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Paediatrics

SYSTEMIC LUPUS ERYTHEMATOSUS. MOLECULAR BASIS DISEASE, PART I

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ABSTRACT The exact etiology of systemic lupus erythematosus(SLE) is unknown and the prognosis remains poor. Multiple genes contribute to disease susceptibility. The genetic factors play an important role in the predisposition of the disease however certain environmental factors are required to trigger the disease. From years 1950 has been observed than there is some relation among the activity of enzyme acetyltransferase and the presence of SLE; has been done researches finding some disorders in structure of collagen during disease and also it was observed changes of enzymes activity in blood as so changes on levels of amino acids in blood and urine of patients with SLE and laboratory animals with clinical characteristics of disease. Diagnostic of disease is done usually in advanced state because clinical characteristics of disease are presents after 6 months of started. For this reason is very important to do an early diagnostic of disease and to give a medical treatment timely because some injuries caused by disease are irreversible. Here is presented some of last researches that help to understand the beginning and evolution mechanisms of disease.

KEYWORDS : Systemic lupus erythematosus, acetyltransferase, amino acids, enzymes

INTRODUCTION

Systemic lupus erythematosus (SLE) is a collagen disease and is defined as a general disease, not infectious, not cancerous, inflammatory and of multifactorial etiology (1). SLE is a prototypic autoimmune disease characterized by the production of antibodies to components of the cell nucleus in association with a diverse array of clinical manifestations; with multiple autoantigens as targets, resulting in damage to many organs of the human body . The collagen disease also are known as connective tissue disease and are included into of rheumatic illness according to classification of American College of Rheumatology. The rheumatic illness are very ancient as so as the man, there are data of them in documents of ancient civilizations Egyptian, Greece, and Roman. The abnormal immune response in the SLE were observed the first time as reactions false positive VDRL test (2). But the modern concept of SLE came after discovery of LE cells. The SLE was descript the first time on year 1895 and year 1941 was descript as disease of vascular collagen. This disease affects predominately females between the ages from 15 to 40 years . The F/M ratio is 4:1 in early childhood increasing up to 9:1 with age. For development of disease participate disturbances of immune system than involve genetic factors and environmental . On humans has been observed some association of SLE with locus D and histocompatibility ; in extended families SLE may coexist with other organ specific autoimmune disease such as hemolytic anemia, immune thrombocytopenic purpura and thyroiditis. However other immune disturbances has the same association , therefore these genes only may create a predisposition towards disease. The incidence of hypergammaglobulinaemia, rheumatoid factor, antinuclear antibodies (ANA) and VDRL false positive are increased among the family members with SLE and also has been found in identical twins . Furthermore there are many subjects with these genotype that are not affected by the disease, therefore are necessary several environmental factors in the induction and exacerbation of SLE so as exposition to infectious agents (3). The lupus syndrome associated to drugs is an example of chemical and pharmacological agents that induce SLE (4). The genetic factors may create a predisposition towards SLE; but the initiation of the disease results from several environmental triggers and exogenous factors such as :

1,-Ultraviolet light (solar radiation).

The exposure to sunlight is a well known environmental factor in the induction and exacerbation of SLE. Recent studies have demonstrated that solar light can cause inflammation, induces cellular apoptosis of human keratinocytes and cause tissue damage; affect approximately 70 per cent of patients. This may to denature DNA producing antibodies to DNA . The injuries between dermis and epidermis have affinity to fix the DNA and therefore in this zone are fixed antibodies to DNA increasing damage .

2.- Reactions to chemicals and drugs..

Some drugs modify cellular responsiveness and immunogenicity of self-antigens; producing ANA and inclusive the characteristic cellular phenomenon of SLE and the clinical symptoms of disease; these symptoms disappear after eliminate the ingest ; the time depend of reaction gravity . Hydralazine and isoniazid disturbance several nuclear antigens when their have interaction with the nucleoproteins. While hydantoin and chlorpromazine them have interaction with denatured DNA (5,6). These drugs disturbances the tertiary structure of DNA and induce the formation of antibodies in humans principally again hystones and also again nucleic acids. Many drugs which are aromatic amines or hydrazynes can induce a lupus-like syndrome, especially in individuals who are genetically slow acetylators. and them are: methyldopa, oral contraceptive, procainamide, chlorpromazine, trimethadione, tetracycline, penicillamine, sulfonamides, streptomycin, griseofulvin, phenylbutazone, phenylhydantoin, and silica.

3.- Viral diseases.-

The viral infections have been linked in the induction and exacerbation of SLE, Infectious agents may induce specific response by molecular mimicry and disturb immune regulation. Several infectious agents are implicated in the pathogenesis of SLE, none of these has been consistently demonstrated in more than few studies. Infectious agents such as viruses might initiate or cause a flare in SLE by activating B cells, damaging tissues to release autoantigens (4) . However viral evidences have not been consistently demonstrated in the tissues of patients with SLE.

4 .- Hormones.

SLE is predominantly a female disease. The Afroamerican women are 3 times more susceptible to develop disease that women of white race. On the other hand has been observed that oral contraceptive pills active the production of antibodies to DNA and provoke exacerbation of disease and is increased the renal damage and this is attributed to oestrogens and not by progesterone (7). In change the androgens have opposite effect for this cause the SLE is more frequent in females. This abnormality might be explained by increased abnormal oestrogen metabolism has been demonstrated in patients with SLE of both sex, with an increase in 16αhydroxylation of oestrone, resulting in significantly raised 16αhydroxyestrone concentrations. Women with SLE also have low

plasma androgens, including testosterone. The concentration of androgens correlate inversely with disease activity. High doses of oestrogens inhibit T cell responses, such as proliferation and interleucine-2 production. Testosterone reduces immunoglobulin production from peripheral blood mononuclear cells of both normal subjects and patients with SLE. On the other hand in patients with emotional problems has been found number of lymphocytes T and B decreased due to stress also there is decrease of synthesis of antibodies (8).

Various genes contribute to disease susceptibility; population studies reveal that the susceptibility to SLE involves human leukocyte antigen (HLA) class 2 gene polymorphisms. An association of HLA DR2 and DR3 with SLE is a common finding in patients of different ethnicities with a relative risk for the development of disease of approximately two to five. With acknowledgment of a genetic predisposition towards SLE and the discovery of LE cell marked a significant advance on research into the pathogenesis of the disease.

IMMUNOLOGIC PATHOGENESIS

LE cell phenomenon.

The LE cells were first described in the bone marrow of patients with SLE. The formation of the LE cell depends on the presence of a IgG antibody that reacts with deoxyribonucleoprotein in the nucleus of damaged leukocytes and in presence of complement, leads to the destruction of the normal chromatin pattern. The DNA, immunoglobulin and complement from the damaged cell and ingested by a polymorphonuclear leukocyte. The LE cell is observed in 75-80% of patients with SLE.

Antinuclear antibodies.

Immunoglobulins of all classes may form ANA. Six different morphologic patterns of immunofluorescent staining have been described, of which have clinical significance the homogeneous pattern that is strongly associated with active SLE; the peripheral pattern is the morphologic expression of anti-dsDNA antibodies that is characteristic of active SLE. The speckled pattern is the morphologic expression of various antigens within the nucleus and nucleolar pattern, this antigen is precursor of ribonucleoprotein and is observed in 24% of patients with SLE. The ANA may act against DNA, RNA, nucleoproteins, nuclear glycoproteins (antigen Sm), ribonucleoproteins and histones. The presence of antibodies is very broad and has been identified more than 25 types different of antibodies of reactive antibodies to several cellular antigens such as antibodies anti-erythrocyte, anti-lymphocyte, anti-mitochondrial, anti-muscle smooth, anti-ribosomal, anti-platelet, anti-factor VIII (circulating anticoagulants), and others (9,10).

Levels of complement decreased.

Serum complement is a group of cationic proteins on human serum; its structure chemical is very similar to that of collagen or glomerular basement membrane. Like collagen the complement contains large amounts of glycine, hydroxylysine and hydroxyproline. Decrease of complement correlates with exacerbation of disease and inclusive can be preceded.

Deposits of immune complex on kidney.

Renal involvement is a frequent and serious feature of SLE. The best characterized organ pathology is in the kidney. Renal biopsies in patients with SLE display mesangial cell proliferation, basement membrane abnormalities and immune complex deposition, comprising immunoglobulins and complement components. In studies of patients with SLE after the anti-DNA antibody, the circulating DNA antigen appears several events that end in the formation of immunocomplexes. These immunocomplexes DNA-antiDNA has a special tropism by the basal membranes and they are quickly deposited in the renal glomerulus.

Activity of T lymphocytes decreased.

SLE is characterized by **a** myriad of immune system aberrations than involve **B** cells**, T** cells and cells of the monocytic lineage, resulting in polyclonal B cell activation, increased numbers of antibody producing cells, hypergammaglobulinaemia, autoantibody production and immune complex formation. The activation of B and T cells requires stimulation by specific antigens. Irritating chemicals such as pristine, bacterial DNA and cell wall phospholipids and viral antigens can induce anti-DNA antibodies in mice. The number of B cells at all stages of activation is increased in the peripheral blood of patients with active SLE. The total number of peripheral blood T cells is usually reduced, probably because of the effects of anti -lymphocyte antibodies.

Several auto-antibodies not specific of organ.

The anti-erythrocyte antibodies belong to all major immunoglobulin classes and can be detected by the direct Coombs test. The prevalence of these antibodies in SLE are from 10-65%. Antiplatelet antibodies are found in 75-80% of patients with SLE. These antibodies induce thrombocytopenia by direct effects on platelet surface membrane. Antibodies to thyroglobulin have been found in 20% of patients.

The SLE presents no single characteristic clinical pattern. The 90% of patients beginning as a rheumatoid arthritis, with rheumatoid factor positive and LE cells negative; after 6 months the disease is present with its typical characteristics. Diagnostic of SLE due to be confirmed with serologic assay of ANA and anti-DNA because the serum level of these antibodies correlate with disease activity (11, 12).

LABORATORY FINDINGS

Blood cytometry.

The 80% of patient with SLE presenting normochromic normocytic anemia; hypocromia, microcytosis, and increased reticulocytes. The 5% develop hemolytic anemia due at the presence of anti-erythrocyte antibodies; also is observed leukopenia on 70% of patients with SLE. The erythrocyte sedimentation rate is increased in 90% of patients. Thrombocytopenia is commonly seen, due present anti-platelet antibodies, has been observed degranulation because platelets are decreased adenosine-diphosphate (ADP), and serotonin.

Anticoagulants.

The IgG antibodies affect the first stages of coagulation. The 5% of patients present circulating anticoagulants. The prothrombin time is increased. The lupus anticoagulant is characterized by the presence of circulating antibodies against phospholipids and thrombocytopenia. Antiphospholipid antibodies can be identified with positive false test for syphilis by VDRL or the lupus anticoagulant assay. Patients with SLE generally react with a negatively charged ´phosphate group present in cardiolipin, phosphatidic acid or phosphatidylserine.

Function renal test .

The blood urea and creatinine may be increased due to renal damage. Urinalysis reveals hematuria, proteinuria, leukocyturia, and red and white cell casts.

Function hepatic test.

These laboratory test commonly are not disturbance. In protein electrophoresis has been observed hypergammaglobulinaemia in 80% of patients and hypoalbuminemia in 35%.

Serum complement.

The evaluation of complement is considered useful in monitoring of LES. Its decreased correlate with exacerbation of disease and inclusive may be preceded. The reduction of serum complement may be the result of increased utilization due to immune complex accumulation in glomerular basement membrane, to reduced synthesis, or a combination of both factors therefore decrease its blood levels.

Anti-DNA antibodies.

Antibodies to DNA may be to either the double stranded native DNA (nDNA) or to denatured single strand DNA (ssDNA). Antibodies to ssDNA are detected in numerous diseases but are not considered clinically relevant. Antibodies to nDNA occur in up to 90% of SLE patients with active disease . Antibodies to DNA of a single strand can bind to purics or pyrimidics basis of DNA, to nucleosides and nucleotides. Antibodies to DNA of double strand only can to bind to poliribose-phosphate and base pairs guanosine-citidine and adenosine-timidine on the form deoxi. Historically, antibodies to nDNA have been considered to be them major antibodies implicated in the pathogenesis of SLE. New research suggests that chromatin and not just DNA may play an important role. The presence and/or increase in the titer of antibodies to nDNA with a concomitant decrease in complement are associated with a flare of disease, particularly renal disease (13).

Anti-nucleoprotein antibodies.

These antibodies are of type IgG and them provoke production of LE

cells. The production of LE cells due to that nucleus is cover with a protein (antibody) that masked the negative charges free of the nucleic acids and the basofilia is decreased. The modern term for nucleoprotein is chromatin. Chromatin is comprised of 40% DNA, 40% histone and 20% non-histone protein. The histones are organized along the DNA as repeating units called nucleosomes. Each nucleosome is composed of a histone core containing 2 each of H2A, H2B, H3 and H4 wrapped around 2 times by 165 bp of DNA with H1 on the outside. The nucleosomes are strung together by linker DNA. Anti-nucleosomes or anti-chromatin antibodies react with DNA, the parts of histones that are exposed in chromatin and conformational epitopes that are formed by the DNA/histone complex. Antibodies to chromatin are the first antibodies to appear and that specific antibodies to DNA and histone develop later. Chromatin antibodies are detected in 50-80% of patients with SLE . Antibodies to the individual histones are also detected in SLE. It has been shown that the peptides derived from histone H3 91-195 and others stimulate the T lymphocytes of patients with lupus erythematosus (but not healthy people) to produce cytokines. Antibodies to both histones and chromatin but not nDNA are detected in drug induced LE (14)

BIOCHEMICAL CHARACTERISTICS

During studies done of isoniazid metabolism, (an anti-tuberculous agent), was observed that main excreted metabolites in urine are acetyl-isoniazid , isonicotinic acid and the parent compound. The urinary excretion of these compounds is different for each subject finding in some them inverted totally. These differences in the rate of isoniazid acetylation are due to a polymorphism of the enzyme acetyltransferase. N-acetyltransferase2 is a crucial enzyme in clinical pharmacology. This enzyme and its gene play an important role in the metabolism of many drugs and xenobiotics (chemical and certain diets). NAT2 gene is one of the most well-known genetic polymorphisms in humans and displays a large genetic variability among different ethnic groups.

From the variation of alleles/haplotypes presented by NAT2 gene it is possible to classify as either slow acetylators, intermediate and fast acetylators (15). Therefore, drug side effects can be directly attributed to differences in acetylator phenotype. There are considerable ethnic differences in the frequency of the acetylator phenotype. Caucasian population, Africans, Indians and Mexicans are slow acetylators. Populations of Japan, China and Korea are fast acetylators. The individuals slow acetylators are easy producing ANA when them ingest procainamide, hydralazine or isoniazid. Also is observed a higher incidence of SLE in slow acetylators. Almost all patients on procainamide therapy for over one year develop ANA. However, development of antibodies for slow acetylators was 2.9 months, whereas in fast acetylators it was 7.3 months. In addition slow acetylators are more likely to develop SLE syndrome. In a research done by Drayer, he found of 134 patients with SLE, 104 of them were slow acetylators (16).

On the other hand has been observed in collagen diseases there is an increase of amino acids excretion urinary 4 times more than in healthy subjects (17). For this fact some times has been done the evaluation of urinary amino acids proline and hydroxi-proline to confirm diagnostic of collagen diseases. However the excretion is dependent of kidney functional status . On the other hand the increased excretion of amino acids in urine has induced to do several research over amino acids composition of collagen protein in patients with SLE. Patients with SLE are characterized by disturbances in collagen protein which has encouraged for to evaluate some amino acids present in the collagen; the amino acids studied were proline and hydroxiproline. Has been observed that urinary excretion of free hydroxyproline conform 3% of totally (0.5 mg/ml) and the rest of hydroxyproline is excreted as little peptides in form of prolil-hydroxyproline that is the 60% and the tripeptide glicil-prolil-hydroxyproline 15%.This are indicating that peptides with containing hydroxyproline are filtrated in renal glomeruli and excretion rate is independent of urinary volume and therefore is constant. The proline and hydroxyproline that are ingested in dairy diet are metabolized completely up to CO2 and ammonia. Therefore the proline used for synthesis of peptides and proteins is produced from others amino acids (18).

The collagen is the most abundant protein in the body; It comprises the third part of the total proteins. The collagen molecule consists of a triple helix with a molecular weight of 300,000 daltons and measures 280 x 1.4 nm; is a protein rich in glycine and contain from 23% to 30% of that all the amino acids, the proline is find in 14%, hydroxyl-proline 12% and lysine 4%; also is find 3-hydroxi-proline and 5-hydroxi-lysine in less amount. Hydroxyproline and hydroxylisine are virtually exclusive for the collagen. The amino acids proline and hydroxyproline are voluminous and these amino acids give rigidity and stability to protein; has been observed that when the protein is synthesized on conditions that inactive the enzyme prolil-hydroxilase, this loss its native configuration, therefore is denatured to 34°C , while the normal collagen is denatured to 39°C. Generally the collagen alterations are due to disturbed of enzymes activity that transform the proline to hydroxyproline and lysine to hydroxylysine, and them are the enzymes lysil-hydroxilase, lysil-oxidase and prolil-hydroxilase. These enzymes for that them functioning require as cofactors, Iron, ascorbic acid, copper and pyridoxal phosphate. Has been observed that hydroxyproline give stability at protein because in absence of this amino acid and deficit of vitamin C as in scurvy, the protein is fast degraded “in vivo” increasing the urinary excretion of peptides of proline, hydroxy-proline and glycine; therefore is evident that ascorbic acid is important for the formation of connective tissue and injury regeneration. Precursor of collagen is a procollagen that is containing approximately 1000 amino acids and is jointed to conform collagen fibril . Has been observed that in process of biosynthesis a share of proline and lysine are hydroxylated after that has been conformed the individual peptides. The final step consists of cross-link formation by the enzyme lysyl-oxidase whose two cofactors are copper and pyridoxal phosphate; this gives the fibril the strength to perform its major tensile role (19).

The biochemical studies on the SLE are very scanty; some studies have evaluated the levels of proline and hydroxyproline in patients blood with SLE and were found the same levels of these amino acids in healthy subjects and patients with SLE . An explanation of because the levels of these amino acids remain normal during the active status of disease is the fact that these amino acids when reach a level determined in blood; after reaching this level begin to eliminate in the urine; therefore there is a renal threshold of the same manner that there is a renal threshold for glucose; for this cause levels of these amino-acids are unalterable in blood. The urinary excretion increased of proline and hydroxyproline may be due at upper production of these amino acids or than these amino acids in urine coming of collagen which is degraded. The inhibition of enzyme peptidil-prolil-oxidase and increased excretion of amino acids in urine indicate that proline metabolism is disturbance even though the blood levels are in normal range, The proline a portion is synthesized from glutamate, but the major quantity is produced in liver and kidney by deamination of ornithine by action of enzyme ornithine-aminotransferase (OAT).

Other important amino acid of the collagen is glycine; during glycine metabolism was observed that one of the products is creatine ; therefore its evaluation of serum levels is an indirect test of glycine levels (figure 1). When are increased the ornithine levels also is increase production of proline. There are evidences that when increase glycine in blood, the creatine also increase due that exist a competition with glycine in the tubular renal reabsorption. The creatine is synthesized in liver and pancreas from 3 amino acids that are glycine, arginine and methionine; then pass at blood torrent and is distributed in all tissues. During evaluation of serum creatíne on patients with SLE was observed that 62% of patients them levels are increased (20). The values of serum creatine in healthy subjects were from 0.6 to 1.6 mg/dl and in patients with SLE are from 1.0 to 2.5 mg/dl._ Reviewing different laboratory tests utilized as support for diagnosis of disease was observed that 65% of patients present leukopenia and present LE cells in the same proportion.; this correlate with values found of serum creatine.

Is well known that from ornithine also are produced others compound physiologically important as creatine and the polyamines by action of the enzymes ornithine-amino- transferase, (OAT), ornithine-transamidinase (OTA) and ornithine-decarboxylase (ODC). Polyamines have been known for a long time as the first one, spermine. They play multiple roles in cell growth, survival and proliferation. Three polyamines, putrescine, spermidine and spermine, are part of the very tightly regulated polyamine metabolic pathway (21). The ornithine among other activities has been observed that participate in pathway of immune response , as the lymphocyte proliferation (22). The ornithine in rats produce increase of thymus size. When was

evaluated blood levels of ornithine in patients with SLE was observed that are increased approximately two times more than in healthy subjects. The healthy subjects present values from 0.4 to 5 mg/dl and the patients with SLE have from 1.5 to 11 mg/dl although only 52% of patients present increased levels and furthermore these values correlate with ANA titers of the same patients (23). The ornithine may be increased due to inhibition of enzymes (ODC) and (OAT) causing accumulation of ornithine in blood. The amino acids proline and ornithine are easily interchangeable in the organism although the ornithine is not incorporated in proteins; only is an intermediary in arginine metabolism.

The ornithine metabolism may be considered in 4 patways. **1**. Participate in urea cycle. **2**. In polyamines biosynthesis. **3**. In creatine synthesis and **4**. React with enzyme OAT producing proline. On the other hand, the proline is synthesized from glycine by action of enzyme glycin-transamidinase and also from arginine by action of enzyme renal arginase (24). The synthesis of polyamines is from ornithine by the enzyme ODC pyridoxal-phosphate dependent. The main source for ornithine is arginine in protein intake of diet. The destiny of ornithine carbon atoms are incorporate as arginine, proline, glutamate, polyamines, aminobutyric acid and its oxidation in Krebs cycle. When is added ornithine to a mixed culture of lymphocytes is inhibited the develop of T lymphocytes, and on the other hand also has been observed that high levels of ornithine inhibit the activity of OAT enzyme and transamidinase. Furthermore the treatment with isoniazide, an anti-tuberculous agent, increase levels of serum ornithine and have been found develop of SLE in patients that have ingested isoniazide (25). The ornithine metabolism is strongly linked with the proline. The deficit of OTC enzyme, cause hiperammonemia with increased urinary excretion of orotic acid. In the urea cycle the ornithine is transformed in citruline by action of the OTC enzyme. The ornithine is not incorporated at proteins, however when its levels is increased the arginase enzyme is inhibited and therefore decrease the polyamines synthesis. The polyamines are synthesized from ornithine by action of ODC enzyme pyridoxal-phosphate dependent producing first putrescine and then is synthesized spermidine and then spermine. The activity of ODC enzyme is increase strongly during the tissue regeneration and also by action of some hormones. When were correlated the ornithine levels with ANA titers was observed that both are increase at the same time. The values increased of blood ornithine is indicating that the metabolism is disturbed due that some enzyme is find inhibited and therefore there is not enzymatic deficiency because in these conditions the ornithine levels do not correlate with the ANA titers. .When there is enzymatic deficiency the values of blood ornithine found are from 30 up to 40 mg/dl. At the present time is few known of etiology of collagen diseases , but there are several chemical compounds that cause SLE. At this time is known that activity of enzymes OAT and transamidinase decrease due some pharmaceutical drugs as cycloserine, canaline, hydroxylamine, thiosemicarbazide and isoniazide. In the treatment of disease are used steroids obtaining good results and them main action at biochemical level is increase the activity of several enzymes as transaminases, arginase, ODC and others. These observations indicate that during the disease is find inhibited or blockade the activity of the enzymes above mentioned and for this reason decrease the synthesis of polyamines that are molecules of low molecular weight . Among their main functions are packaging of nucleic acids, modulation of membrane receptors and ion channels, regulation of gene expression and cell signaling. The polyamines are compounds policationic and them major action is interact with molecules negatively charged, so as DNA, RNA, proteins and into cell membrane; the polyamines bind to the phosphate-sugar skeleton without altering the structure of the DNA; this union favors the stabilization of the DNA double chain and protects it from denaturation and ionizing agents such as solar radiation; and on the other hand they participate in protein and DNA synthesis, growth and cellular division and proteins phosphorylation(21). When the polyamines decrease, the DNA and/or the structure of the chromatin is altered and the toxicity of the drugs increases. The synthesis of DNA is interrupted therefore decreases the cell growth rate observing the disappearance of spermidine. When spermidine is added in cell cultures, the proteins synthesis is normalized (26). Therefore when is decreased synthesis of polyamines giving as final result erythropenia and leukopenia that is observed in almost all patients with SLE; the decrease in T lymphocytes is also observed. This would be an explanation of why solar radiation affects patients with SLE; and this is due that the synthesis of polyamines is decreased therefore the nucleic acids are unprotected. This will be reviewed in more detail in a next article.

Table 1. Serum levels of amino acids found in blood patients with SLE and healthy subjects

Amino acid	healthy subjects	patients with SLE
	mg/dl	mg/dl
Proline	0.6-3.0	0.6- 2.9
Hydroxyproline	0.6-2.6	0.6- 2.6
Creatine	0.6- 1.7	0.9- 2.5
Ornithine	0.4- 5.0	1.5- 11.0

Figure 1. Synthesis of glycine and creatine from serine. (THF)= tetrahydrofolic acid. (SAM)= S-adenosil-methionine

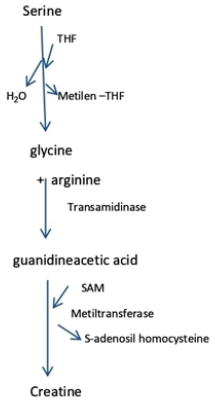
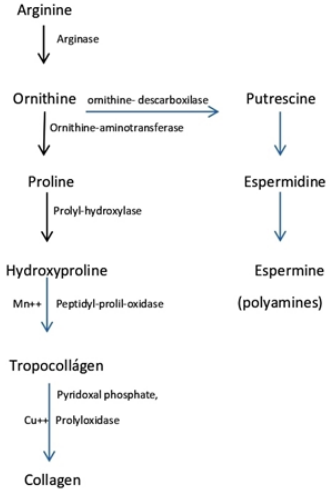


Figure 2. Synthesis of collagen protein and polyamines from arginine



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