CHAPTER II

REVIEW OF LITERATURE

New Knowledge of Osteoarthritis must be gained if the later years of our
lengthening lives are not be plagued by increasing pain and disability.

- J. H. Kellgren

2.0. Overview of the Chapter

This chapter discusses the review of literature works done by other scholars. The review
of literature is broadly classified into various categories based on the objectives. They are:

1. Review of literature pertaining to prevalence of Osteoarthritis and especially Knee
Osteoarthritis in India and other Countries were studied.

2. Literature pertaining to inflammatory marker of ESR level in Knee Osteoarthritis
patients and patients’ demographic profile.

3. Literature pertaining to serum enzymes of Matrix Metalloproteinase-3 (MMP-3)
and Matrix Metalloproteinase-13 (MMP-13) of Knee Osteoarthritis patients and
controls.

4. Finally, reviews pertaining to serum enzymes of Matrix Metalloproteinase-3
(MMP-3) and Matrix Metalloproteinase-13 (MMP-13) especially Knee
Osteoarthritis patients and controls by using ELISA method of assessment.
2.1. Prevalence of Osteoarthritis especially for Knee Osteoarthritis

The name “Osteoarthritis” arose from observation of the striking overgrowth of marginal and subchondral bone by the pathologists and radiologists.

**Hinman et al. (2010)** study reveals that, the global statistics over 100 million people worldwide suffer from Osteoarthritis, which is one of the most common causes of disability.

**Mathers et al. (2003) and Felson et al. (1987)** studies reveals that, globally, Osteoarthritis is the eighth leading cause of disability with the joint most frequently associated with disability being the knee.

**Maurer (1979)** the study found that, prevalence of Knee Osteoarthritis increases with age; therefore, the impact of this disease will become even more substantial with the aging of the population. Symptomatic knee OA (SOA) is defined as radiographic OA with knee pain.

**Samuel, Turek’s** defined as Osteoarthritis is the most common joint disease and is the major cause of morbidity and disability in the elderly. The degenerated process first affects the articular cartilage.

**Herrero-Beaumont et al. (2009)** study described the three subsets of Osteoarthritis (Flow Chart 2.1).
Flow Chart 2.1: Three subsets of Osteoarthritis with distinct etiological, clinical and therapeutic characteristic

**Estrogen deficiency–related Osteoarthritis**
- Alterations in chondrocytes and extracellular matrix
- High subchondral bone turnover
- Loss of bone mass/osteoporosis
- Loss of muscle mass, strength and functional capacity
- Increased joint laxity
- Increased fat mass associated with higher adipokine levels

Musculoskeletal menopause (Pre-osteoarthritic changes)

**Genetically-induced Osteoarthritis**
- Susceptibility genes for osteoarthritis, bone mineral density and skeletal shape
- Heritability-determined cartilage volume and osteoarthritis progression
- Gene mutations causing alterations in chondrocytes and extracellular matrix
- Premature osteoarthritis and dwarfism in skeletal dysplasia’s

**Ageing-related Osteoarthritis**
- Alterations in chondrocytes and extracellular matrix
- Decreased subchondral thickness and density
- Sarcopenia and decline in regenerative capacity
- Tendon stiffness
- Loss of proprioception and balance
- Increased joint laxity

Musculoskeletal aging (Pre-osteoarthritic changes)

**Osteoarthritis-related factors**
- Obesity/metabolic syndrome
- Joint injury/instability

**Osteoarthritis**

Source: Herrero-Beaumont et al. (2009)
According to Thompson (1988), in United States of America, prevalence of symptomatic Knee Osteoarthritis is estimated as 12 per cent of the adults older than 65 years of age. In the United States approximately 6 per cent of the population 30 years of age or older and 12 per cent of those 65 years of age or older suffer from symptomatic Knee OA. In the UK, the proportion of Knee Osteoarthritis in the population aged 65 years and older is expected to rise by a quarter from 15 per cent in 1985 to 21 per cent by 2030.

Kim et al. (2010) and Cho et al. (2011) studies found that, in Korea, it is estimated to be 38 per cent for radiographic OA, 26 per cent for SOA and 6.5 per cent for advanced OA warranting surgery.

Parka and Leea (2011) study reveals that, women have significantly higher prevalence for all 3 stages. Many genetic, demographic, and personal characteristics are involved in the risk of Osteoarthritis.

Peat et al. (2001) study reveals that, among United States adults age 60 or older, Knee Osteoarthritis is one of the five leading causes of disability and approximately 12–16 per cent have symptomatic knee OA. Studies have shown that knee OA greatly diminishes health status in the elderly (iii, iv). In the Asia-Pacific region, the prevalence of Knee Osteoarthritis was 7.50% in Chinav, 5.78 per cent in rural Indiavi, 22.00 per cent −28.00 per cent in urban and 25.00 per cent in the rural population of North Pakistanvii, and 10.20 per cent in Bangladeshviii. Knee Osteoarthritis is incurable with currently available therapeutic options. The only way for reduction of the burden of the disorder is prevention.
Chopra et al. (2001) study reveals that, the epidemiological profile of this disease in India is not clear but it is estimated that Osteoarthritis (OA) is the second most common rheumatological problem and is most frequent joint disease with prevalence of 22 per cent to 39 per cent in India. Prevalence of OA in India is reported to be in the range of 17-60.6 per cent\textsuperscript{ix}. OA is the most frequent form of arthritis and joint disorder worldwide. Eleven COPCORD* (Community Oriented Program for Control of Rheumatic Disorders) reports show knee OA data: there were 3,328 knee OA patients out of a total surveyed pooled sample of 41,884. The pooled prevalence of knee OA thus becomes eight percentages. Knee Osteoarthritis is a common condition which represents a major contribution to the burden of physical disability. Prevalence increases with age, so that about 11 per cent of all women over the age of 60 year have symptoms due to knee Osteoarthritis.

As per a recent report published by the Times of India (2009) regarding Osteoarthritis, over 40 per cent of the Indian population in the age group of 70 years or above suffers from Osteoarthritis. Nearly 2 per cent of these undergo severe knee pain and disability. As per a recent statement quoted by Piramal Healthcare Limited in a nationwide campaign against chronic diseases, India is expected to be the chronic disease Capital, with 60 million people with arthritis, by 2025. The government, private sector, the medical fraternity and NGOs should come together against the onslaught of chronic disease. Also majority of those suffering from Osteoarthritis are deprived of access to quality treatment.
The study highlights that, knee involvement occurs less frequently than hand Osteoarthritis, although similarly it is more common in women, with female-to-male ratios varying between 1.5:1 and 4:1. Prevalence rates for knee OA, based on population studies in the US, are comparable to those in Europe. These studies report that severe radiographic changes affect 1 per cent of people aged 25-34 and this figure increases to nearly 50 per cent in those 75 years and above. Among participants aged over 45 years in the Framingham Study, the prevalence of radiographic knee OA was 19.2 per cent and, in those over 80 years, the figure rose to 43.7 per cent. According to data produced by the Dutch Institute for Public Health, the prevalence of knee OA in those aged 55 and above was 15.6 per cent in men and 30.5 per cent in women.

**Race or Ethnicity:** The prevalence of Knee Osteoarthritis and patterns vary among different racial and ethnic groups.

Jones et al. (2008) examined the relationship of the patient race and pain coping strategies in a sample of patients with knee or hip Osteoarthritis. The study surveyed 939 OA patients (ages 50–79 years) who were receiving primary care. The study found racial differences in pain coping strategies.

Gandhi et al. (2008) surveyed 1,609 patients undergoing primary total knee or hip joint arthroplasty. Study reveals that, they assessed patients’ risk awareness and found that patients of non-European origin had greater awareness of surgical risk compared with those of European origin. The National Health Interview Survey is an annual health survey of more 30,000 adults conducted by the National Center for Health Statistics. This study reports first-ever national estimates of arthritis prevalence for Asian
Americans/Pacific Islanders (8%) and American Indians/Alaska Natives (25%) and documents disparities in work limitation, activity limitation, and severe pain (Table 2.1).

<table>
<thead>
<tr>
<th>Race/Ethnicity</th>
<th>Prevalence</th>
</tr>
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<tbody>
<tr>
<td>Non-Hispanic White</td>
<td>23.8%</td>
</tr>
<tr>
<td>Non-Hispanic Black</td>
<td>19.4%</td>
</tr>
<tr>
<td>Hispanic</td>
<td>11.1%</td>
</tr>
<tr>
<td>American Indian/Alaska Native</td>
<td>25.2%</td>
</tr>
<tr>
<td>Asian/Pacific Islander</td>
<td>8.4%</td>
</tr>
<tr>
<td>Multiracial/Other</td>
<td>20.7%</td>
</tr>
</tbody>
</table>


Andersen (1978) study reveals that, fewer racial differences are observed for Osteoarthritis of the knee and such differences that have been observed may have been affected by occupational factors.

Age: Age is one of the important risk factor for Osteoarthritis.

Lawrence et al. (1966) showed that not only was there a marked increase in the occurrence of severe Osteoarthritis (equivalent to Kellgren and Lawrence system grades 3 and 4) with advancing age, but that this age-related increase appeared to be exponential after 50 years of age. Nevertheless, the interrelationship between ageing and Osteoarthritis is not yet clear. For example, Osteoarthritis may begin at a relatively young age but only progress to become clinically apparent or symptomatic, and therefore 'more prevalent' as people grow older.
Brandt and Fife (1986) and Sandell (1995) studies reveals that, there is certainly some evidence to suggest that Osteoarthritis does not occur as a direct consequence of normal ageing and studies have shown articular cartilage from patients with OA differs in a number of ways from cartilage of normal elderly individuals.

Mohamed Ahmed et al. (2012) a study on prescribing patterns in the management of arthritis in the department of Orthopaedics, the study reveals that out of 75 osteoarthritis patients, about 60% are in the age group between 51-65 years.

Dinesh Bhatia (2013) the study reveals that the prevalence of Osteoarthritis between the ages of 30 to 65 years. The prevalence of OA increases indefinitely with age, because the condition is not reversible. Men are affected more often than women among those aged <45 years, whereas women are affected more frequently among those aged >55 years.

A community-based cross-sectional study was carried out by in an urban resettlement colony in South Delhi Harshal Salve (2010), to study the prevalence of Knee Osteoarthritis in women aged =40 years and treatment seeking behavior of women suffering from Osteoarthritis found 47.3 per cent of women (123/260) to be suffering from Knee Osteoarthritis. Most studies show increasing risk of Knee Osteoarthritis with age and radiological surveys suggest that knee osteophyte (bony outgrowth) development increases by 20 per cent per 5-year increase in age. It was the sixth leading cause of years of living with disability at the global level, accounting for 3 per cent of the total global years of living with disability. Its impact can be described by health state descriptions developed as part of the global burden of disease 2000 project disability.
Arya and Vijay Jain (2013) study reveals that, the age is not the only factor that plays a role in the evolution of Osteoarthritis. Other risk factors are obesity, joint hypermobility or instability, sport stress with high impact loading, repetitive knee bending or heavy weight lifting, specific occupations, peripheral neuropathy, injury to the joint, history of immobilization and family history. Zhang et al. (2009) study described the Knee Osteoarthritis diagnostic test and study design (Flow Chart 2.2).

Flow Chart 2.2: Major components in the diagnosis of knee osteoarthritis

Source: Zhang et al. (2009)
2.2. Inflammatory marker of Erythrocyte Sedimentation Rate (ESR) level in Knee Osteoarthritis patients

The method for the erythrocyte sedimentation rate (ESR) was first described in 1921 by Dr. R. Fahraeus and Dr. A. Westergren (*Fahraeus 1921 and Westergren 1921*), and it rapidly became a common screening test worldwide for acute phase proteins and chronic diseases. Despite its limitations and the introduction of other more specific markers of inflammation, the ESR remains a widely used test for the screening and monitoring of infectious, autoimmune, malignant and other disease processes that affect plasma proteins and the sedimentation rate.

*Bijlsma et al. (2011)* the study reveals that, Osteoarthritis (OA) is a highly prevalent disease that has been associated with decreased muscle strength and activity limitations.

*Konttinen et al. (2012) and Pelletier et al. (2001)* the studies highlights that, even though Osteoarthritis has traditionally been considered a non-inflammatory disease compared with RA, evidence has recently shown a low grade of inflammation mainly associated with synovitis in this group of patients.

*Sharif et al. (1997); Pearle et al. (2007)* studies highlights that, however, in contrast to patients with well-known inflammatory diseases like RA in which inflammatory markers such as CRP and ESR are usually elevated, in patients with Osteoarthritis only slight or moderate elevations of inflammatory markers (i.e. CRP and ESR) have been described.
Diana and Sanchez-Ramirez (2012) study revealed that, the muscle strength was more strongly associated with ESR ($P < 0.001$) than with CRP ($P = 0.03$). A possible explanation might be the longer half-life of ESR in the system compared with the rapid changes in concentration of CRP. Although CRP and ESR are considered non-specific tests, their values can contribute to the detection of diverse conditions associated with inflammation. Both ESR and CRP are commonly used as markers of acute-phase response of inflammation. However, CRP is more sensitive than ESR to changes in the onset of acute-phase response, increasing rapidly within hours of the stimulus and then returning to normal values following resolution.

Schaap et al. (2006) and Schaap et al. (2009) the studies reveals that, the relationship found between elevated inflammatory markers and lower muscle strength is coherent with findings of previous studies carried out in the general elderly population, in which elevated levels of inflammatory markers were associated not only with lower muscle strength, but also with loss of muscle mass and sarcopenia.

Keenan (2008) the study found that, ESR and CRP was more elevated in RA patients then osteoarthritis patients, the cut off values used for elevated levels for both ESR and CRP. Some consider ESR>30 mm/hr as a better number for inclusion, therefore excluding some outliers.

Caswell (1993) study reveals that, the normal ESR also increases with age. The upper limit of normal for males, less than 50 years of age is 15 mm/hr, and for females, less than 50 years of age is 20 mm/hr.
2.3. Serum enzymes of Matrix metalloproteinases (MMP-3) and Matrix metalloproteinases (MMP-13) of Knee Osteoarthritis patients and controls

Enzymes are biological catalysts or assistants. Enzymes consist of various types of proteins that work to drive the chemical reaction required for a specific action or nutrient. Enzymes can either launch a reaction or speed it up. The chemicals that are transformed with the help of enzymes are called substrates. In the absence of enzymes, these chemicals are called reactants.

Benedetti et al. (2010) and Ahmad et al. (2009) studies reveals that, among various biological markers associated with Osteoarthritis, matrix metalloproteinases (MMPs) play a primary role in cartilage degradation in human joint disease and function downstream of OA signalling pathways.

Vincenti et al. (1994) the study shown that, matrix metalloproteinases (MMPs) play an important role in the degradation of the matrix in OA and rheumatoid arthritis (RA).

Beekman et al. (1996) the study highlights that, several methods have been used for detection of MMP activity in OA SF. These methods include enzyme-linked immunosorbent assay (ELISA), gelatin zymography, and Western blotting. ELISA has been frequently used for measurement of total amounts of pro-form MMPs plus MMP-TIMP complexes, where- as measurement of MMP in the active form is more appropriate in assessment of the potential of matrix degradation from MMPs. In terms of sensitivity gelatin zymography and Western blotting are superior in their detection of MMPs;
however, due to time-consuming and cumbersome practices, they are unsuitable for rapid high-throughput screening of larger samples.

Matrix metalloproteinases (MMPs)

Matrix metalloproteinases are a family of structurally-related, zinc-containing enzymes that have the ability to breakdown connective tissue. MMPs are a large family of calcium-dependent zinc-containing endopeptidases, which are responsible for the tissue remodeling and degradation of the extracellular matrix (ECM), including collagens, elastins, gelatin, matrix glycoproteins, and proteoglycan.

Martel-Pelletier et al. (2001) study that, MMPs are a family of functionally and structurally related zinc endopeptidases that cleave proteins of the extracellular matrix, including collagens, elastin, matrix glycoproteins and proteoglycans and are considered to be responsible for much of the degeneration of articular cartilage. Most of the MMPs are optimally active at neutral.

Nagase (1997) study reveals that, most MMPs are composed of three distinct domains: an amino-terminal propeptide involved in the maintenance of enzyme latency; a catalytic domain that binds zinc and calcium ions and a hemopexin-like domain that is located at the carboxy terminal zone of the protease and that plays a role in substrate binding. All MMPs are synthesized as preproenzymes and most of them are either secreted from the cell or bound to the plasma membrane in an inactive or proenzyme state. Several proteolytic cleavages are required to activate them and are critical steps leading to extracellular matrix breakdown.
Birkedal-Hansen et al. (1993) and Lee and Murphy (2004) studies found that, the human genome codes for 24 MMPs which can be classified depending on which components of the cartilage matrix they degrade.

Nagase and Woessner (1999) studies reveals that, the MMPs that are the most important in cartilage extracellular matrix degradation are the collagenases (MMP-1, -8 and -13), the stromelysins (MMP-3, -10 and -11) the gelatinases (MMP-2 and –9), matrilysin (MMP-7) and the membrane type MMPs, in particular MMP-14 which can also act as a collagenase. Matrix metalloproteinases (MMPs) comprise more than 20 proteinases, each of which is the product of a different gene, and some MMPs are produced abundantly by chondrocytes and synovial cells in arthritic joints (Table 2.2).

Yasuo Yoshihara (2000) the objective of the study is to stead state levels of different MMPs. The study found that, the levels of MMP-13 also seem to be higher in RA than in OA, as they were detectable in more than 45 per cent of the RA SF samples but measurable only in fewer than 20 per cent of the OA samples. MMP-3 is capable of not only degrading many cartilage ECM components such as aggregcan but also of activating other proMMPs.
Table 2.2: Classification of Matrix Metalloproteinase enzymes

<table>
<thead>
<tr>
<th>Sl. No.</th>
<th>MMP No.</th>
<th>Class</th>
<th>Enzyme</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>MMP-1</td>
<td>Collagenases</td>
<td>Collagenase-1</td>
</tr>
<tr>
<td>2.</td>
<td>MMP-8</td>
<td></td>
<td>Neutrophil collagenase</td>
</tr>
<tr>
<td>3.</td>
<td>MMP-13</td>
<td></td>
<td>Collagenase-3</td>
</tr>
<tr>
<td>4.</td>
<td>MMP-18</td>
<td></td>
<td>Collagenase-4</td>
</tr>
<tr>
<td>5.</td>
<td>MMP-2</td>
<td>Gelatinases</td>
<td>Gelatinase-A</td>
</tr>
<tr>
<td>6.</td>
<td>MMP-9</td>
<td></td>
<td>Gelatinases-B</td>
</tr>
<tr>
<td>7.</td>
<td>MMP-3</td>
<td>Stromelysins</td>
<td>Stromelysin-1</td>
</tr>
<tr>
<td>8.</td>
<td>MMP-10</td>
<td></td>
<td>Stromelysin-2</td>
</tr>
<tr>
<td>9.</td>
<td>MMP-11</td>
<td></td>
<td>Stromelysin-3</td>
</tr>
<tr>
<td>10.</td>
<td>MMP-27</td>
<td></td>
<td>Homology tostromelysin-2 (51.6%)</td>
</tr>
<tr>
<td>11.</td>
<td>MMP-7</td>
<td>Matrilysins</td>
<td>Matrilysin (PUMP)</td>
</tr>
<tr>
<td>12.</td>
<td>MMP-26</td>
<td></td>
<td>Matrilysin-2</td>
</tr>
<tr>
<td>13.</td>
<td>MMP-14</td>
<td>MT-MMP (membrane type)</td>
<td>MT1-MMP</td>
</tr>
<tr>
<td>14.</td>
<td>MMP-15</td>
<td></td>
<td>MT2-MMP</td>
</tr>
<tr>
<td>15.</td>
<td>MMP-16</td>
<td></td>
<td>MT3-MMP</td>
</tr>
<tr>
<td>16.</td>
<td>MMP-17</td>
<td></td>
<td>MT4-MMP</td>
</tr>
<tr>
<td>17.</td>
<td>MMP-24</td>
<td></td>
<td>MT5-MMP</td>
</tr>
<tr>
<td>18.</td>
<td>MMP-25</td>
<td></td>
<td>MT6-MMP</td>
</tr>
<tr>
<td>19.</td>
<td>MMP-12</td>
<td>Other enzymes</td>
<td>Macrophage metalloelastase</td>
</tr>
<tr>
<td>20.</td>
<td>MMP-19</td>
<td></td>
<td>RASI 1</td>
</tr>
<tr>
<td>21.</td>
<td>MMP-20</td>
<td></td>
<td>Enamelysin</td>
</tr>
<tr>
<td>22.</td>
<td>MMP-21</td>
<td></td>
<td>MMP identified on chromosome 1</td>
</tr>
<tr>
<td>23.</td>
<td>MMP-22</td>
<td></td>
<td>MMP identified on chromosome 1</td>
</tr>
<tr>
<td>24.</td>
<td>MMP-23</td>
<td></td>
<td>From human ovary cDNA</td>
</tr>
<tr>
<td>25.</td>
<td>MMP-28</td>
<td></td>
<td>Epilysin</td>
</tr>
<tr>
<td>26.</td>
<td>MMP-29</td>
<td></td>
<td>Unnamed</td>
</tr>
</tbody>
</table>

Source: Birkedal-Hansen et al. (1993) and Lee and Murphy (2004)

Kraus et al. (2011) and Rousseau et al. (2010) studies examined, selected biomarkers currently being investigated for the evaluation of Osteoarthritis biomarkers related to other non-collagenous proteins MMP-1, MMP-3, MMP-9, MMP-13 and TIMP.
Pelletier et al. (2010) study reveals that, in 161 patients with Knee Osteoarthritis showed that levels of the Matrix metalloproteinases of MMP-1 and MMP-3 were predictive of cartilage volume loss as evaluated by quantitative Magnetic Resonance Image (MRI) over 2 years (both P<0.05).

2.3.1. Matrix Metalloproteinase-3 (MMP-3) or (Stromelysin-1)

Okada et al. (1999) study reveals that the MMP-3, a proteoglycan degrading enzyme, can be localized to the zones of cartilage with active proteoglycan depletion.

Flannery et al. (1992) study highlights that, Stromelysin-1 can degrade aggrecan, denatured collagens and inter helical collagen domains, as well as aggrecan and link protein. Importantly, stromelysin-1 can cleave the aggrecan molecule at the MMP site, at the Asn341-Phe342 bond, to liberate the G1 domain from the remainder of the molecule.

Suzuki et al. (1990) study shown that stromelysin-1 can activate the pro forms of collagenases and that this activation is a key step in cartilage degradation.

Okada et al. (1992) study reveals that, Matrix metalloproteinase-3 (MMP-3 or stromelysin-1) capable of degrading cartilage proteoglycans and type IX collagen was immunolocalized in osteoarthritic and normal cartilage. In osteoarthritic cartilage, stromelysin-1 is localized in chondrocytes of the superficial and transition zone and its strongest mRNA expression is found in early degenerative articular cartilage.

Mehraban et al. (1998) the study indicating that, both cell types can produce stromelysin-1. It has been shown that in humans, the plasma level of stromelysin-1 was a significant predictor of joint space narrowing in knee osteoarthritis.
**Bassiouni et al. (2011)** reveals that, the aim of the study was to examine the relationship among three different parameters used to assess cartilage in Osteoarthritis (OA) of the knee. These parameters are Phonoarthrography (Phono-A), Musculoskeletal ultrasonography (MSUS) from the 4 condyles and biochemical marker: notably (MMP-3) and tissue inhabitor of proteinase (TIMP-1). The study results shows that Phono-A values were inversely correlated with cartilage thickness and mean levels of MMP-3 is elevated and continued to rise with increasing radiological grades until grade 4.

**Rego-Perez et al. (2011)** study conducted by Advance Knowledge of Osteoarthritis - the study shows that a significant influence of the haplogroups on the serum level of MMP-3 and MMP-13 was detected (p=0.027 and p=0.035 respectively) with OA with haplogroup H showed higher serum level of MMP-3 than healthy controls. The serum levels of MMP-13 were significantly higher in patients with Osteoarthritis.

**Heinaz Farouk Abdul et al. (2003)** study found that the serum concentrations of MMP-3 and MMP-9 were significantly higher in RA patients than in OA patients. The ELISA sandwich method technique was used to measure the serum concentrations of MMPs. The sensitivity (*limit of detection*) of the assay system was 2.35 ng/ml for MMP-3, 0.6 for MMP-9 and 1.25 ng/ml for TIMP-1. The samples were drawn from in the different age group; the ESR level is highly significant in all the 30 RA patients.

**Ari Kobayashi et al. (2007)** study found that, the levels of MMP-3 in serum samples were collected by venus puncture from 20 Osteoarthritis patients were measured by the 1-step sandwich enzyme immunoassay system. The serum samples were significantly
higher in rheumatoid arthritis than in Osteoarthritis and the levels correlated directly with each other.

2.3.2. Matrix metalloproteinase-13 (MMP-13) or (Collagenase-3)

Matrix metalloproteinase (MMP-13) is a major enzyme that targets cartilage for degradation.

Freije et al. (1994) the Collagenase-3 was first cloned from human breast carcinoma in 1994.

Reboul et al. (1996) study highlights; MMP-13 it is predominantly a product of chondrocytes.

Mitchell et al. (1996) study reveals that, MMP-13 has been shown to be expressed in human osteoarthritic cartilage.

Salminen et al. (2002) study shows that, subchondral bone and hyperplasic synovial membrane in an Osteoarthritis mouse model.

Gebauer et al. (2005); Vincenti and Brinckerhoff (2001) studies reveals that, Matrix metalloproteinase-13 expression is strongly induced by interleukin-1 (IL-1) an important proinflammatory cytokine encountered in Osteoarthritis.

Poole et al. (2001) study reveals that, Collagenase-3 degrades type II collagen preferentially, but also cleaves collagens type I, III, VII and X, aggrecan and gelatins.

Knauper et al. (1996) studies have shown that, MMP-13 can cleave type II collagen about 5 times faster than type I collagen and about 6 times faster than type III collagen.
Mitchell et al. (1996) study found that, type II collagen is its preferred substrate and because it can cleave type II collagen a least 5 to10 times faster than collagenase-1, collagenase-3 is considered to be one of the most important MMPs in Osteoarthritis.

Knauper et al. (1996) study reveals that, the collagenase with the most efficient gelatinolytic activity. Many different in vivo studies have shown the importance of MMP-13 in Osteoarthritis.

2.4. Summary

The outline of this chapter is review of literature on prevalence of Osteoarthritis especially Knee Osteoarthritis, inflammatory marker of ESR level in Knee Osteoarthritis patients and followed by serum enzymes of Matrix Metalloproteinase-3 (MMP-3) and Matrix Metalloproteinase-13 (MMP-13) in Knee Osteoarthritis patients and controls. The various studies outcome reveals that there is significant correlation between inflammatory markers of ESR on Knee Osteoarthritis patients. The Matrix Metalloproteinases are degrading enzymes. In Knee Osteoarthritis patients MMPs are one among the enzymes directed related to cartilage degradation.