Microstructural white matter changes in metabolic syndrome

A diffusion tensor imaging study

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ABSTRACT

Background: Although metabolic syndrome is associated with cardiovascular disease and stroke, limited information is available on specific brain damage in patients with this syndrome. We investigated the relationship of the syndrome with white matter (WM) alteration using a voxel-based approach with diffusion tensor imaging (DTI).

Methods: We compared fractional anisotropy (FA) and apparent diffusion coefficient (ADC) measurements of DTI in 19 patients with metabolic syndrome aged between 50 and 80 years and 19 age-matched controls without any vascular risk factors for the syndrome.

Results: Patients with metabolic syndrome showed an anterior–posterior pattern of deterioration in WM with reduced FA and increased ADC values compared with controls. WM changes were not related to any isolated vascular risk factor.

Conclusion: Although the mechanism of this damage is not clear, the results indicate microstructural white matter alterations in patients with metabolic syndrome, mainly involving the frontal lobe. *Neurology*® 2009;73:438–444

GLOSSARY

ADC = apparent diffusion coefficient; **ADC Cont** = ADC mean values in the control group; **ADC SdMet** = ADC mean values in the patient group; **ant** = anterior; **c** = corpus; **corr** = corrected; **DICOM** = Digital Imaging and Communications in Medicine; **DTI** = diffusion tensor imaging; **F** = frontal lobe; **FA** = fractional anisotropy; **FA Cont** = FA mean values in the control group; **FA SdMet** = FA mean values in the patient group; **fas** = fasciculus; **FOV** = field of view; **FWHM** = full-width at half-maximum; **HDL** = high-density lipoprotein; **inf** = inferior; **Lb** = limbic lobe; **MNI** = Montreal Neurological Institute; **NCEP** = National Cholesterol Education Program; **SPM** = Statistical Parametric Mapping; **Sub** = sublobar; **sup** = superior; **T** = temporal lobe; **TE** = echo time; **TI** = inversion time; **TR** = repetition time; **WM** = white matter.

Metabolic syndrome is a cluster of vascular risk factors defined by the National Cholesterol Education Program (NCEP) as the presence of at least 3 of the following vascular risk factors: hypertension, hyperglycemia, hypertriglyceridemia, low levels of high-density lipoprotein (HDL) cholesterol, and central obesity as measured by waist circumference.[1] The worldwide prevalence of the syndrome is rising: in the United States, 43.5% of the population aged 60–69 years are affected,[2] whereas in Europe, approximately one quarter of the adult population have the syndrome, the prevalence depending on the specific characteristics of the population (age, geographical location, the criteria used to define the syndrome).[3]

Until now, metabolic syndrome has been associate with a higher risk of stroke,[4,5] the presence of silent lacunar infarcts,[6] intracranial arteriosclerosis,[7] periventricular hyperintensities, and subcortical white matter (WM) lesions,[8] although to date there is little evidence regarding the association of brain damage.[9,10]

Diffusion tensor imaging (DTI) is a technique that provides information on subtle WM changes associated with aging[11] and with cerebrovascular disease[12,13] by detecting microstructural alterations.

Supplemental data at www.neurology.org

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The variables most often analyzed by DTI are fractional anisotropy (FA) and the apparent diffusion coefficient (ADC). FA is a measure of tract directionality and integrity, whereas ADC is a measure of water diffusivity.[14]

We hypothesized that metabolic syndrome, as a cluster of vascular risk factors, would be associated with a subtle pattern of WM deterioration. To test this possibility, we performed a comparative study between patients with metabolic syndrome and healthy controls without vascular risk factors, using the DTI approach.

METHODS

Subjects. The study included 19 subjects who fulfilled the criteria for metabolic syndrome as described by the NCEP,[1] along with 19 healthy controls from 2 public medical centers of Barcelona province (Centres d'atenció primaria) in Cerdanyola del Vallés and Sant Just Desvern, Barcelona (Spain). Metabolic syndrome diagnosis requires as a minimum the presence of 3 of the 5 possible risk factors (table e-1 on the *Neurology*® Web site at www.neurology.org). Subjects in the patient group fulfilled 3, 4, or 5 of the diagnostic criteria.

The criterion for selecting healthy control subjects was the absence of any vascular risk factor included in the criteria for metabolic syndrome.

All the participants were volunteers, right handed, and aged between 50 and 80 years. The exclusion criteria were uncorrected visual or auditory deficits, alcoholism (more than 28 standard drink units per week for men and more than 17 standard drink units per week for women[e1] or other drug abuse, a history of developmental disorders, and current neurologic, hematologic, hormonal, or nutritional disorders and neoplasm. We also excluded subjects with a history of cardiovascular disease or a history of acute stroke or TIAs. None of the participants presented neurologic symptoms according to the Modified Rankin Scale scores = 0.[e2]

All selected participants completed a screening interview to check the medical information from their records. A modified structured clinical interview based on the Structured Clinical Interview for DSM-IV Axis I disorders[e3] was administered to exclude major psychiatric diseases.

We obtained measures of glucose, HDL cholesterol, and triglycerides for all participants from blood tests performed in the reference laboratory of each public medical center. Blood pressure measures and participants' waist circumference were recorded during the screening sessions.

All subjects had normal general cognitive performance according to the Mini-Mental State Examination[e4] (scores >26). Global IQ was estimated by the Vocabulary subtest of the Wechsler Adult Intelligence Scale, 3rd edition.[e5] All participants underwent comprehensive neuropsychological assessment[e4] (table e-2).

The study was approved by the ethics committee of the University of Barcelona.

All enrolled subjects signed an informed consent form before taking part in the study.

MRI data acquisition. DTI sequences were obtained on a 3-T Siemens Magnetom Trio scanner (Erlangen, Germany) belonging to the Institut d' Investigacions Biomédiques August Pi i Sunyer at the Radiology Service of the Hospital Clinic of Barcelona. The DTI sequences were acquired with the following parameters: repetition time (TR) = 5,533 msec, echo time (TE) = 88 msec, acquisition matrix = 122 × 122, field of view (FOV) = 250 × 250 mm^2, diffusion directions = 30, slice thickness = 2 mm, gap distance = 0.6 mm, number of slices = 44, b values: 0 and 1,000 s/mm^2, IPAT factor = 2, total scan time 3:10 minutes. The magnetic resonance protocol included T1-weighted images to be used for anatomic reference. T1-weighted images were acquired using a sagittal 3-dimensional isotropic magnetization-prepared rapid gradient echo sequence: TR = 2,300 msec, TE = 2.98 msec, inversion time (TI) = 900 msec, flip angle = 9°, FOV = 256 × 256 mm^2, acquisition matrix = 256 × 256, slice thickness = 1 mm, IPAT factor = 2, total acquisition time = 7′48″.

Image preprocessing. All image processing was performed using SPM5 (Statistical Parametric Mapping, Wellcome Department of Imaging, Institute of Neurology, University College London, UK) running in Matlab 7.6 (MathWorks, Natick, MA). The DTI protocol was administered as follows. FA maps and ADC maps were obtained from Digital Imaging and Communications in Medicine (DICOM) DTI sequences. B0 image and FA and ADC maps were reoriented according to the anterior–posterior commissure line using the same parameters. The coregister parameters of B0 values were applied to T1. These parameters were applied to FA and ADC maps to coregister these maps to the structural image. In this step, we observed a small mismatch in some areas due to a subtle geometric B0 image distortion produced by eddy currents. We therefore decided to create a FA template and to normalize FA maps to it to obtain a better matching between normalized FA maps.[e6] For this purpose, high-resolution T1 images were segmented to obtain WM in native space. WM partitions in native space were normalized to WM SPM prior maps to ensure good WM normalization.[e7] Normalization parameters were then applied to FA maps. Normalized FA maps were averaged and smoothed with a 6-mm full-width at half-maximum (FWHM) gaussian kernel to create a customized template of FA images of our sample. In the second step, each individual FA map was normalized to this FA template. The same normalization parameters were applied to ADC maps. A physics PhD (C.F.), an expert in neuroimage analysis, carefully inspected the result of the second normalization to ensure its accuracy. An 8-mm FWHM gaussian kernel was used to smooth final ADC and FA images.

Statistical procedure. Two binarized brain masks were used as an explicit mask in the FA and ADC analyses. In the FA analysis, we used a mask obtained by thresholding the FA template (threshold value = 0.5), and in the ADC analysis, we used the "a priori" SPM5 template (threshold value = 0.3). The processed FA and ADC images were analyzed using the *t* test group comparison in SPM5. Specifically, the contrasts were patients < controls for FA, and patients > controls for ADC. The reverse contrasts were also performed. For the FA and ADC contrasts between groups, we set the threshold at an uncorrected voxel *p* value of <0.005, because we only expected subtle WM changes in our patients, who were normal individuals with vascular risk factors. However, for statistical purposes we only report clusters at a corrected cluster *p* level (<0.05).

Multiple regression analyses were also performed for the patient group, testing for a possible relationship between FA and ADC values and each vascular risk factor.

For the FA and ADC correlation analyses, we set the threshold at an uncorrected voxel *p* value of <0.001.

Table 1 Between-groups differences in FA (patients < controls)

Anatomical region[e11]	Lobe	p Value (corr)	Size, mm³	MNI coordinates x	y	z	t	FA Cont	FA SdMet	r
R ant c callosum	F	0.001	5,195	11	25	−17	4.51	0.33	0.28	0.60
R ant c callosum	F			17	45	−16	4.00	0.33	0.28	0.55
R uncinate fas	F			29	27	−2	3.81	0.35	0.32	0.54
L ant c callosum	F	0.043	2,886	−10	26	−18	4.37	0.32	0.27	0.59
L uncinate fas	Sub			−27	19	−9	4.34	0.34	0.30	0.59
L ant c callosum	Lb			−10	34	−9	3.59	0.32	0.29	0.51

FA = fractional anisotropy; MNI = Montreal Neurological Institute; corr = corrected; Size = cluster size; *t* = Student *t* test values; FA Cont = FA mean values in the control group; FA SdMet = FA mean values in the patient group; *r* = effect size; ant = anterior; c = corpus; F = frontal lobe; fas = fasciculus; Sub = sublobar; Lb = limbic lobe.

Neuropsychological differences between groups were compared using SPSS WIN (version 14.0). Because of the sample size, the nonparametric Mann–Whitney *U* test was used for quantitative variable analyses.

RESULTS **Clinical and demographic characteristics.** The sample comprised a patient group of 11 women and 8 men with a mean age of 61.26 (SD = 7.19) years and mean years of education of 10.37 (SD = 3.55), and a control group with 11 women and 8 men with a mean age of 59.63 (SD = 5.37) years and mean years of education of 11.68 (SD = 3.59).

Laboratory tests results for the patients were as follows: mean glucose 117.40 (SD = 35.45) mg/dL, mean HDL cholesterol 48.92 (SD = 14.15) mg/dL, mean TG 169.20 (SD = 95.48) mg/dL, mean systolic/diastolic blood pressure 136.00 (SD = 14.15)/80.16 (SD = 9.66) mm Hg, and mean waist circumference measure 105.82 (SD = 8.78) cm. In the control group, laboratory test results were as follows: mean glucose 86.05 (SD = 8.36) mg/dL, mean HDL cholesterol 69.05 (SD0 13.61) mg/dL, mean TG 78.05 (SD = 24.54) mg/dL, mean systolic/diastolic blood pressure 121.21 (SD = 8.41)/75.05 (SD = 5.90) mm Hg, and mean waist circumference measure 84.71 (SD = 8.54) cm.

There was no difference between the groups in age, years of education, or sex. All the patients fulfilled the criteria for diagnosis of metabolic syndrome. Of our patients, 47.4% had 3 vascular risk factors of metabolic syndrome, 26.3% had 4 factors, and 26.3% had 5.

The most prevalent vascular risk factor among patients was central obesity (100%), followed by hypertension (78.94%), low levels of HDL cholesterol (73.68%), fasting glucose (73.68%), and hypertriglyceridemia (57.89%).

Patients and controls did not present statistical differences in cognitive performance (table e-2).

FA results. The results obtained in the *t* test for the contrast of patients < controls showed significant differences in FA in the frontal lobe bilaterally (table 1 and figure A). No significant results were found in the reverse contrast.

The correlation analysis of each vascular risk factor with FA did not show any results at a p level < 0.001 uncorrected.

ADC results. The results for the contrast of patients > controls in the *t* test analysis of ADC images are summarized in table 2 and figure B. Patients with metabolic syndrome showed higher ADC values in WM of temporal and frontal lobes bilaterally. No significant results were found in the reverse contrast.

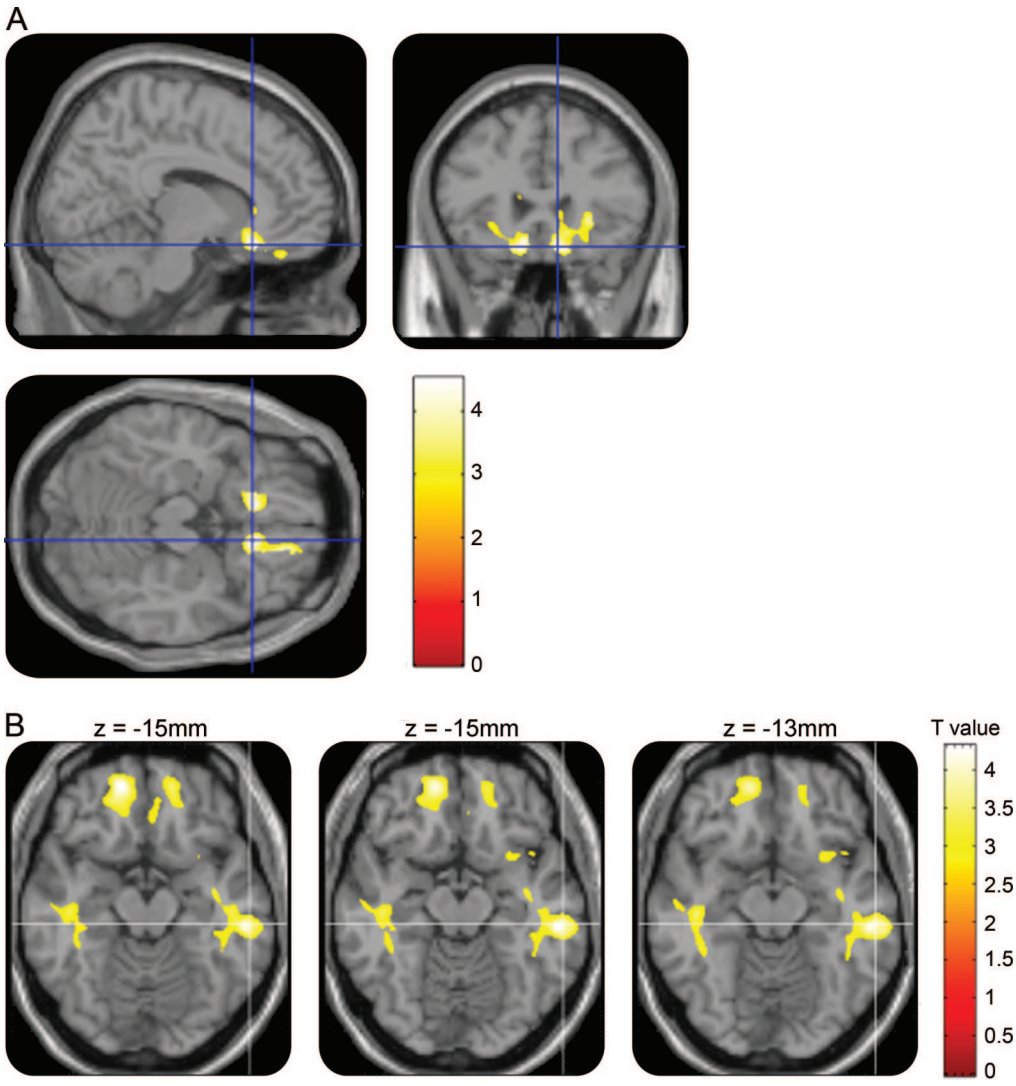
The correlation analysis of each vascular risk factor with ADC did not show any results at a p level < 0.001 uncorrected.

DISCUSSION The DTI results indicated that metabolic syndrome involves an alteration in brain microstructure. The pattern of damage observed in our sample showed an anterior–posterior gradient of decrease in FA, that is, a greater deterioration of frontal lobe structures. This FA pattern has been described in human aging[15] and confirmed in animal models.[16] In fact, age-sensitive regions of the neocortex are later areas in terms of phylogenetic evolution and tend to be the last to mature during brain development.[17]

It remains unclear how metabolic syndrome affects the brain. Recent findings showed an inverse association of cardiovascular risk and structural integrity[18] and glucose metabolism[19] of the frontal lobe. Studies of isolated vascular risk factors also reported brain abnormalities, specifically in the frontal lobe.[20–22] The pathophysiologic mechanisms underlying these changes are still not clear. The mechanisms currently proposed are increased action of free radicals, reduction of insulin transport into the brain, inflammatory activity, and neurotrophic factor changes.[20,22–24]

Histopathologic studies have related microvessel alteration in frontal WM with peripheral atheroscle-

Figure Fractional anisotropy and apparent diffusion coefficient differences between groups



The selected image illustrates the significant regions where patients showed a decrease in fractional anisotropy values compared with controls (A) and an increase in apparent diffusion coefficient values with respect to controls (B). The color bar represents *t* scores. Statistical Parametric Maps (SPMs) are represented according to neurologic convention (left corresponding to the left hemisphere) and are displayed superimposed on an SPM brain template.

rosis and aging.[25] WM alterations correspond to axonal loss and gliosis processes.[26] An animal model of ischemia showed that chronic hypoperfusion in the brain induces glial changes, especially in anterior brain regions.[27] The processes reported above were proposed as the pathologic mechanisms underlying the WM changes seen in FA and ADC in aging and cerebrovascular disease.[12,28] In a study of symptomatic and asymptomatic cerebrovascular disease patients, the FA decrease and the mean diffusivity increase correlated with changes in the *N*-acetylaspartate neuronal marker relating the axonal loss/dysfunction to the changes in DTI measures.[29]

The disturbances associated with the syndrome promote pathologic changes in arteries.[4] In fact, patients with metabolic syndrome have a higher risk of stroke,[30] reflecting the influence of the syndrome in altering brain-supplying large arteries. However, the syndrome is also associated with intracranial atherosclerosis,[31] which may be the cause of small-vessel disease. In turn, small-vessel disease could be responsible for microstructure alteration, due to a chronic state of vascular deregulation in the brain mostly affecting the WM.

There is a growing interest in the study of the early phases of microangiopathies. These diseases are frequent in the elderly and constitute an independent risk factor for recurrent vascular events and cognitive impairment.[32] Therefore, the detection and follow-up of prodromal states of pathology could elucidate the relevant factors that influence the progression of the disease and provide useful information for developing prevention programs.

Table 2 Between-groups differences in ADC (patients > controls)

Anatomical region[e11]	Lobe	p Value (corr)	Size, mm^3	MNI coordinates			t	ADC* Cont	ADC* SdMet	r
				x	y	z				
L inf longitudinal fas	T	0.000	22,673	−54	−28	−14	4.31	79.48	86.39	0.58
L inf longitudinal fas	T			−43	−8	−29	4.22	81.13	88.61	0.58
L inf longitudinal fas	T			−36	1	−38	4.20	82.27	87.09	0.57
R inf longitudinal fas	T	0.009	4,732	44	−25	−7	4.12	85.07	90.79	0.57
R inf longitudinal fas	T			49	−34	−6	3.86	81.90	87.60	0.54
R inf longitudinal fas	T			46	−21	−32	3.41	82.27	93.94	0.47
L ant c callosum	F	0.013	4,480	−18	14	40	3.99	74.88	80.29	0.55
L ant c callosum	Lb			−8	13	44	3.21	92.51	102.25	0.47
L sup longitudinal fas	F			−37	3	20	3.19	77.24	81.54	0.47
R ant c callosum	F	0.013	4,452	17	51	−17	4.61	89.64	107.51	0.61
R ant c callosum	F			14	36	−22	4.11	95.15	110.86	0.57
R ant c callosum	F			9	40	−35	2.91	94.57	116.83	0.44

*Apparent diffusion coefficient (ADC) values ($mm^2/s \times 10^{-6}$).
MNI = Montreal Neurological Institute; corr = corrected; Size = cluster size; t = Student t test values; ADC Cont = ADC mean values in the control group; ADC SdMet = ADC mean values in the patient group; r = effect size; inf = inferior; fas = fasciculus; T = temporal lobe; ant = anterior; c = corpus; F = frontal lobe; sup = superior; Lb = limbic lobe.

Metabolic syndrome is a cluster of vascular risk factors that is frequently concomitant with other pathologies such as coronary artery disease, peripheral arterial disease and stroke, chronic kidney disease, nonalcoholic fatty liver disease,[e8] polycystic ovary syndrome,[e9] and obstructive sleep apnea.[e10] We sought to avoid these pathologies through our sample selection and thus be able to identify the initial effect of the syndrome on the adult brain in isolation from other influences. We matched groups by age and applied strict exclusion criteria to avoid the possible confounding effects of other diseases. At the same time, these criteria reduced the number of subjects included in the sample and limited the number of subjects with 4 or 5 metabolic syndrome vascular risk factors who are usually excluded because of their cardiovascular complications; therefore, almost half of our sample comprised persons with 3 factors, the minimum required to fulfill the syndrome diagnosis.

Another limitation is the fact that the control sample comprised people without any vascular risk factors. These criteria enabled us to ensure a healthy control group but, at the same time, made it impossible to compare people without vascular risk factors, people with 1 or 2 factors, and patients with metabolic syndrome. Moreover, the patients were not homogeneous in relation to the specific vascular risk factor suffered, even though all of them fulfilled the criteria for metabolic syndrome diagnosis (according to the established definition[1]). In fact, these 2 limitations meant that we could not study the synergic effects of the vascular risk factors in our sample.[33] These limitations need to be resolved in future studies.

Previous studies have linked some isolated vascular risk factors of the syndrome with WM damage, such as hypertension,[34] obesity,[35] and type 2 diabetes.[36] However, in our study the correlation analysis did not show significant results. These negative results could be due to the small sample size and the resulting lack of statistical power.

Among the vascular risk factors of the syndrome, hypertension seems to be the one most closely associated with WM abnormalities.[29,34] The lack of a significant correlation in our study could be due to the effects of antihypertensive drugs. This is an important issue in the study of aging,[37] because antihypertensive drugs reduce the risk of dementia[38] and reduce the neuropathologic changes in Alzheimer disease.[39] In fact, earlier studies found only a moderate risk of WM damage in controlled hypertensive patients compared with normotensive controls, and a higher risk in poorly controlled hypertensive patients.[40] In view of these findings, and because all patients in our study who had this risk factor were moderately hypertensive and receiving treatment, our results may in fact have been influenced by the effect of medication.

Follow-up studies of these patients might show how the profile of brain damage evolves and also help to define any possible cognitive impairment derived from WM deterioration in these patients. At all events, the control of metabolic syndrome and its evolution should be a principal target of study in societies in which there is a progressive increase in its prevalence and an increasingly aging population.

AUTHOR CONTRIBUTIONS

The statistical analysis was conducted by Bàrbara Segura, Department of Psychiatry and Clinical Psychobiology, University of Barcelona.

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Classification scheme requirements for therapeutic questions

Class I. A randomized, controlled clinical trial of the intervention of interest with masked or objective outcome assessment, in a representative population. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences.

Class II. A randomized, controlled clinical trial of the intervention of interest in a representative population with masked or objective outcome assessment that lacks one criterion a-e in Class I or a prospective matched cohort study with masked or objective outcome assessment in a representative population that meets b-e in Class I. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences.

Class III. All other controlled trials (including well-defined natural history controls or patients serving as their own controls) in a representative population, where outcome is independently assessed, or independently derived by objective outcome measurements.

Class IV. Studies not meeting Class I, II, or III criteria including consensus or expert opinion.

AAN classification of recommendations

A = Established as effective, ineffective, or harmful (or established as useful/predictive or not useful/predictive) for the given condition in the specified population. (Level A rating requires at least two consistent Class I studies.)

B = Probably effective, ineffective, or harmful (or probably useful/predictive or not useful/predictive) for the given condition in the specified population. (Level B rating requires at least one Class I study or two consistent Class II studies.)

C = Possibly effective, ineffective, or harmful (or possibly useful/predictive or not useful/predictive) for the given condition in the specified population. (Level C rating requires at least one Class II study or two consistent Class III studies.)

U = Data inadequate or conflicting; given current knowledge, treatment (test, predictor) is unproven.