

Undifferentiated Connective Tissue Disease (UCTD): Frequently Asked Questions

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1. What does the term undifferentiated connective tissue disease (UCTD) mean?

This term is used to refer to patients who don't quite meet the "criteria" - the features doctors use to make the diagnosis of a disease -- for one of the well-defined connective tissue diseases, such as rheumatoid arthritis or lupus. A person with UCTD may have a couple of the symptoms seen in one or more of these diseases -- but does not have enough of them to make the diagnosis. The lab tests for these diseases may even be negative (suggesting the disease is not present) in patients with UCTD. Although the word "undifferentiated" sounds vague, rheumatologists know this term describes a real problem. It does not mean that your doctor does not know what to call what you have. For more information, read our full [In-Depth Disease Overview on UCTD](#).

2. What are the most common problems in UCTD?

- Arthralgia (joint achiness)
- Arthritis (joints that are swollen and hot, often with redness of the overlying skin)
- Rashes, usually on the face, which can worsen in the sun
- Hair loss
- Raynaud's phenomenon (color changes in your hands and feet in response to cold)
- Ulcers inside the mouth
- Dryness of the eyes (due to decreased tears) or mouth (due to decreased saliva)
- Low-grade fever (usually under 100° F)
- Leukopenia (decreased numbers of white cells in your blood)
- Anemia (decreased numbers of red blood cells in your blood)

Occasionally, pleuritis or pericarditis (inflammation of the lining surrounding the lungs or heart, respectively, which can cause chest pain especially with breathing) or neuropathy (abnormal nerve sensations, usually in the fingers or toes, ranging from numbness to tingling to pain) may occur. Problems with the kidneys, liver, lungs or brain are almost unheard of. The problems seen with UCTD usually are not life-threatening, nor do they typically get worse over the years.

3. What causes UCTD?

UCTD, like well-defined connective tissue diseases, is a condition felt to be caused by the immune system not working the way it should. For some reason, the immune system, which is meant to fight invaders such as bacteria, may start to think of the body itself as foreign and begin to fight against it. This is why it is called an "autoimmune" disease. We think this may be set in motion by the environment (exposures or viruses for example) or because of genetic causes (things that you were born with), however, the cause is not very well understood. Luckily, this "autoimmune" phenomenon seems to occur at a low level in the body because there is not much

tissue damage seen in patients with UCTD. UCTD is not contagious. read our full [In-Depth Disease Overview on UCTD](#).

4. What is the likelihood that I will develop lupus?

Studies to date have shown that the likelihood of developing a defined connective tissue disease such as lupus is very small. Less than one-third of patients ultimately turn out to have a well-defined connective tissue disease. The longer a patient stays diagnosed as "undifferentiated," the greater the likelihood that another disease will never develop. Just as many, if not more patients with UCTD go into remission, with symptoms disappearing. For more information, read our full [In-Depth Disease Overview on UCTD](#).

Undifferentiated Connective Tissue Disease - In-Depth Overview

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I. Definition

The term "undifferentiated connective tissue disease" (UCTD) is used to describe people who have symptoms and certain lab test results that look like a systemic autoimmune disorder or connective tissue disease. But they don't have enough of such characteristics to meet the diagnosis for a **well-defined** connective tissue disease, such as rheumatoid arthritis, lupus, or scleroderma. Thus, they seem to have another, similar disorder that doctors call undifferentiated connective tissue disease."

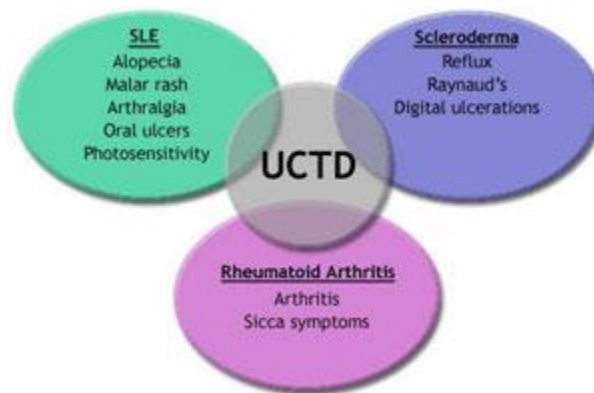
[A systemic autoimmune disorder means that it affects your whole body (systemic) and that your immune system, which normally protects you from outside invaders such as bacteria, turns on parts of your own body and attacks them as if they were invaders. Connective tissue is the "glue" that supports and connects various parts of the body; it includes skin, cartilage, and other tissue in the joints and surrounding the heart and lungs and within the kidney and other organs.]

Although the word "undifferentiated" sounds vague, rheumatologists know this term describes a real problem. It does not mean that your doctor does not know what to call what you have.

This undifferentiated category is distinctly separate from another group of vague-sounding disorders called "overlap syndromes." People with these syndromes have enough features of more than one connective tissue disease to meet the diagnoses for several at the same time. Thus, they "overlap" two or more diseases. (For example, mixed connective tissue disease [MCTD] is just such an "overlap" syndrome.)

In contrast, patients with UCTD will not have enough of the features of any one rheumatic disease to be firmly classified as such by the currently established diagnostic criteria. However, because they may have features from several known diseases, they are said to be "undifferentiated." (See Fig. 1)

Figure 1



The term undifferentiated connective tissue disease was first used in 1980's to identify people who were recognized as being in the early stages of a connective tissue disease (CTD) but who did not yet meet the standard criteria for a well-defined CTD. At that time, it was noted that a substantial proportion of these patients remained undifferentiated - or experienced a disease **remission** (in which symptoms went away) - and never evolved in to a more defined rheumatic disease. Other names used early on to describe some of these patients included "latent lupus" and "incomplete lupus erythematosus," which meant that some features suggestive of lupus were present, but not enough to fulfill make the diagnosis. **As many as a quarter of all patients seen by rheumatologists have UCTD.**

Many researchers have been studying people with UCTD. They have been trying to identify serologic profiles (markers in the blood) that may predict who will eventually develop a well-defined connective tissue disease. They are also looking for markers to help predict whether the disease may go away, remain unchanged, or get worse. It is currently believed that less than 20% of patients with UCTD go on to develop a definite connective tissue disease. As many as one-third will experience a remission of their symptoms. The rest continue with generally mild disease in the undifferentiated form.

II. Pathogenesis

Pathogenesis refers to the origin and development of a disease. The actual cause of UCTD, like many rheumatic diseases, is not well understood. Indeed, there have been no rigorous attempts to

define the basic science of UCTD. It is presumed that many of the same immunologic mechanisms that play a role in lupus and rheumatoid arthritis may be involved. Theories in those diseases include a genetic predisposition, which is subsequently triggered by some environmental factor, such as an infection, that is improperly handled by the immune system. This in turn causes the immune system to be "turned up high," or activated, when it shouldn't be and to target the tissues of one's body instead of foreign invaders (such as bacteria). Which of - or whether - these elements might be involved in UCTD remains unknown. UCTD will be difficult to study because it includes a heterogeneous population - people with so many different symptoms and blood markers. UCTD is not contagious.

III. Clinical Presentation

In the studies of patients that have been done to date, the most common symptoms of UCTD are:

- arthralgia (joint achiness);
- arthritis (joints that are swollen and hot, often with redness of the overlying skin);
- rashes, usually on the face, which can worsen due to sun exposure;
- alopecia (hair loss);
- Raynaud's phenomenon (color changes in your hands and feet in response to cold);
- oral ulcers (sores inside the mouth);
- xerophthalmia (dryness of the eyes due to decreased tears);
- xerostomia (dry mouth due to decreased saliva);
- low-grade fever (usually under 100° f);
- photosensitivity (development of rashes or other symptoms after sun exposure).

Some people also develop:

- leukopenia - decreased numbers of white cells (cells that help fight infection) in your blood;
- anemia - decreased numbers of red blood cells (cells that carry oxygen to tissues in the body) in your blood;
- thrombocytopenia - an abnormal decrease in the number of platelets (the parts related to blood clotting);
- pleuritis or pericarditis - inflammation of the lining surrounding the lungs or heart, respectively, which may cause pain in the chest, especially with breathing;
- neuropathy - abnormal nerve sensations, usually in the fingers or toes, ranging from numbness to tingling to pain.

Problems with the kidneys, liver, lungs, or brain are almost unheard of in UCTD.

The overwhelming majority of people with UCTD do not develop major organ damage or life-threatening disease. The hallmark of UCTD is its mild course and low likelihood of progression to a more serious state.

"Criteria" are the list of problems that a doctor looks for to make a diagnosis. There are no commonly accepted criteria yet for UCTD, as there are for many other rheumatic diseases.

However, preliminary one has recently been proposed (See Mosca in Annotated Bibliography below) as follows:

Preliminary Classification Criteria for UCTD

- **Signs and symptoms suggestive of a CTD, but not fulfilling the criteria for any of the defined CTDs, for at least three years**
- **Presence of ANA identified on two different occasions**

(ANA refers to antinuclear antibodies found in the blood. These markers may indicate that your immune system is forming antibodies to parts of your body.)

At the present time, UCTD is diagnosed clinically by your doctor when the symptoms, labs and history fit the "pattern" which doctors are used to seeing with this disease. It is not based on meeting a checklist of required "criteria" alone. As doctors develop more specific criteria for UCTD, however, it will be easier to study the disease and learn about its causes and best treatments.

IV. Laboratory Findings

A. Immunologic

Some markers in your blood indicate possible abnormal function of your immune system. While most studies note that the majority of patients with UCTD have antinuclear antibodies (ANA), a broad range of immunologic abnormalities can be seen in people with UCTD. These may include:

- elevated erythrocyte sedimentation rate (ESR - an indicator of inflammation);
- antiphospholipid antibodies (which can affect blood clotting and may increase your risk of miscarriage),
- hypergammaglobulinemia (an excess of gamma globulin, often called IgG, a protein in the blood that's involved in resistance to infection);
- hypocomplementemia, (a decreased level of complement -- proteins that help destroy bacteria and other cells -- commonly referred to as C3 and C4);
- a false positive blood test for syphilis, known as "RPR" (meaning the lab test indicates you have syphilis but you really don't, which can be proven by a more complex test);
- positive evidence of other markers of autoimmune disease, such as anti-dsDNA (double-stranded DNA) antibodies, anti-Ro/SSA, anti-SM (Smith), anti-RNP, rheumatoid factor (RF); and anti-Ku antibodies.

B. Hematologic

As noted above, several blood disorders - thrombocytopenia, leukopenia, and anemia - may also occur in patients with UCTD. They are rarely severe enough to require treatment alone.

C. Predictive Value of Laboratory Findings

Research has attempted to determine which, if any, of the laboratory test findings may predict the evolution of UCTD to lupus or other connective tissue diseases.

In a study of 148 patients who had detectable anti-Ro/SSA antibodies and a diagnosis of UCTD for at least one year, leukopenia was more frequent in those patients who ultimately developed a defined connective tissue disease. Anti-dsDNA antibodies were predictive of evolution to SLE. However, the majority of patients in this study who developed a connective tissue disease progressed to primary Sjogren's syndrome (50%) - which is notable for dry eyes and dry mouth.

Another study found that anti-RNP antibodies were significantly correlated with Raynaud's phenomenon and arthritis. Anti-Ro antibodies also correlated with dry eyes and dry mouth. . Most interestingly, 82% of those studied were found to have a simple autoantibody profile characterized by a single specificity. The serologic profile of these UCTD patients remained unchanged in follow-up.

Among those UCTD patients with features more suggestive of lupus (termed incomplete lupus), it has been noted in a group of 87 patients that elevated dsDNA and decreased C4 (one type of complement) were associated with subsequent development of lupus. Others have noted that the presence of homogeneous ANA (one of several "patterns" of ANA that are seen in the microscope) and presence of anti- Sm antibody predicted the development of lupus.

One physical finding which is thought to predict evolution to a defined CTD is abnormalities in the capillaries (the tiniest blood vessels) in the folds of fingernails or toenails. One study followed 43 patients with UCTD; it found that 23% of those with abnormal capillaries progressed to definite scleroderma (also called systemic sclerosis). Similar studies have suggested that the rate of progression might be even higher. If you are worried about this, your doctor - or a doctor to whom you are referred - can examine your nailfolds under a microscope. However, nailfold capillary abnormalities have been seen in many other diseases, such as dermatomyositis, lupus, and Sjogren's syndrome, and psoriasis.

It is always wise to discuss your laboratory tests with your doctor and ask for explanations of what they mean. You may want to ask for copies of your test results to keep in a folder at home so you can see how they change - or do not change - over time.

V. Differential Diagnosis

Many different diseases can cause symptoms similar to those of UCTD. Differential diagnosis is the process by which the physician figures out which one is causing your problems. This is important because diseases that may cause such symptoms are often treated in a very different manner from UCTD.

Other well-defined connective tissue diseases that need to be considered in the process of differential diagnosis include: rheumatoid arthritis, systemic lupus erythematosus (SLE), myositis, Sjogren's Syndrome, and scleroderma. Diffuse body pain without other objective

features, even in the presence of a positive ANA, argues more strongly for fibromyalgia than a true connective tissue disease.

A thorough history, exam and laboratory evaluation to rule out these other rheumatic diseases is important. In this sense, the diagnosis of UCTD is one of exclusion. When the suspicion of an autoimmune disease is high in a patient because several features of one or more of these diseases is present, but signs and symptoms are insufficient to meet their criteria, UCTD is diagnosed. However, the threshold for reconsideration of a more definite CTD must be low if, and when, new symptoms present in such patients.

VI. Initial Treatment

No formal study of various treatments in patients with UCTD has been conducted. Most therapies are borrowed from physicians' experiences of their effectiveness in other rheumatic diseases. However, it is unknown to what degree a particular therapy improves the symptoms of UCTD or decreases the rate of flare or the likelihood of evolution to a more defined connective tissue disease.

Most therapies are symptomatic and include:

- 1. analgesics (pain killers such as acetaminophen) and non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen for musculoskeletal symptoms, such as joint and muscle aches or pains;**
- 2. topical corticosteroids (creams, lotions or gels that have anti-inflammatory action) and anti-malarial pills such as hydroxychloroquine (Plaquenil) for skin and mucous tissue symptoms. (Antimalarials have been found to modify immune system function.)**

For symptoms that don't respond to these drugs, the physician may occasionally prescribe low dose corticosteroids in pill form (such as prednisone) for short periods of time. High doses of corticosteroids, cytotoxic agents (such as cyclophosphamide, brand named Cytoxan), and immunosuppressives (such as azathioprine, brand named Imuran) are almost never used.

However, there is one interesting study of another immunosuppressive drug, methotrexate (brand named Rheumatrex) that evaluated its use in lupus patients who did not have kidney disease and in 15 UCTD patients whose most common clinical findings were positive ANA, non-erosive polyarthritis, and Raynaud's phenomenon. Overall efficacy was noted in 53% of patients, including six out of 10 with arthritis; 60% had side effects, with 33% discontinuing the drug. It is possible that this drug may be useful for hard-to-treat joint and skin problems, although it is not commonly used at present.

VII. Long-Term Management Issues

Pregnancy: outcome, impact on flare rate and disease evolution

To date there has only been one study addressing the issue of pregnancy in patients with UCTD. Out of 25 pregnancies in 20 patients with the diagnosis for at least one year, 22 pregnancies were successfully brought to term. Complications were observed in six out of 22 of the successful pregnancies, but most were just early delivery and lower birth weight of the baby.

Some systemic autoimmune diseases tend to have alternating remissions (periods of no symptoms) and flares (periods of increased disease activity). In this pregnancy study, flares of UCTD were seen in six patients, with symptoms including arthritis, fever, and skin rash. One patient developed systemic lupus erythematosus. The flare rate was higher than the incidence of flares in a control population of non-pregnant UCTD patients. This suggests that your condition should be closely monitored during pregnancy.

Occurrence of Thyroid Disease

Thyroid disease, especially hypothyroidism (an underactive thyroid gland), is a common autoimmune condition which can be seen more frequently in patients with other autoimmune diseases, such as SLE and RA. One small study of 75 patients with UCTD showed that thyroid disease was present in 6%, suggesting that monitoring for the occurrence of thyroid disease by your doctor may be appropriate.

VIII. Prognosis

A prognosis is a forecast about the likely course of a disease. Patients with UCTD have an excellent prognosis. Almost all studies to date indicate a low likelihood of progression to any involvement of organs such as the kidney, lungs, and brain. A small minority of patients (<20%) go on to develop a well-defined connective tissue disease, but this becomes much less likely if the disease has been present unchanged for greater than five years.

In a substantial proportion of patients, the disease is mild and no treatment is needed. Rarely, in some people, the symptoms can go away completely. The majority of patients can be treated symptomatically, and very few patients ever require the use of immunosuppressive medications.

IX. When to Seek Referral to a Specialist

If your primary care physician suspects that you may have UCTD - or if you are believed to have any other systemic autoimmune or connective tissue disease - you should be seen by a rheumatologist for evaluation and to confirm the diagnosis. Consultation with a rheumatologist if UCTD is suspected is important to exclude the presence of any other definite connective tissue disease.

Once your symptoms have stabilized with effective medical management, ongoing monitoring should be done at least twice a year by the rheumatologist. Checking kidney and liver function and blood counts several times a year is sufficient unless new symptoms develop. Any new symptoms should be promptly evaluated to consider the possibility that the UCTD has evolved to a well-defined connective tissue disease that merits more aggressive treatment.

X. Annotated Bibliography

Alarcon GS. Unclassified or undifferentiated connective tissue disease. *Baillieres Best Practice Clin Rheumatol*. 2000 Mar;14(1):125-37.

A good review of the 10-year clinical outcomes in UCTD.

Mosca M, Neri R, Bombardieri S. Undifferentiated connective tissue diseases (UCTD): A review of the literature and a proposal for preliminary classification criteria. *Clin Exp Rheumatol* 1999 Sept-Oct;17(5):615-620. Review

This paper addresses need to systematically categorize those patients who should most appropriately be termed "undifferentiated." Classification criteria are proposed.

Mosca M, Neri R, Strigini F, Carmignani A, Totti D, Tavoni A, and Bombardieri S. Pregnancy outcome in patients with undifferentiated connective tissue disease: a preliminary study on 25 pregnancies. *Lupus* 2002;11(5):304-7.

This important study finds UCTD patients are at higher risk of pregnancy complications and argues for careful monitoring of these patients during pregnancy.

Williams HJ, Alarcon GS, Joks R, Steen VD, Bulpitt K, Clegg DO, Ziminski CM, Luggen ME, StClair EW, Willkens RF, Yarboro C, Morgan JG, Egger MJ, Ward JR. Early undifferentiated connective tissue disease (CTD). VI. An inception cohort after 10 years: disease remissions and changes in diagnoses in well established and undifferentiated CTD. *J Rheumatol* 1999 Apr 26(4):816-25.

This includes data on patients with UCTD followed over 10 years (the longest documented study) and makes the important observation that even with disease this far out, many patients still have not evolved into a more defined CTD.