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EVALUATION OF LIPID PROFILE IN CASES SUFFERED FROM RHEUMATOID ARTHRITIS

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Abstracts
Rheumatoid arthritis is a chronic systemic inflammatory disease of undetermined etiology involving primarily the synovial membranes and articular structures of multiple joints. The disease is often progressive and results in pain, stiffness, and swelling of joints. In late stages, deformity and ankylosis develop. Rheumatoid arthritis can also cause significant extra-articular manifestations most probably related to systemic inflammation. Hence based on above findings the present study was planned for Evaluation of Lipid Profile in Cases Suffered from Rheumatoid Arthritis.
The present study was planned in Anugrah Narayan Magadh Medical College and Hospital, Gaya, Bihar, India. In the present study 50 patients were evaluated. Out of that 25 cases of the arthritides were enrolled in Group A and remaining 25 control cases were evaluated in the Group B. For the biochemical parameters to be analyzed, blood sample were drawn from the anticubital vein avoiding venostasis. In all subjects a blood sample was collected after an overnight fast plain vials are used for the determination of lipid profile, Total cholesterol and HDL Cholesterol were measured by Henly‟s method. Serum triglyceride was estimated by Rosenberg and Gottfrieds.
The data generated from the present study concludes that the lipid profile is altered in Rheumatoid arthritis characterized by low TC and LDL with lower RA factor titres. However, the mean triglycerides, HDL, LDL, VLDL, TC/HDL and mean LDL/HDL did not show a significant difference between subgroups of the patients having different titres of RA factor.
Keywords: Lipid profile, Rheumatoid arthritis, Periarticular osteopenia, Hypercholesterolemia, Hypertriglyceridemia, RA factor, etc.

Introduction

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease whose hallmark feature is a persistent symmetric polyarthritis (synovitis) that affects the hands and feet (see the image below). Any joint lined by a synovial membrane may be involved, however, and extra-articular involvement of organs such as the skin, heart, lungs, and eyes can be significant. RA is theorized to develop when a genetically susceptible individual experiences an external trigger (eg, cigarette smoking, infection, or trauma) that triggers an autoimmune reaction.

The pathogenesis of RA is not completely understood. An external trigger (eg, cigarette smoking, infection, or trauma) that sets off an autoimmune reaction, leading to synovial hypertrophy and chronic joint inflammation along with the potential for extra-articular manifestations, is theorized to occur in genetically susceptible individuals.
Synovial cell hyperplasia and endothelial cell activation are early events in the pathologic process that progresses to uncontrolled inflammation and consequent cartilage and bone destruction. Genetic factors and immune system abnormalities contribute to disease propagation.

CD4 T cells, mononuclear phagocytes, fibroblasts, osteoclasts, and neutrophils play major cellular roles in the pathophysiology of RA, whereas B cells produce autoantibodies (ie, rheumatoid factors). Abnormal production of numerous cytokines, chemokines, and other inflammatory mediators has been demonstrated in patients with RA, including the following:

- Tumor necrosis factor alpha (TNF-α)
- Interleukin (IL)-1
- IL-6
- IL-8
- Transforming growth factor beta (TGF-ß)
- Fibroblast growth factor (FGF)
- Platelet-derived growth factor (PDGF)

Ultimately, inflammation and exuberant proliferation of the synovium (ie, pannus) leads to destruction of various tissues, including cartilage (see the image below), bone, tendons, ligaments, and blood vessels. Although the articular structures are the primary sites involved by RA, other tissues are also affected.
The cause of RA is unknown. Genetic, environmental, hormonal, immunologic, and infectious factors may play significant roles. Socioeconomic, psychological, and

lifestyle factors (eg, tobacco use, the main environmental risk [1]) may influence disease development and outcome.

Genetic factors account for 50% of the risk for developing RA. [2] About 60% of RA patients in the United States carry a shared epitope of the human leukocyte antigen (HLA)-DR4 cluster, which constitutes one of the peptide-binding sites of certain HLA-DR molecules associated with RA (eg, HLA-DR beta *0401, 0404, or 0405). HLA-DR1 (HLA-DR beta *0101) also carries this shared epitope and confers risk, particularly in certain southern European areas. Other HLA-DR4 molecules (eg, HLA-DR beta *0402) lack this epitope and do not confer this risk.

Genes other than those of the major histocompatibility complex (MHC) are also involved. Results from sequencing genes of families with RA suggest the presence of several resistance and susceptibility genes, including PTPN22 and TRAF5. [3-4]

Juvenile idiopathic arthritis (JIA), also known as juvenile rheumatoid arthritis (JRA), is a heterogeneous group of diseases that differs markedly from adult RA. JIA is known to have genetically complex traits in which multiple genes are important for disease onset and manifestations, and it is characterized by arthritis that begins before the age of 16 years, persists for more than 6 weeks, and is of unknown origin. [5] The IL2RA/CD25 gene has been implicated as a JIA susceptibility locus, as has the VTCN1 gene. [6]

Some investigators suggest that the future of treatment and understanding of RA may be based on imprinting and epigenetics. RA is significantly more prevalent in women than in men, [7-8] which suggests that genomic imprinting from parents participates in its expression. [9-10] Imprinting is characterized by differential methylation of chromosomes by the parent of origin, resulting in differential expression of maternal over paternal genes. [11]

Epigenetics is the change in DNA expression that is due to environmentally induced methylation and not to a change in DNA structure. Clearly, the research focus will be on environmental factors in combination with immune genetics.

For many decades, numerous infectious agents have been suggested as potential causes of RA, including Mycoplasma organisms, Epstein-Barr virus (EBV), and rubella virus. This suggestion is indirectly supported by the following evidence: Occasional reports of flulike disorders preceding the start of arthritis; The inducibility of arthritis in experimental animals with different bacteria or bacterial products (eg, streptococcal cell walls); The presence of bacterial products, including bacterial RNA, in patients' joints; The disease-modifying activity of several agents that have antimicrobial effects (eg, gold salts, antimalarial agents, minocycline).

Emerging evidence also points to an association between RA and periodontopathic bacteria. For example, the synovial fluid of RA patients has been found to contain high levels of antibodies to anaerobic bacteria that commonly cause periodontal infection, including Porphyromonas gingivitis. [12-13]

Sex hormones may play a role in RA, as evidenced by the disproportionate number of females with this disease, its amelioration during pregnancy, its recurrence in the early postpartum period, and its reduced incidence in women using oral contraceptives. Hyperprolactinemia may be a risk factor for RA. [22]

All of the major immunologic elements play fundamental roles in initiating, propagating, and maintaining the autoimmune process of RA. The exact orchestration of the cellular and cytokine events that lead to pathologic consequences (eg, synovial proliferation and subsequent joint destruction) is complex, involving T and B cells, antigen-presenting cells (eg, B cells, macrophages, and dendritic cells), and various cytokines. Aberrant production and regulation of both pro inflammatory and anti-inflammatory cytokines and cytokine pathways are found in RA.

T cells are assumed to play a pivotal role in the initiation of RA, and the key player in this respect is assumed to be the T helper 1 (Th1) CD4 cells. (Th1 cells produce IL-2 and interferon [IFN] gamma.) These cells may subsequently activate macrophages and other cell populations, including synovial fibroblasts. Macrophages and synovial fibroblasts are the main producers of TNF-a and IL-1. Experimental models suggest that synovial macrophages and fibroblasts may become autonomous and thus loose responsiveness to T-cell activities in the course of RA.

B cells are important in the pathologic process and may serve as antigen-presenting cells. B cells also produce numerous autoantibodies (eg, RF and ACPA) and secrete cytokines.

The hyperactive and hyperplastic synovial membrane is ultimately transformed into pannus tissue and invades cartilage and bone, with the latter being degraded by activated osteoclasts. The major difference between RA and other forms of inflammatory arthritis, such as psoriatic arthritis, lies not in their respective cytokine patterns but, rather, in the highly destructive potential of the RA synovial membrane and in the local and systemic autoimmunity.

Whether these 2 events are linked is unclear; however, the autoimmune response conceivably leads to the formation of immune complexes that activate the inflammatory

process to a much higher degree than normal. This theory is supported by the much worse prognosis of RA among patients with positive RF results.

Worldwide, the annual incidence of RA is approximately 3 cases per 10,000 population, and the prevalence rate is approximately 1%, increasing with age and peaking between the ages of 35 and 50 years. RA affects all populations, though it is much more prevalent in some groups (eg, 5-6% in some Native American groups) and much less prevalent in others (eg, black persons from the Caribbean region).

First-degree relatives of individuals with RA are at 2- to 3-fold higher risk for the disease. Disease concordance in monozygotic twins is approximately 15-20%, suggesting that non genetic factors play an important role. Because the worldwide frequency of RA is relatively constant, a ubiquitous infectious agent has been postulated to play an etiologic role.

Women are affected by RA approximately 3 times more often than men are, [15, 16] but sex differences diminish in older age groups. [15] In investigating whether the higher rate of RA among women could be linked to certain reproductive risk factors, a study from Denmark found that the rate of RA was higher in women who had given birth to just 1 child than in women who had delivered 2 or 3 off spring. [23] However, the rate was not increased in women who were nulliparous or who had a history of lost pregnancies.

Time elapsed since pregnancy is also significant. In the 1- to 5-year postpartum period, a decreased risk for RA has been recognized, even in those with higher-risk HLA markers. [24]

The Danish study also found a higher risk of RA among women with a history of preeclampsia, hyperemesis during pregnancy, or gestational hypertension. [23] In the authors' view, this portion of the data suggested that a reduced immune adaptability to pregnancy may exist in women who are predisposed to the development of RA or that there may be a link between fetal microchimerism (in which fetal cells are present in the maternal circulation) and RA. [23]

Outcome in RA is compromised when diagnosis and treatment are delayed. The clinical course of RA is generally one of exacerbations and remissions. Approximately 40% of patients with this disease become disabled after 10 years, but outcomes are highly variable. [25] Some patients experience a relatively self-limited disease, whereas others have a chronic progressive illness.

Rheumatoid arthritis is a chronic systemic inflammatory disease of undetermined etiology involving primarily the synovial membranes and articular structures of multiple joints. The disease is often progressive and results in pain, stiffness, and swelling of joints. In late stages, deformity and ankylosis develop. Rheumatoid arthritis can also cause significant extra-articular manifestations most probably related to systemic inflammation. Hence based on above findings the present study was planned for Clinical Evaluation of Lipid Profile in Cases Suffered from Rheumatoid Arthritis.

Methodology:

The present study was planned in Anugrah Narayan Magadh Medical College and Hospital, Gaya, Bihar, India. In the present study 50 patients were evaluated. Out of that 25 cases of the arthritis were enrolled in Group A and remaining 25 control cases were evaluated in the Group B. For the biochemical parameters to be analyzed, blood sample were drawn from the anticubital vein avoiding venostasis. In all subjects a blood sample was collected after an overnight fast plain vials are used for the determination of lipid profile, Total cholesterol and HDL Cholesterol were measured by Henly‟s method. Serum triglyceride was estimated by Rosenberg and Gottfrieds .

All the patients were informed consents. The aim and the objective of the present study were conveyed to them. Approval of the institutional ethical committee was taken prior to conduct of this study.

Those patients who exhibited diseases of other systems like diabetes mellitus, hypothyroidism, liver or kidney disease, Cushing's syndrome, obesity, familial dyslipidemia were excluded from the study. Patients were also excluded if they had a history of receiving medications affecting lipid metabolism such as lipid lowering drugs, beta blockers, oral contraceptives (estrogen, progestins etc.), thyroxine and vitamin E.

Results & Discussion:

Rheumatoid arthritis (RA) is a chronic systemic disease affecting primarily the synovium, leading to joint damage and bone destruction1 RA causes significant morbidity as a result of synovial inflammation, joint destruction and associated disability. Epidemiological studies have shown an increased premature mortality in patients with RA compared with the general population. Several investigators reported an excess of cardiovascular morbidity and mortality among RA patients. Though rheumatoid vasculitis in severe RA cases with high rheumatoid factor titres occasionally causes acute myocardial infarction the overwhelming majority of cardiovascular deaths in RA result from accelerated atherosclerosis. Risk factors for atherosclerotic events and cardiovascular disease include male sex, increased age, elevated plasma total cholesterol (TC) and lowdensity lipoprotein cholesterol (LDL-C), decreased high-density lipoprotein cholesterol (HDL-C), high blood pressure,

smoking and diabetes mellitus. Approximately 50% of atherosclerotic coronary artery disease (CAD) in the community occurs in the absence of traditional risk factors.

In general, and with some variations between different studies, the lipid profile of patients with active or untreated RA is primarily characterized by a decrease in serum levels of HDL-C whereas contrasting results have been published on the serum levels of TC and LDL-C15-20. Importantly, the reduction in HDL-C has as a consequence the increase in the TC/HDL-C ratio. This ratio represents an atherogenic index, which is an important prognostic marker for cardiovascular disease. Indeed, the risk of myocardial infarction increases considerably when this ratio is higher than five, and it should ideally be four or less.

Table 1: Demographic Parameters

Parameters	Group A	Group B
Cases of	**Arthritides**	**Control**
Total Cases	**25**	**25**
Age:		
21 – 30 years	5	4
31 – 40 years	6	7
41 – 50 years	13	14
51 & above years	1	0

Table 2: Type of Arthritides

Parameters	Group A
Cases of	**Arthritides**
Total Cases	**25**
Rheumatoid Arthritis	16
Inflammatory Arthritis	3
Osteoarthritis	2
Ankylosing Spondylitis	1
Other	3

Table 3: Lipid Profile

Parameters	Group A	Group B
Cases of	**Arthritides**	**Control**
Total Cases	**25**	**25**
Cholesterol mg/dL	163. 4 ± 24.8	158.7 ± 26.6
Triglycerides mg/dL	114.1 ± 28.5	118.3 ± 25.6
HDL mg/dL	34.7 ± 9.8	37.3 ± 8.5
LDL mg/dL	105.7 ± 24.8	99.5 ± 24.8
VLDL mg/dL	22.5 ± 4.6	22.9 ± 5.3

Lipids may contribute to the synovitis in RA through participation in the arachidonic acid pathway within the joint space. [18] Increased levels of total cholesterol, LDL cholesterol and triglyceride have been reported in patients with rheumatoid arthritis. [19]. However, Lazarevic et al.; [20] reported decreased concentration of total serum lipids, serum total cholesterol, low density lipoprotein (LDL) cholesterol, high density lipoprotein (HDL) cholesterol among the patients with rheumatoid arthritis when compared with healthy controls. The serum total cholesterol and HDL cholesterol levels in rheumatoid arthritis are inversely correlated with disease activity suggesting a potential role for inflammation in the atherogenic profile and higher atherosclerotic risk observed in RA. [21-22]. As a consequence of reduction in HDL cholesterol, the atherogenic ratio of total cholesterol/HDL cholesterol as well as LDL cholesterol/HDL cholesterol were significantly higher in RA.

Patients with Rheumatoid Arthritis (RA),who by definition manifest persistent high levels of inflammation are at greater risk of developing cardiovascular disease. [23] Several pieces of evidence indicate that rheumatoid arthritis (RA) is a pro- atherogenic disease associated with increased cardiovascular (CV) mortality. [24-25] Beside genetic and traditional CV risk factors [26-27], chronic inflammation has emerged as a pivotal component implicated in the development of this process. Despite some similarities, there are also some differences between patients with chronic inflammatory diseases and the general population.

The abnormalities in lipid and lipoprotein pattern produces number of pathological diseases including cancer. [28] Altered lipid levels have been reported in various inflammatory diseases including rheumatoid arthritis. [29] Increased levels of total cholesterol and LDL-cholesterol has been reported in patients with rheumatoid arthritis. [30] Hypocholesterolemia has been observed in several inflammatory diseases such as rheumatoid arthritis, myelo proliferative disorders, systemic lupus erythematosus and sarcoidosis. [31] Lazarevic et al. [32] reported that rheumatoid arthritis patients had significantly decreased concentrations of total serum lipids, total serum cholesterol, cholesterol in low-density lipoprotein (LDL) and cholesterol in high-density lipoprotein (HDL) compared with healthy blood donors.

It has already been established that systemic inflammation can be a notable contributor of lipid profile changes. [33] Conversely, evidence indicates that lipids can have a direct modulating effect on inflammation. For example, hypercholesterolemia induces inflammation by increasing circulating inflammatory cells. [34-35] Some studies have demonstrated an association between oxidized LDL cholesterol and proinflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor alpha (TNFα). [36]

Fatty acids are organic acids and form the fundamental constituents of many important lipids, including triglycerides. Their oxidation also brings about raised LDL cholesterol level. Some fatty acids can be synthesized by the body, others the essential fatty acids, must be obtained from the diet. Linoleic acid and α - Linolenic acid are examples of essential fatty acids and much of the work on rheumatoid arthritis and lipids focuses on them and their derivatives. They are the precursors of the two main

classes of polyunsaturated fatty acids (PUFA), the omega-3 (or n-3) and omega -6 (or n-6) families. It is the role of these essential fatty acids in inflammation and immunoregulation that has lead to the idea that they may be the key to a new approach in treating rheumatoid arthritis (RA). Fatty acids consumed in the diet are metabolised to arachidonic acid. Arachidonic acid is the precursor of eicosanoids (prostaglandins, thromboxanes and prostacyclines) of the 2 series and leukotriennes of the 4 series, which have potent pro-inflammatory and immunoregulatory properties. The arachidonic acid is converted by cyclo-oxygenase enzyme, and series- 4 leukotriennes by lipooxygenase enzymes.

Conclusion:

The data generated from the present study concludes that the lipid profile is altered in Rheumatoid arthritis characterized by low TC and LDL with lower RA factor titres. However, the mean triglycerides, HDL, LDL, VLDL, TC/HDL and mean LDL/HDL did not show a significant difference between subgroups of the patients having different titres of RA factor.

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