life, non-compliance with management regimens and loss of productivity. While depression in patients with diabetes responds to pharmacological treatment, its biological basis remains unknown. The purpose of this study was to examine the neurobiological basis of depression in patients diagnosed with type 2 diabetes using magnetization transfer to examine components of the cortical-subcortical circuits. Cortical-subcortical circuits have been implicated in the pathophysiology of mood and related behavioral disorders and we were interested in examining the status of proteins in both gray and white matter regions - frontal white and subcortical nuclei - in order to characterize the neurobiological changes underlying depression.

Methods: Our samples were comprised of 22 patients diagnosed with type 2 diabetes (mean age: 60.68 [SD:9.79])using established clinical criteria, 17 patients with diabetes and major depression (MDD) (mean age: 58 [SD:10.38])and 31 non-depressed, non-diabetic healthy control subjects (mean age: 55.06 [SD: 10.88]). All patients diagnosed with MDD met established clinical criteria for the diagnosis and had Hamilton Depression Rating Scale Scores of 15 or greater. All patients with diabetes were recruited from the medical/endocrinological clinics associated with the University of California in Los Angeles (UCLA) Medical Center. Healthy controls were recruited from the community. All subjects were studied on a 1.5 Tesla GE signa scanner.

MT Methods: Axial imaging with and without off-resonance pulse will be performed using TR/TE/NEX = 2500ms/15ms/1 with the same slice thickness (3 mm), field of view and matrix size. The magnetization transfer pulse of 16 ms duration will be applied 2.5 KHz off-resonance to the main water peak. MT ratio images will be generated from the PD weighted images with and without the off resonance pulse using the formula: MT ratio= M_0-M_t/M_0 x100, where M_0 represents the signal from the image without the off-resonance pulse and M_t represents the signal from the image with the off-resonance pulse applied. A voxel size of 3 x 2 x 2 mm cubed was used for region of interest placement and extraction of MT ratios. T_2 weighted images were closely examined for hyperintensities in these regions in order to avoid these lesions while placing our voxel/region of interest. The MT ratio images were generated automatically using a program written in-house in the interactive display language (IDL) (Eastman Kodak, Rochester, New York) and the aforementioned formula.



Legend for Figure 1
Scan shows the voxels at different locations from where the MT ratio was extracted.

Table 1 : A summary of groups mean and standard deviation of the magnetization transfer ratio (MTR) from the subcortical nuclei collected from subjects across groups.

Groups	Right caudate nucleus	Left caudate nucleus	Right putamen	Left putamen
Nondiabetic-nondepressed (a)	35.15 □ 1.22	35.09 □ 1.26	34.70 □ 1.04	35.45 □ 1.55
Diabetic-nondepressed (b)	31.89 □ 2.34 +	32.14 □ 2.47	34.09 □ 1.93	33.97 □ 2.25 *
Diabetic-depressed (c)	30.07 □ 2.09 ++	28.90 □ 3.11	33.23 □ 2.51	34.40 □ 2.15 *

+ Significantly different from (a) p<0.05
++ Significantly different from (a) and (b) p<0.05
*** Significantly different from (a) p <0.05**

Results: MT ratios were significantly lower in the groups with diabetes, with and without depression, when compared with the healthy control group (p<0.05), with the depressed diabetic group showing the lowest MT values and the diabetic controls having MT ratios falling between the depressed and the healthy controls. In the putamen, the depressed and non-depressed diabetic groups have MT values that were significantly lower than the healthy controls but did not differ from one another. MT values in the dorsolateral white matter did not differ across the three groups.

Conclusions: These data suggest that depression and diabetes are associated with changes in protein integrity in subcortical nuclei when compared with healthy controls. Depression in patients with diabetes is associated with striking abnormalities in the protein structure in the head of the caudate nucleus and this physiological abnormality may provide an important substrate to MDD in patients with diabetes.