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Systemic factors associated with temporomandibular joint disease in women

Author
Peikoff, Elana M.

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SYSTEMIC FACTORS ASSOCIATED WITH TEMPOROMANDIBULAR JOINT DISEASE IN WOMEN

by

ELANA M. PEIKOFF

THESIS

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SYSTEMIC FACTORS ASSOCIATED WITH TEMPOROMANDIBULAR JOINT DISEASE IN WOMEN

Elana M. Peikoff, D.M.D.

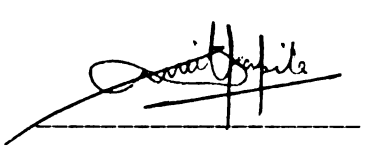
ABSTRACT

Temporomandibular joint disorders (TMD) is a spectrum of conditions which are associated with a wide range of clinical signs and symptoms involving the temporomandibular joint (TMJ) and muscles of mastication. Despite the debilitating nature of TMDs and a sex predilection as high as 10:1 in women, the etiology and pathogenesis of these diseases remain unknown. Their diagnosis therefore continues to be empirical and their treatment palliative. Because of the sex distribution and high incidence of TMDs in women between 16 and 45 years of age, some investigators have proposed a role of female hormones, particularly estrogen, in these disorders. However, little evidence to support this theory has been presented to date. Additionally, while it has been suggested that the hormone relaxin may be linked to increased systemic joint laxity (SJL), no study has been done to examine the potential association between joint disease, hormone levels and systemic hypermobility. The purpose of the present study was to identify systemic factors found in association with TMJ disease in women of child-bearing age. Specifically we compared the presence and severity of SJL and serum levels of β-estradiol and relaxin between women with symptomatic and asymptomatic TMJs.

Thirty-four symptomatic and 32 asymptomatic subjects were recruited for the study on the basis of predetermined criteria. Each of these groups were further subdivided into individuals utilizing or not utilizing oral contraceptives. Each subject was evaluated by a study protocol which included completion of a questionnaire, clinical and radiographic examination of the TMJ, assessment of systemic joint flexibility and quantitation of serum β-estradiol and relaxin levels. An objective TMJ diagnosis was derived from the clinical and radiographic TMJ findings into the categories of a) no disease, 2) positive history of TMJ disease, c) arthralgia,

d) osteoarthrosis and e) osteoarthritis. The quantitative findings on severity of TMJ disease, SJL and hormone levels were compared between the four groups of subjects by ANOVAs and Fisher's multiple comparison test with the significance level set at $P < 0.05$. Similarly findings on SJL and hormone levels were compared between asymptomatic individuals and subjects in the 4 TMJ diagnostic categories by the same statistical analysis.

As expected, most clinical and radiographic indices of TMJ disease were significantly higher in individuals with TMJ disease as compared with asymptomatic controls. Systemic flexibility was also found to be significantly higher in the symptomatic TMJ group. Within the symptomatic subjects, systemic joint laxity was significantly higher in the osteoarthritis group as compared to other TMJ disease categories or with asymptomatic controls. No significant differences were found in the levels of β-estradiol and relaxin in the symptomatic and asymptomatic groups. Evaluation of hormone levels in the different TMJ diagnostic categories revealed higher levels of β-estradiol and relaxin in the osteoarthritis group than in the other groups, although these differences were not statistically significant. This study demonstrates that individuals with TMJ diseases demonstrate increased systemic joint laxity, and suggests a potential association of systemic joint laxity and specific female hormones with TMJ diseases in women.



Thesis Advisor

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I. BACKGROUND, SIGNIFICANCE AND SPECIFIC AIMS

A. INTRODUCTION

Temporomandibular disorder (TMD) is a term encompassing a wide spectrum of diseases involving the temporomandibular joint (TMJ), muscles of mastication and associated structures. While the relative contribution of the muscles of mastication and the joint to TMDs remain unknown, in a substantial number of patients, TMDs result secondary to TMJ diseases. These include osteoarthritis, internal derangement and joint hypermobility (Westling et al., 1992; McNeill, 1993). Additionally, women, usually between the ages 18 and 45 years of age, comprise a significantly greater proportion of patients seeking treatment for TMDs. This unique sex and age distribution which may indicate that TMDs are linked to specific factors in women of child-bearing age. However, the etiology and pathogenesis of these diseases remain unknown.

From a clinicians perspective, patients experiencing an ongoing TMJ disease present with variable clinical findings, a cyclical nature of symptoms, and inconsistent skeletal and dental relationships, making these patients some of the most difficult to manage. This impacts on the ability of the clinician to provide optimal and timely treatment to patients with these arthropathies. Furthermore, current diagnostic procedures involving corrected tomograms or magnetic resonance imaging (MRI) (Helkimo, 1974; Raustia et al, 1994) provide important diagnostic information, but at best, detect the arthropathies at relatively advanced stages. From a preventive standpoint it would be extremely valuable to have the ability to recognize those individuals who are predisposed to TMDs. This requires an understanding of the etiology and pathogenesis of TMDs. However, at present, aside from trauma, no etiologies have been identified for non-rheumatoid diseases of the TMJ.

While the determination of causative factors remains elusive, the unique age and sex distribution of TMDs points towards some potential etiologic factors. In this case control study we examined the potential association between TMJ disease and systemic levels of the female hormones β-estradiol and relaxin. Furthermore, because of the higher predilection of systemic joint laxity (SJL) in women than in men and the potential association between SJL and relaxin levels, we evaluated if TMJ diseases are also associated with joint hypermobility. For a further clarification for the basis of these studies, this chapter provides insights into diseases of the TMJ, the prevalence and distribution of these diseases and the current diagnostic and therapeutic approaches for managing these conditions. This discussion is followed by an outline of the hypothesis, specific aims and significance of this study.

B. TEMPOROMANDIBULAR DISORDERS

TMD is a collective term encompassing a spectrum of clinical signs and symptoms involving the masticatory musculature, the temporomandibular joint (TMJ) and associated structures (reviewed in Clark and Solberg, 1987; McNeill, 1993). TMDs have been identified as a major source of non-dental pain in the orofacial region. In addition to complaints of pain, patients with these disorders frequently have limited or asymmetric mandibular movement and TMJ sounds including clicking, popping, grating and crepitus. While the relative contribution of the muscles of mastication and the temporomandibular joint to TMDs are variable, a substantial proportion of these disorders are related to diseases of the joint itself, which is the focus of our studies. These arthropathies of the TMJ include deviation in form, disc displacement with or without reduction, dislocation, inflammation, osteoarthrosis, osteoarthritis and ankylosis, as described in further detail below.

1. Deviation in Form

This condition involves a painless mechanical dysfunction due to developmental or acquired factors.

2. Disc Displacement

Articular disc displacement is the most common TMJ arthropathy and is characterized by several stages of clinical dysfunction involving the disc-condyle relationships. The usual direction for displacement of the disc is in an anterior or antero-medial direction (Isberg-Holm et al., 1982; Farrar et al., 1983). No agreement exists as to the causes of disc displacement. However, it is often thought to result from the stretching or tearing of ligaments which bind the disc to the condyle (Stegenga, 1991). Depending on the clinical presentation of this condition, disc displacement is subdivided into two categories, namely disc displacement with or without reduction.

i) *Disc displacement with reduction.* This disorder has been described as an abrupt alteration or interference of the disc-condyle structural relation during the translatory component of opening and closing of the mouth. The temporarily misaligned disc "reduces", or improves its structural relation with the condyle, producing a joint noise (click). It usually presents as "reciprocal clicking", whereby a noise is heard during the opening movement; and again in closing, just before the teeth occlude. Pain, if present, is precipitated by joint movement and usually occurs at the time of the disc reduction. Painful disc displacement with reduction is thought to be due to gross injury that results in stretching or tearing of the disc ligaments and / or capsule of the joint.

ii) *Disc displacement without reduction.* .In this disorder, the misalignment of the disc-condyle relation is maintained during mandibular translation. Thus, the disc is "non-reducing", or permanently displaced. In an acute stage, it is painful and

characterized by sudden limited jaw motion because of a jamming of the disc secondary to disc adhesion, deformation and / or dystrophy (Stegenga, 1989). Clinically, it is manifested as a straight-line deviation to the affected side on opening, a marked limited laterotrusion to the contralateral side and a lack of joint noise. In the chronic stage, the pain is markedly reduced and the opening range may approach normal values (McNeill et al., 1993).

3. TMJ Dislocation

TMJ dislocation or open-lock describes a condition in which the condyle is positioned anterior to the articular eminence and is unable to return to the closed position. Clinically, the individual is unable to close his or her jaws. The patient is only able to recover normal jaw function with manipulation by a clinician. There is usually a history of excessive range of motion that was not painful. Pain usually accompanies the dislocation and lingers for some time afterwards. Dislocation may result from 1) a physical jamming of the disc-condyle complex beyond the articular eminence; 2) a true hyperextension of the complex beyond its normal maximum translation position or 3) failure of the disc to rotate about the condyle during closure due to disc distortion and attachment elongation.

4. Inflammation and Arthralgia

Inflammatory conditions, including synovitis and capsulitis, usually occur secondary to trauma, irritation, or infection (Schule, 1986). Synovitis is described as an inflammation of the synovial lining of the TMJ. It is characterized by localized pain that is exacerbated by function and superior and / or posterior joint loading. This condition may be accompanied by swelling which decreases the ability to occlude on the ipsilateral posterior teeth. Capsulitis is an inflammation of the capsule related to sprain of capsular ligaments. Clinically, it is difficult to differentiate capsulitis from synovitis.

5. *Osteoarthrosis of the TMJ*

Osteoarthrosis (OAosis) is defined as a degenerative, non-inflammatory condition of the joint characterized by structural changes of the joint surfaces (DeBont et al., 1985). Clinically, it presents as a painless condition. It is often associated with crepitus, a limited range of motion and deviation to the affected side during opening (Rasmussen, 1981). Radiographic evidence of structural changes are evident only at later stages of the condition. It is believed that osteoarthrosis is due to a physiologic imbalance between the stress applied to a joint and the ability of soft tissue, cartilage and bone to withstand the stresses of loading (Bland et al., 1985).

6. *Osteoarthritis of the TMJ*

Osteoarthritis (OAitis) is a degenerative condition which is accompanied by secondary inflammation of the TMJ. The disease is usually slowly progressive, but may have remissions and cartilage regeneration characterized by deterioration of the articular cartilage and secondary bone formation. Clinical findings include point tenderness on palpation, crepitus, limited range of motion with deviation on opening to the affected side, and radiographic evidence of structural bony changes.

7. *Ankylosis of the TMJ*

Ankylosis is defined as a restricted mandibular movement with deviation to the affected side on opening that often results as a long-term sequel of trauma, including mandibular fracture.

While the classification above provides some level of structure to a complex spectrum of conditions, it should be emphasized that this categorization is entirely based on clinical and radiographic presentation of the disease and reflects little if any understanding of the etiology or pathogenesis of these conditions. In many instances, the categories described above may indeed reflect a continuum from milder to more severe forms of the disease and

indeed many of these states may occur together. Furthermore, most of these conditions reflect relatively advanced stages of the diseases, whereby it is impossible to recognize the etiologic agent. It is increasingly apparent that in order to better comprehend diseases of the TMJ, new and unique approaches need to be made on the basis of an understanding of the biology and the potentially diverse etiologies. Such an understanding will permit a more appropriate classification of TMJ diseases and will allow for specific and rational treatment approaches. While much information still needs to sought towards this end, some insights into the current prevalence patterns, concepts on pathogenesis and proposed etiologic factors provide directions for the present and future studies.

C. PREVALENCE, ETIOLOGY AND PATHOGENESIS OF TMJ DISEASES

1. Prevalence

Interpretation of the results of epidemiological and clinical studies on the prevalence of TMD are somewhat complicated by a lack of consistency in definition, data collection and analytic approaches. These studies also cover a spectrum of conditions and the prevalence of a specific TMDs, particularly those primarily involving the TMJ, are difficult to determine due to the lack of a universally accepted classification scheme and diagnostic criteria.

Cross-sectional studies of non-patient populations demonstrate that approximately 75% have at least one sign and 33% have at least one symptom of TMD (Rugh and Solberg, 1985; Schiffman and Fricton, 1988). Joint sounds or deviation on mouth opening occur in approximately 50% of healthy non-patient populations. Other signs are relatively rare (Huber and Hall, 1990). Signs and symptoms of TMD generally increase in frequency and severity beginning in the second decade of life (Agerberg et al., 1989; Salonen, 1990).

The majority of patients seeking treatment for TMD are between the ages 15 and 45 years of age (Howard, 1991).

2. Gender Distribution of TMDs

In 1824, Cooper observed that young women generally were subject to painful snapping and subluxation of the jaws. The preponderance of women in patient reports has since been striking (von Staplemohr, 1929; Schwartz and Cobin, 1957; Franks, 1964; Kruse, 1965; Perry, 1968; Carraro et al., 1969; Carlsson et al., 1982). More contemporary studies on non-patient populations found that women tend to have a greater incidence of individual symptoms such as headaches, TMJ clicking, TMJ tenderness and muscle tenderness (reviewed in Clark and Solberg, 1987; McNeill, 1993). Studies utilizing internal derangement as a specific diagnosis report a higher preponderance of this condition in women than in men (Burman and Sinberg, 1946; Foged, 1949; Christie, 1953; Isaacson et al., 1989; Wilkes, 1989). In patient population studies, the percentage of women seeking treatment is disproportionately greater than men, ranging anywhere in a ratio from 3:1 to 9:1 (Zarb and Thompson, 1970; Cohen, 1978; Solberg, 1982; McNeill, 1993). Patients not responsive to non-surgical treatment of the TMJ are almost exclusively women. A large proportion of these females are of child-bearing age, between 13 and 45 years (Carlsson et al., 1967; Isaacson et al., 1986). The reasons for these disparities in gender distribution remain unknown.

3. Proposed Etiologies

Aside from trauma, no universally recognized etiology has been identified for non-rheumatoid diseases of the TMJ. However, several theories on the potential etiologies, such as anatomic factors, psychosocial factors, pain threshold, systemic joint laxity, and endocrine factors have been proposed as outlined below. Of these theories on pain

threshold, systemic joint laxity and endocrine factors have also been used to explain the disparity in incidence of TMDs between males and females.

a. Anatomic factors

Anatomic factors comprise "maladaptive biomechanical factors that can be genetic, developmental, or iatrogenic in nature" (McNeill, 1993). Severe skeletal discrepancies, inter- and intra-arch discrepancies are included in this category. While still controversial, some dental professionals since the 1930's have viewed occlusion as playing a primary role in the etiology of TMD. The theory behind Costen's Syndrome is that abnormal condylar movement caused by the loss of posterior teeth and overclosure produces sensory irritation of branches of the auriculotemporal nerve when the condyle is pushed upward against an atrophic or perforated meniscus. However, studies have failed to show any significant relation between these variables (Whittaker et al., 1990). More recently, occlusal features such as working or non-working interferences and discrepancies between centric relation (CR/RCP) and centric occlusion (CO/ICP) have been suggested to be predisposing and / or perpetuating factors in TMDs. Again, the literature does not support these views (Hannam, 1977; DeLaat et al., 1986; Seligman, 1991). Extensive overbite was associated with joint sounds in one study (Runge et al., 1989), but these findings were not duplicated by other investigators (Roberts et al., 1987; Cachiotti et al., 1991). Similarly the association between excessive overjet and TMD was not been substantiated (Lieberman et al., 1985; Castaneda et al, 1989). Unilateral maxillary posterior lingual crossbite has been found to be more common in TMD patients (Seligman, 1991). Overall, studies to date suggest that occlusion is not likely to be of primary importance in the etiology of TMD, but may exacerbate symptoms once TMD has been established for other reasons.

b. Psychosocial Factors

There is evidence that some patients with TMD experience more anxiety than do healthy control groups (McCreary et al., 1991). Chronic TMD patients have been found to have psychosocial characteristics similar to patients with lower back pain and headache (Turk et al., 1990). However, a recent study found that TMD patients were not significantly different from other pain patients or healthy controls in personality type, attitudes toward health care, or ways of coping with stress (Schnurr et al., 1990).

c. Pain Threshold

It has been suggested that the incidence of TMDs is similar in men and women, but that women exhibit a lower threshold of pain and / or a higher reporting frequency (Dworkin, 1983). This theory has been challenged by other investigators, who demonstrated that women actually seek medical attention for painful conditions less frequently than men (Davis, 1981). Furthermore, autopsy studies indeed report a higher incidence of internal derangement and osteoarthrosis of the TMJs in females than in males (Solberg, 1982).

d. Systemic Joint Laxity

Another hypothesis is predicated on the fact that women tend to exhibit a higher incidence of SJL or joint hypermobility. Joint mobility may be described as the maximum range of motion in all directions for a given joint. The range of motion is determined by a variety of factors (Beighton et al., 1983; Hesse and Hanson, 1988). The main ones are the muscular tone, the laxity of the collagen that contributes to the joint capsule and surrounding structures, and the shape of the articulating surfaces. Biochemical diversities in collagen and elastin structure may account for the variation in laxity in a population. The tissues of patients with SJL exhibit lower quantities of type I collagen than normal joints (Child et al., 1984; Westling et al., 1992), indicating a possible structural and molecular basis for this phenomenon. Hypermobility Syndrome is a term referring to individuals with pronounced

systemic joint laxity. Studies have found that individuals with this syndrome have a high incidence of connective tissue defects, including valvular defects of the heart and varicose veins (Westling et al, 1993).

Clinically, joint laxity is characterized by increased distensibility of the joints in passive movements and by hypermobility in active movements. Joints which are unduly lax may be injured by minor degrees of trauma which would be harmless to joints of normal stability. These joints are therefore liable to develop traumatic synovitis which may later progress to osteoarthritis (Kirk et al., 1967; Bird et al., 1978; Grahame, 1981; Scott et al., 1979; Bird and Wright 1989; Finsterbush and Pogrund, 1982).

The prevalence of hypermobility in one or more joints is markedly higher in females than in males (Westling, 1992; Larsson et al., 1993; Pountain, 1992). Extreme laxity which was found only in females, was associated with increased joint symptoms in those aged 16-25 (Pountain, 1992). These findings may help explain the significantly higher clinical incidence of both TMJ internal derangement and osteoarthritis in women (Bates et al., 1984; Westling, 1992). It has also been shown that hypermobility develops in the peripheral joints of women during pregnancy. Increased levels of hormones, particularly relaxin, are thought to be responsible for such changes in laxity (Calguneri et al., 1982) as discussed later. Therefore, increased laxity in an already unstable TMJ capsule may impart a susceptibility to disease of the joint and, as indicated previously, an important manifestation of TMJ laxity is open dislocation (luxation).

e. Endocrine Factors

Because of the age and sex distribution of the signs and symptoms of TMD, it is logical that investigators have begun to study the potential role of female sex hormones in the etiology of these disorders. Estrogen is one hormone currently being investigated for its contribution to osteoarthritis of hips and knees. Recent studies have also focused on the presence of estrogen and its receptors in tissues of the TMJ (Aufdemorte et al., 1986;

Milam et al., 1987; Abubaker, 1991; Chander and Specter, 1991; Campbell et al., 1993). While one study found no correlation between internal derangement of the TMJ and the presence of estrogen receptors in the TMJ disc (Campbell et al., 1993), another reported high estrogen receptor levels in symptomatic females (Abubaker, 1991). In another study, oral contraceptive users were 19% more likely to seek TMD care than a control group not using oral contraceptives (LeResche et al., 1993). It is likely that hormones other than estrogen may be involved in these disorders. One likely candidate is relaxin, which is found systemically in fertile and pregnant women.

D. RELAXIN AND JOINT DISEASES

Relaxin is a 6 kDa polypeptide hormone which has the highest serum concentrations during the mid-luteal phase of the menstrual cycle and in the first trimester of pregnancy. Relaxin is produced by several organs and tissues, including the uterus, the corpus luteum and the breast of fertile non-pregnant and pregnant females. In males, this hormone has been localized in the prostate, but is not present in the circulation (reviewed in Bryant-Greenwood and Schwabe, 1994). Relaxin acts by endocrine, paracrine and autocrine modes in several known tissues, including the pelvic joint, where it increases mobility of the joint (Calguneri, 1985; MacLennan, 1991; Saugstad, 1991).

In humans, relaxin exists as two gene products, H1 and H2. Thus far, the only function ascribed to relaxin H1 is that of relaxation of smooth muscles (reviewed in Bryant-Greenwood and Schwabe, 1994). In contrast, relaxin H2 appears to have long-term effects on collagenous tissues by altering the turnover of collagen. This appears to be brought about by relaxin increasing the degradation and decreasing the synthesis of collagen in connective tissues (Unemori and Amento, 1990; Unemori et al., 1992; Unemori et al., 1993). In dermal fibroblasts, for example, relaxin stimulates the expression of

collagenase, a matrix-degrading enzyme belonging to the matrix metalloproteinase (MMP) family of proteinases (Unemori and Amento, 1990). A similar effect has been demonstrated in uterine cervical cells (Mushayandebvu and Rajabi, 1995). Relaxin also causes a concomitant decrease in the level of the inhibitor of these enzymes, the tissue inhibitor of metalloproteinases (TIMP), synthesized by these cells. Together, these events result in an increase in active collagenase which is likely to be accompanied by increased collagen degradation. Further alterations in tissue collagen are brought about by the inhibition of the synthesis of type I collagen by relaxin.

The findings of the mechanisms of relaxin H2 function on collagen turnover had until recently been demonstrated only in human dermal fibroblasts and uterine cervical cells. Current studies (Kapila et al., 1996) in our laboratory demonstrate for the first time that relaxin induces the expression of collagenase and stromelysin specifically in TMJ disc cells but not in synoviocytes, and that the expression of these MMPs are enhanced when disc cells are primed with β-estradiol. The potential link between relaxin and joint disease is further supported by findings demonstrating that pelvic joint instability is linked to relaxin oversecretion in some women (Saugstad, 1991). Although only a small increase in joint mobility is necessary for human parturition, some women experience great degrees of pelvic girdle relaxation during pregnancy (Calguneri et al., 1982, MacLennan, 1991, Saugstad, 1991), while others demonstrate a generalized increase in joint laxity, both of which have been linked to relaxin (Calguneri et al., 1982). The deliveries in this group of women are marked by a significant increase in congenital hip dysplasia. A similar finding has been reported in Labrador dogs (Goldsmith et al., 1994). Other data indicate that relaxin may have similar long-term effects in women which persist for years after delivery (Saugstad, 1991). One study evaluating biomechanical factors in low back pain in pregnant women found a strong correlation between peripheral joint laxity and an increase in abdominal diameter and stretch marks. These findings were attributed to "collagen insufficiency caused by the hormone relaxin..." (Ostgaard et al., 1993). A recent study

found that oral contraceptive use increases the levels of relaxin and estrogen throughout the cycle and the levels of relaxin correlated positively with symptoms of sacroiliac pain (Wreje et al, 1995). Despite the association of relaxin to these clinical events and to the induction of matrix degrading enzymes *in vitro*, direct evidence of the involvement of this hormone in joint pathology is still lacking.

E. CURRENT METHODS FOR THE DIAGNOSIS AND TREATMENT OF TMJ DISEASES

Because of a lack of understanding of the etiology of and pathogenesis of TMJ diseases, current diagnostic and treatment methods are both subjective and palliative. Clinically, diagnosis of TMJ disease is based upon findings during the clinical examination including the evaluation for the presence of tenderness to palpation, range of motion and joint noises. Additionally specific imaging techniques are often utilized to provide additional diagnostic information. Typically these imaging techniques include one or more of the following (Helkimo, 1974; Raustia, 1994): a) Panoramic films are used to screen gross bony pathology, b) corrected tomograms in the open and closed mouth positions are used to evaluate hard tissue morphology and joint mobility, c) magnetic resonance imaging help to evaluate integrity of the soft tissues, namely the disc, ligaments and capsule of the TMJ complex, and d) arthrography is used to further visualize joint morphology.

These clinical and imaging procedures frequently provide important diagnostic information, but at best detect the arthropathies at relatively advanced stages. Because of the limitation of current diagnostic techniques, there exists a need develop methods for early and accurate diagnosis of the disease processes in joints in general, and specifically for the TMJ. The palliative nature of current treatment approaches further attest to the lack of an understanding of diseases of the TMJ. The available treatment options are diverse and include conservative approaches, such as soft diet, intermediate treatments including

physical therapy, splint therapy and medications, and invasive therapies including arthroscopy, arthrocentesis, condylectomy and restoration of joints by implants. The appropriate treatment approaches for these conditions are currently a subject of substantial debate amongst clinicians and scientists alike (Sessle et al., 1995), and are likely to remain so until specific etiologic or pathogenic agents that cause TMJ diseases are identified.

F. HYPOTHESIS, SPECIFIC AIMS AND SIGNIFICANCE

On the basis of the sex and age distribution of TMJ diseases, we hypothesized the serum levels of relaxin and β-estradiol as well as systemic joint hypermobility are increased in individuals with TMJ disease as compared to asymptomatic controls. The specific aims of this study were to:

1. Determine and compare by objective and quantitative measures the presence and severity of clinical and radiographic TMJ disease in subjects with symptomatic and asymptomatic TMJs.
2. Evaluate and compare the magnitude of systemic joint laxity determined by an objective scoring criteria in subjects with symptomatic and asymptomatic TMJs.
3. Quantitate and compare the serum levels of relaxin and β-estradiol in individuals with and without TMJ disease.
4. Determine if subjects with asymptomatic TMJs and those with various TMJ diagnoses demonstrate differences in the severity of systemic joint laxity and serum levels of relaxin and β-estradiol.

The findings from these studies may provide insights into the etiology of diseases of the TMJ in women. If an association between levels of specific hormones and disease severity are indeed noted, the findings of this study could lead to the development of more accurate diagnosis and specific treatments addressing the underlying cause for this disorder than are

currently available. Similarly, since no equivalent studies have been performed on other joints, the knowledge gained from these studies may have important implications for pathologies in these joints. For the dentist, findings of this study could be used to provide a more accurate assessment of the status and prognosis of TMJ disease prior to commencing any treatment and may provide a biologically rational therapeutic basis for controlling the disease process before, during and after dental treatment. These studies will not only provide new information for TMJ pathology, but are likely to introduce new findings for diarthrodial joints in general.

II. MATERIALS AND METHODS

A. RECRUITMENT AND CRITERIA FOR INCLUSION OF SUBJECTS

All procedures for recruitment and investigation of subjects were performed according to established protocols for human research and following approval of the study by the Committee on Human Research at the University of California San Francisco.

Based on standard power analysis tables (Cohen, 1988), it was decided that the study would aim to include thirty-five subjects with positive history for TMJ symptoms as outlined below and thirty-five asymptomatic controls. Subjects were recruited by announcing the study via flyers posted throughout the Parnassus campus of the University of California San Francisco (Appendix 1). Those interested in participating in the study contacted the examiner by phone for an appointment to further establish their candidacy as a participant.

Both the asymptomatic and symptomatic subjects were required to satisfy specific criteria for inclusion in the study. These criteria included an age range between 13 and 45 years, absence of any systemic diseases, not be pregnant and have a regular menstrual cycle. Subjects were assigned to the symptomatic group if they satisfied one or more of the following additional criteria 1) present or previous history of localized TMJ pain with or without masticatory muscle pain, or 2) presence of TMJ disease as determined by the finding of disc displacement without reduction (closed-lock), or disc dislocation (open-lock). Individuals assigned to the asymptomatic group were those who had a negative history of known TMJ signs or symptoms, including significant clicks, pain and impairment of TMJ function.

A total of 72 individuals volunteered to participate in the study. Of these individuals, 1 subject was excluded because of a systemic illness and 5 subjects were excluded since they did not meet the criteria for either group. The final study population comprised of 34 subjects in the symptomatic category and thirty-two subjects in the asymptomatic control group. Once a subjects eligibility for participation in the study was established and all aspects of the study explained, both the patient and examiner signed a consent form (Appendix 2).

B. PATIENT EVALUATION AND DATA COLLECTION

Specific data required to address our hypothesis was derived from a patient questionnaire, a systemic hypermobility test, clinical and radiographic TMJ examination, and quantitative assessment of near-peak systemic levels of β-estradiol and relaxin. The pertinent information from the questionnaire included determination of potential local and systemic factors which could predispose to TMJ disease. The clinical and radiological evaluation of the TMJ provided a descriptive as well as a quantitative assessment of severity and classification of joint disease. A quantitative assessment of systemic hypermobility and serum levels of β-estradiol and relaxin were derived to determine if any relationship existed between these indices and TMJ disease. These findings were used to provide descriptive statistics about the sample and the measured variables and to determine by inferential statistics whether specific TMJ variables were associated with systemic hypermobility and hormone levels.

1. Questionnaire

Each subject completed a questionnaire (Appendix 3) which provided information on the subject's history of trauma, TMJ signs and symptoms, pertinent medical conditions and surgical treatment, psychological survey and demographics. Specific questions were

formatted to facilitate the quantification of data with possible responses being either a yes or no for medical history and demographics or delineated on a visual analog scale for TMJ history and psychological survey as described previously (Dworkin, 1992).

The questions relating to health history served to exclude individuals with systemic diseases or other variables which may bias the data. History of trauma may yield an insight into flexibility-related issues, such as are flexible individuals more prone to joint trauma and is a specific joint laxity measurement now impaired due to a previous traumatic event? The information on childbirth and pregnancies could be utilized to evaluate if these events contribute to present levels of hormones and to any association with TMJ disease. Subjects were also asked to assign a grade to presence of pain in their lower back on a scale of 0 to 3. The psychological survey was intended to allow for future correlation of comprehensive TMJ diagnosis, hormonal levels and impact of psychological factors on TMJ impairment and was not utilized in the present study. Demographic information could yield insight into the distribution of TMJ disease in various populations for future studies.

2. Clinical TMJ Examination

The clinical assessment of the TMJ were performed by a single examiner and followed the standard format utilized at the Center for Temporomandibular Disorders and Orofacial Pain at the University of California San Francisco. The clinical assessment included determination of joint pain, range of motion, joint noises and muscle examination.

Location and severity of pain was graded by the participant while being subjected to the following procedures: preauricular palpation, intraauricular palpation, jaw opening, retrusive loading and superior loading. For location, pain in any particular region was ranked by the subject as 0 (absent); L (left side only); R (right side only) or B (bilateral). Pain severity was quantified by the patient as 0 (absent); 1 (mild); 2 (moderate) and 3 (severe which produces a provoked response to the manipulation). Because of the limited reproducibility of score 1 and to exclude false positives, this score was assigned as absence

of pain for subsequent analysis. Therefore, the equivalent of the subject score with the modified examiner assigned scores was as follows:

Participant grading	Modified Score
0 or 1	0
2	1
3	2

Since 5 procedures were used to determine the pain levels, this method of scoring provided for a total maximum score of 10 for pain in each TMJ.

Range of motion was measured in millimeters with a disposable Therabite Gauge (MDC Inc.). Measurements included both active and passive jaw opening and lateral excursions. Passive measurements were used for data tabulation. Since laterotrusion was a parameter used for determination of TMJ hypermobility, the larger value from the two joints was used for further analysis.

Presence of joint noises was evaluated with a two-way stethoscope. To discern sounds from a single TMJ, the rubber tubing on the stethoscope from the contralateral joint was obstructed. Clicking in each joint was recorded during opening and closing as reproducible or non-reproducible and early or late. Evidence of crepitus was also noted.

Other variables documented in the clinical examination for use in future studies included overjet, overbite, evidence of dental wear and history of orthodontics and/or dental extractions.

3. Systemic Hypermobility Examination and Scoring

The methods used for measurement of joint laxity are based on those developed by Beighton and Horan (1969). The clinical exam is performed to bilaterally measure the flexibility of the wrist and the range of motion of three joints, namely the fifth digit, elbow, and knee. The range of motion or the total amount of motion of the latter 3 joints is measured with a goniometer (Fig. 1). These measurements are obtained by placing the two arms of the goniometer along the proximal and distal bones adjacent to the joint under

consideration. The starting position for measuring the range of motion is the anatomic position. In this position, the upper and lower extremity joints equal zero degrees for flexion or extension. The portion of the flexion and extension range of motion available beyond zero degrees is then recorded as degrees of hypermobility by the goniometer. Flexion and extension of the upper and lower extremities occur in the sagittal plane around a coronal axis.

The range of motion is affected by age, sex and other factors, including the type of motion being performed. The active range of motion is the measurement recorded when the subject performs the joint motion without the assistance of the examiner. The passive range of motion is the amount of motion recorded without the help of the subject. Usually the passive range of motion is greater than the active range of motion. In this study, the measurements for passive range of motion were recorded.

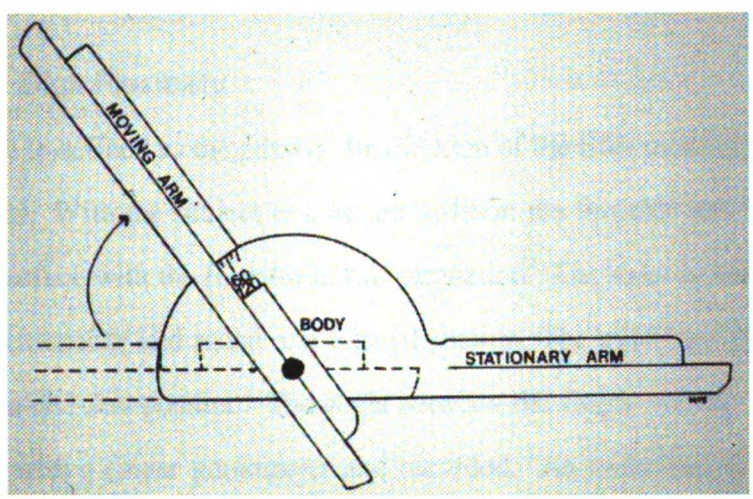

Figure 1: Diagram of goniometer used for measuring joint flexibility. (Reprinted from Antoniotto and Rocabado, 1990).

The extent of the passive range of motion is determined by the structure of the joint being tested. In some joints, the capsule limits movement in a particular direction, while in others, ligaments, muscle or contact with joint surfaces may limit range of motion. The structure will impart a resistance to further motion, which is detected by the examiner as the end-feel. In this study, joint angulations were assessed using a small goniometer for the fifth digit and a large goniometer for the elbows and knees (MDC, Inc.). The details of flexibility testing for each of the joints as well as determination of total systemic flexibility are described below:

a. Wrist Flexibility

This measure is derived by evaluating passive opposition of the thumb to the flexor aspect of the forearm (Fig. 2a). This assessment is the only one of the four measurements made without the goniometer. The patient sits with the shoulder abducted ninety degrees and the elbow flexed ninety degrees. The elbow rests on the arm-rest of the chair. The examiner pushes the thumb toward the wrist to its firm end-feel. If the thumb can passively touch the flexor aspect of the forearm the wrist is considered to be hypermobile and given a score of 1. When the thumb does not contact the flexor surface of the forearm the flexibility is considered normal and given a score of 0.

b. Fifth Digit Flexibility

This measure is defined as the passive dorsiflexion of the fifth metacarpophalangeal (MCP) joint (Fig. 2b). With the subject in a seated position the forearm and hand are rested on a supporting surface with the forearm in full supination. The wrist is held at zero degrees of flexion and extension and radial and ulnar deviation. The examiner pushes the fifth digit dorsally to its end-feel position. The angle between the finger and the dorsum of the hand is measured with a finger goniometer and recorded. An individual is considered to have excessive flexibility in the fifth digit when this finger can be passively dorsiflexed to an angle of 90 degrees or less. An angle of greater than 90 degrees is considered to have

normal mobility and given a score of 0. For deriving means for comparisons of fifth digit flexibility with other factors, the angle of the more flexible digit between the right and left sides was utilized.

c. Elbow Flexibility

Elbow flexibility is determined by the ability of the elbows to hyperextend (Fig. 2c). The patient is positioned with the shoulder in zero degrees of rotation and abduction and ninety degrees of extension. The wrist is in the flexed position. Landmarks utilized in this parameter are the styloid of the radius, the lateral epicondyle of the humerus and the acromion. Using the large goniometer, the joint is held at the styloid of the radius. The two legs of the goniometer are extended toward the lateral epicondyle of the humerus distally, and the acromion proximally. The angle beyond 0 degrees is recorded. An angle greater than or equal to 10 degrees is considered hypermobile. An angle of less than 10 degrees demonstrates normal flexibility. These measurements were performed bilaterally, and the larger reading of the two measurements from the right and left sides was used for comparison of elbow flexibility with other factors.

d. Knee Flexibility

Knee flexibility is measured by the determining the magnitude of hyperextension of the knees (Fig. 2d). This measurement is made with the patient standing up and with the shoes off. The hip is placed in zero degrees of abduction, adduction, flexion, extension and rotation. With the assistance of the examiner, the patient is instructed to "push the knees back" to the firm end-feel. The angle is measured placing the joint of the goniometer on the lateral epicondyle of the femur, with the legs of the goniometer extending toward the lateral malleollus distally, and the greater trocanter proximally. The scoring for this joint is similar to that used for the elbow joint. The values from each individual's right and left

sides were recorded and the higher of the two values used for comparisons with other factors.

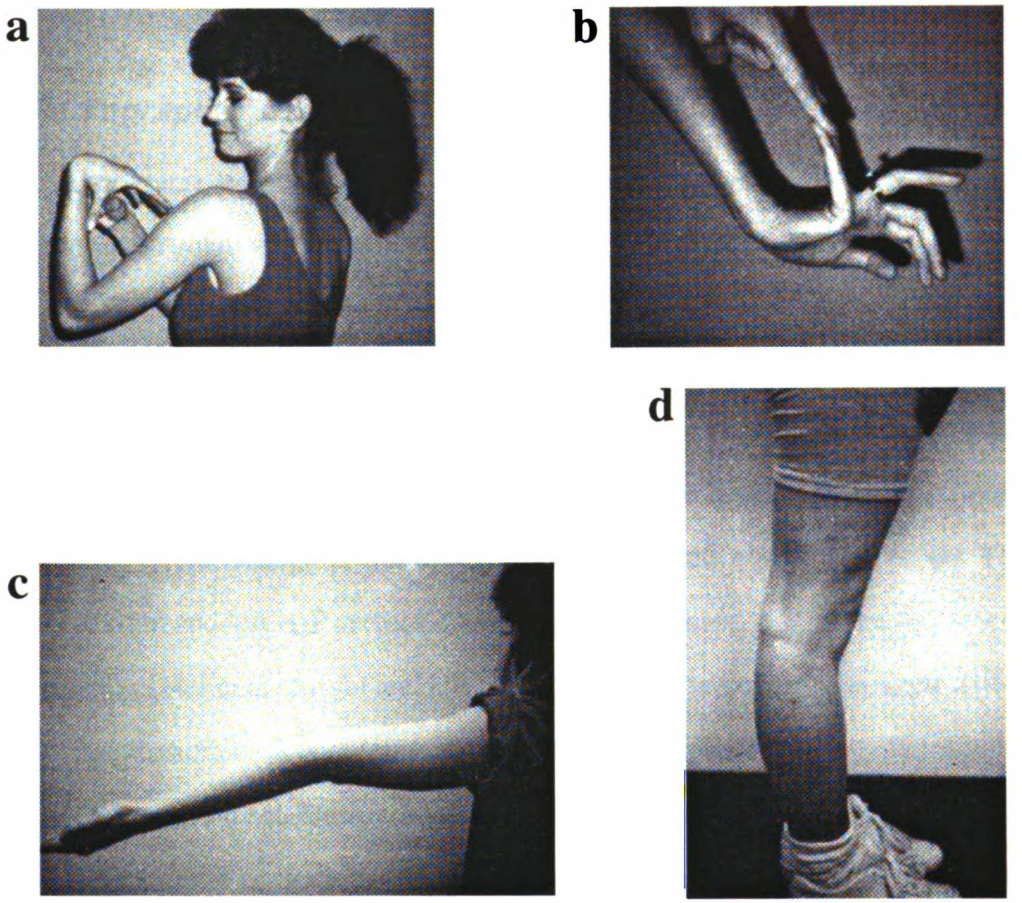

Figure 2: Technique for determination of systemic joint laxity involved assessment of wrist flexibility by passive opposition of the thumb to the flexor aspect of the forearm (a), fifth digit flexibility by passive dorsiflexion of this digit to an angle of 90 degrees (b), elbow flexibility by hyperextension of the elbow beyond 10 degrees (c), and knee flexibility by hyperextension of the knee beyond 10 degrees. (Adapted from Antoniotto and Rocabado, 1990).

e. Total Flexibility Score

A total flexibility score was derived by assigning each of the 4 joints bilaterally a score of 0 if it demonstrated normal mobility or a score of 1 if demonstrated hypermobility. The assignment of these flexibility scores to individual joints provided a total flexibility score ranging from 0 to 8 for an individual.

4. Radiographic Evaluation of the TMJ

The TMJ tomograms were used for radiographic quantitation of TMJ disease and for assessing condylar rotation.

a. Radiographic Quantitation of TMJ Disease

A standard set of diagnostic radiographs considered to provide sufficient diagnostic information for the purposes of the study were taken for each subject. This set consisted of: a) submentovertex radiograph used for making corrected tomograms of the TMJ, b) center cuts of right and left A-P corrected tomograms in a closed and protruded mandibular position, and c) center cuts of right and left lateral corrected tomograms in open and closed position of the mandible. Tomograms were taken with the head of the subject parallel to Frankfort-Horizontal Plane. During imaging of the condyle in the open position, subjects were instructed to open as wide as possible, despite temporary discomfort. Interpretation of images was performed by three examiners, utilizing a single-blinded design. The examiners were calibrated and inter- and intra- examiner reliability was established using a random sample of radiographs from ten subjects.

The tomograms were scored for condylar flattening, condylar erosion and osteophyte formation on a scale of 0 to 3 by each examiner. Each examiner independently scored for

the three radiographic TMJ criteria with a total maximum score of 9 for each TMJ. Descriptions utilized the above radiographic observation were as follows:

i. *Condylar flattening:* The normal anatomy of a condyle has a rounded outline in radiographic form (Fig. 3a). Flattening is evident when an articulating surface of a condyle is not rounded, but congruent with its opposing surface on the fossa or eminence (Fig. 3b). A condyle is diagnosed with flattening when detected on two or more tomographic projections.

ii. *Condylar erosion (Fig. 3c):* Unlike the smooth cortical surface of an intact condyle, a condyle with erosion has concave interruptions in the cortical surfaces.

iii. *Osteophytes (Fig. 3d):* An osteophyte is an osseous projection of dense cortical bone, most commonly projecting from the anterior portion of the articulating surface of the condyle. An osteophyte must, by definition, increase the articulating surface area of the condyle.

For purposes of subsequent statistical analyses, the radiographic TMJ disease score assigned to a given subject was the larger of the scores from the two TMJs since this was considered to reflect the potential net severity of TMJ disease for the particular individual. The total score assigned for radiographic TMJ disease from the cumulative score of the 3 examiners was derived on the basis following grading system:

Cumulative Score /9	Assigned Score
0,1,2	0
3,4	1
5,6,7	2
8,9	3

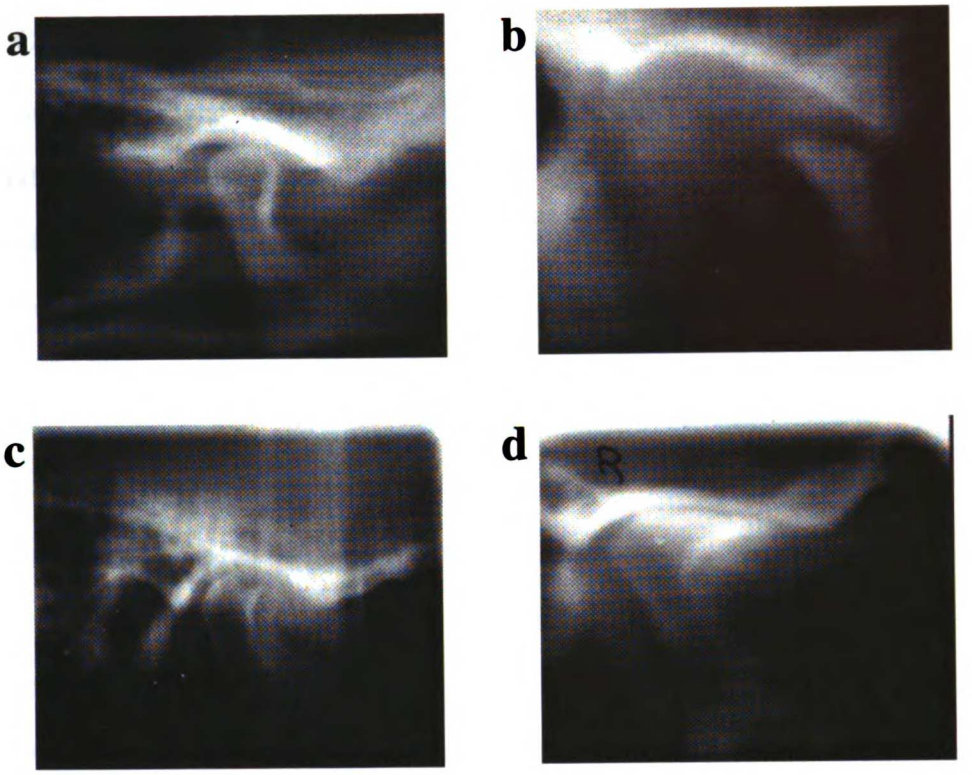

Figure 3: Sagittal images on corrected tomograms demonstrating a normal TMJ (a), condylar flattening (b), condylar erosion (c) and osteophyte formation.

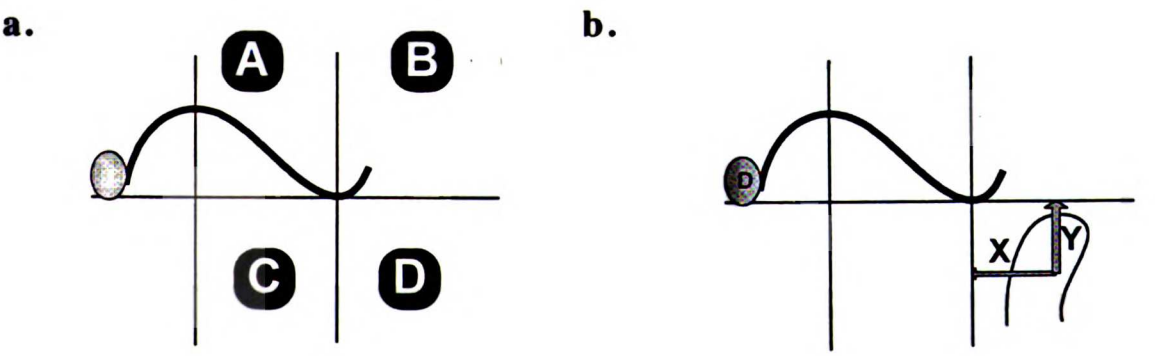

Figure 4: Schematic representation of technique used to measure condylar rotation. Tracings depict construction of horizontal and vertical lines (a) and measurement of movements along X and Y axis (b).

b. Condylar Rotation

The amount of condylar rotation from the closed to the open position in each joint was evaluated on lateral corrected tomograms taken in open and closed positions using the following standardized protocol. A piece of acetate tracing paper was taped into place over the condyle in the closed position. The condyle, the fossa, the eminence and structures visible in the cranium were traced using a 0.5 mm lead pencil. Two horizontal lines were then drawn parallel to the bottom of the frame, tangent to the height of the fossa (line A) and the crest of the eminence (line B) (Fig. 4a). A vertical line, parallel to the side of the frame was also drawn at the depth of the fossa (line C). A second square of acetate paper was then taped on top of the first one. The condyle and constructed lines were transferred onto the second piece of acetate. Both pieces of acetate were then removed from the image of the condyle in the closed position. Next, the first piece of acetate was superimposed onto the image of the condyle in the open position using the best fit of the fossa and cranial structures. The second piece was also superimposed onto this image using the best fit of the condylar head and neck (Fig. 4b). The eminence and a vertical line through it (line D) was then drawn and the resultant angle between the two vertical lines, C and D on the two tracings was measured to represent the condylar rotation during opening.

5. Further Classification and Assessment of TMJ Status

Besides providing the descriptive and quantitative assessment of TMJ disease, the clinical and radiographic assessments of the joint were used for a composite assessment of TMJ hypermobility and for classifying joint disease.

a. Hypermobility of the TMJ

The mobility of the TMJs was determined clinically. The vertical depression of the mandible was recorded with a Therabite gauge indicating the millimeter distance between the upper and lower incisors. Both active and passive measurements were obtained. For

transverse measurements, the patient was asked to slide the mandible to one side as far as possible and the linear distance between the upper and lower incisors was documented. The procedure was then repeated to the opposite side.

b) TMJ Diagnosis

Since TMJ disease in our study incorporates a broad description and because this spectrum of conditions is likely to have varied etiopathogenesis in different subjects, individuals were further classified into subsets on the basis of specific radiographic and clinical findings. A composite and objective TMJ diagnosis was assigned to each subject based on findings from both the clinical examination and the radiographic evaluation. These diagnoses were made on the basis of the criteria outlined below.

a) No TMJ disease: No reported history and no radiographic or clinical signs or symptoms of TMJ disease.

b) Previous history of TMJ disease: The individual is currently free of radiographic changes or pain in the TMJ but had a previous positive history of pain and / or locking of the TMJs.

c) Arthralgia: The subject presents with painful right and / or left TMJs with a modified pain score equal to or greater than 2.

d) Osteoarthrosis: The individual presents with a modified pain score of < or = 1 in the TMJ, but demonstrates any one or more of the following scores on radiographic condylar changes: flattening > or = 2; erosions > or = 2; osteophytes > or = 2.

e) Osteoarthritis: A subject demonstrating a modified pain score of > or = 2, in addition to radiographic condylar changes consistent with the above definition of osteoarthrosis.

6. *Phlebotomy and Processing of Serum*

Because the levels of relaxin and β-estradiol vary substantially during the menstrual cycle, it was necessary to predetermine a specific time-point in the cycle to assay for these hormones. We chose to evaluate the hormone levels on day 24 (± 1 day) of the menstrual cycle (Bryant-Greenwood et al., 1994 Wreje et al., 1995) where day 1 corresponds to the onset of menstrual bleeding, since the levels of relaxin and β-estradiol are approximately at their peak levels at this time of the cycle. Since some patients reported an irregular cycle adjustments were made to most closely approximate the appropriate day of the cycle.

Ten milliliters of blood were drawn from each subject by a single phlebotomist in the Oral Medicine Clinic at University of California San Francisco. The blood was collected into a serum separating tube and immediately centrifuged at 1000 g. The serum supernatant was separated from the cells and stored at -70 degrees Celsius (Johnson et al., 1993) for later analysis for β-estradiol and relaxin levels as described below.

Since oral contraceptive use substantially affects the levels of systemic β-estradiol and relaxin (Wreje et al., 1995) and because several of the study participants were taking oral contraceptives, additional information was obtained on the precise quantity and formulation of estradiol and progesterone in each subject's prescription. Furthermore, the use of oral contraceptives added an additional variable to the study population necessitating the further classification of groups into asymptomatic controls and symptomatic subjects not taking birth control pills (AN and SN, respectively), and asymptomatic and symptomatic subjects taking birth control pills (AB and SB, respectively).

C. QUANTIFICATION OF RELAXIN AND β-ESTRADIOL

1. ELISA for Relaxin

An enzyme-linked immunosorbent assay (ELISA) for relaxin (kindly provided by Connective Therapeutics Inc., Palo Alto) was utilized to quantify relaxin levels in the blood samples. All buffers and diluents were prepared fresh prior to testing. Four microtiter 96-well plates were coated with 100 µl of rabbit anti-human relaxin antibody diluted 1:1500 in coating buffer (0.05 M sodium carbonate, pH 9.6). The plates were incubated at 2 degrees Celsius for 24 hours and then washed 4 times for 2 minutes each in wash buffer (PBS with 0.05% Polysorbate 20). Three hundred µl of buffer diluent (PBS with 0.5% BSA, 0.05% Polysorbate 20, 0.01% thimerosal) were pipetted into each well and agitated at room temperature for 2 hours. After a single washing, 100 µl per well of diluted standards (0 to 625 pg/ml) prepared in serum diluent (pooled normal male serum with 0.01% thimerosol) or samples were pipetted in triplicate into each well. The plates were incubated at 2 degrees Celsius for 24 hours and then washed 4 times as described above. Each well was then incubated with 100 µl of signaling (diluted 1:250 in buffer diluent) anti-relaxin antibody conjugated to horseradish for 4 hours. Each well was washed as before and incubated with 100 µl of substrate solution (3,3',5,5' - tetramethylbenzidine; TMB Microwell Peroxidase, KPL, Gaithesburg, MD) for 20 minutes. The reaction was stopped with 100 µl of 0.18 M sulfuric acid and the optical density read at 450 nm.

2. RIA for β-Estradiol

Radioimmunoassays were used to quantify the systemic levels of b-Estradiol using a commercially available kit (Pantex Extraction I-125 Estradiol; Santa Monica, CA.) according to the manufacturers instruction. Briefly, the protocol involves a double

antibody assay for β-estradiol. The RIA for β-estradiol was performed in the Department of Reproductive Endocrinology at UCSF.

D. STATISTICAL METHODS

Thirty-four symptomatic and thirty-two asymptomatic subjects were included in the study on the basis of a standard power analysis table (Cohen, 1988). The groups were further sub-divided, as mentioned above, according to oral contraceptive status. This resulted in an uneven division within the symptomatic group, with the number of those taking oral contraceptives adding up to only 9.

1. Error of Method

The method of error of the examiner was tested to verify the reliability of the measurements made. The examiner performed three repeated examinations of the TMJ and hypermobility tests on ten subjects, each done at least 1 week apart three times each. The values were subjected analysis by intra-class coefficient which provided an r-value for each variable. The results presented in Table I show a high degree of reliability of the measurements.

Table I: Intraclass correlation coefficients for measured TMJ and Flexibility variables.

	Variable	Intra-Class Coefficient (r-value)
TMJ EXAM	Passive TMJ opening	0.96
	Laterotrusion	0.94
JOINT LAXITY	Wrist	0.96
	Fifth Digit	0.94
	Elbow	0.90
	Knee	0.88

2. *Statistical Analysis*

All statistical evaluation were performed with the guidance of Dr. John Neuhaus, Department of Biostatistics, UCSF. Analysis of Variance (ANOVA) using the Fisher's multiple comparisons test set at a 95% level of confidence were performed on all quantitative data to provide information about specific differences between the four subgroups SB, SN, AB and AN of subjects. These comparisons were made from data obtained from the questionnaire, clinical and radiographic TMJ exam, joint laxity and hormonal levels. Data from the questionnaire which was compared using ANOVAs included the patients age and degree of low back pain. It was necessary to compare the mean ages of each group in order to determine whether the sample populations in the four groups were age-matched. Back pain was compared between the groups since a recent study (Wreje et al., 1995) found a correlation between low back (sacroiliac) pain and increased serum levels of relaxin. Data obtained from the TMJ exam which were evaluated by ANOVAs included joint pain and vertical and lateral range of motion. Similarly, comparisons between the four groups were also made for radiographic signs of flattening, erosions and osteophytes and TMJ rotation. Comparisons were also made between the four groups for joint flexibility for the fifth digit, elbow, knee and total flexibility score using ANOVAs.

Since the symptomatic individuals are likely a heterogeneous population with regard to disease status, these subjects were further divided into 4 categories of disease state on the basis of objective clinical and radiographic findings. In order to determine whether the systemic flexibility levels or hormonal levels differed between the 4 groups and the asymptomatic controls, ANOVA with the Fisher's test were performed as described above.

III. RESULTS

In this study we compared specific systemic factors of joint flexibility and serum hormone levels between individuals with TMJ disease and asymptomatic controls. Descriptive and inferential statistics demonstrated important differences between the two groups of subjects. Below we present findings on study population profile and information obtained from questionnaires, clinical and radiographic examinations and hormone assays on sera from the subjects in this study.

A. PROFILE OF STUDY POPULATION

The study comprised a total of 66 patients, 34 with symptomatic (S) TMJs and 32 with asymptomatic (A) TMJs. Of the symptomatic group, 9 subjects were using oral contraceptives (B), while the remaining 25 were not (N) (Table II). In the asymptomatic group, 14 of the 32 participants were taking oral contraceptives. The mean ages of the subjects were not significantly different between the four groups as revealed by ANOVA (P = 0.99) (Fig. 5). The overall ages of study population ranged from 14.25 to 51.58 years. All participants involved in the study were experiencing normal menarche.

Table II: Number of subjects, mean age (± S.D.) and age range in each group of the study population.

Group	Oral Contraceptive Use	Numbers (N)	Age (years) Mean	S.D.	Range
Symptomatic (S)	BCP (B)	9	28.58	8.95	20.08-47.33
	No BCP (N)	25	29.47	7.96	14.25-51.58
Asymptomatic (A)	BCP (B)	14	28.96	5.53	22.42-41.33
	No BCP (N)	18	28.88	5.43	22.33-40.42

(BCP = Birth control pill)

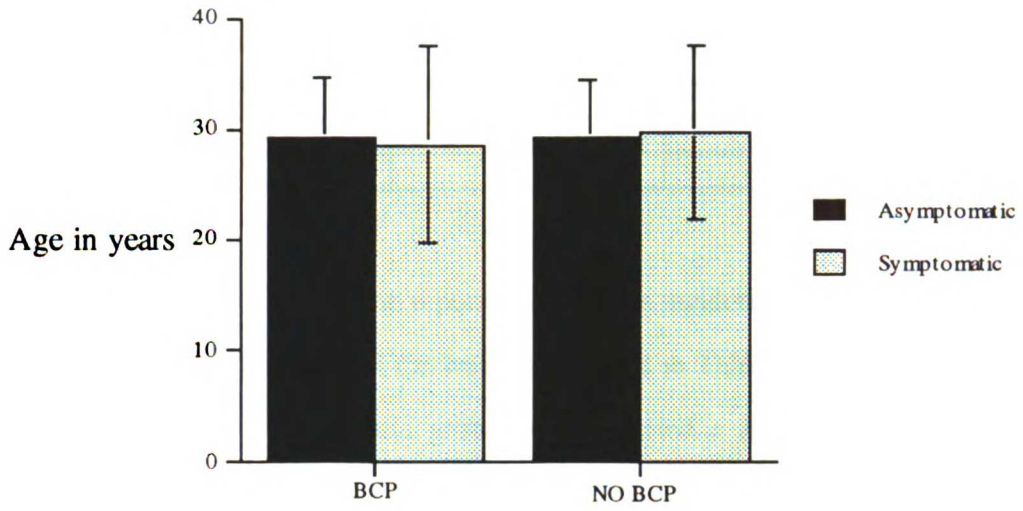

Figure 5: Histograms of mean (± S.D.) age of individuals in the 4 groups.

The patient questionnaire provided additional information regarding the number of childbirths, history of TMJ disease, low back pain and types of oral contraceptive drugs used. Overall, six patients in the study reported at least one successful childbirth (Table IV). There were a total of three childbirths in the symptomatic group and three in the asymptomatic group. The number of reported pregnancies not carried to term was substantially higher in all groups than the number of reported childbirths. The number of individuals per group reporting pregnancy and the number of pregnancies are presented in Table III.

Table III: Numbers and percentage of subjects in each group reporting pregnancies.

Group	Number of individuals reporting pregnancy (5)	Number of pregnancies
SB	3/9 (33.3)	3
SN	11/25 (44)	20
AB	3/14 (21.4)	7
AN	2/18 (11.1)	2

Table IV: Summary of pertinent information retrieved from questionnaire.

Group	Childbirths Number (%)	% Subjects with History of Jaw Locking	Low Back Pain	
			% Subjects	Mean Score (S.D.)
SB	0/9 (0)	88.89%	66.67%	1.33 (1.12)
SN	3/25 (12.0)	88%	68%	1.04 (.98)
AB	1/14 (7.14)	7.14	7.14%	.07 (.27)
AN	2/18 (11.1)	0%	44.4%	.44 (.51)

The percentage of patients who reported a previous incident of "locking in the jaw joint so that it won't open or close all the way" is outlined in Table IV. The combined percent of individuals in the symptomatic group who reported a positive history of locking was 88.24% (SB = 88.89%; SN = 88%), as compared to 3.12% (AB = 7.14; AN = 0%) in the asymptomatic controls.

We also evaluated the subjects responses to an inquiry on lower back pain (Fig. 6) on a scale of 0 to 3 since higher levels of relaxin have been found in patients with sacroiliac pain (Wreje et al, 1995). The proportion of subjects that assigned a score of 2 or greater for lower back pain were 66.67% in the SB group and 68% in the SN group, which were substantially greater than the 7.14% and 44.4% of individuals in the AB and AN groups, respectively, reporting of lower back pain. Furthermore the mean lower back pain was significantly greater in the SB than in the AB group ($P < 0.001$) and in the SN versus the AN group ($P < 0.05$) as determined by ANOVA. No significant differences in the mean lower back pain scores were observed between the two symptomatic groups ($P = 0.341$) or the two asymptomatic groups ($P = 0.188$).

Each of the subjects on oral contraceptives utilized one of 6 different medications (Table V). The common active ingredient in all these drugs is ethinyl estradiol, which has the effect of inhibiting endogenous estradiol, while itself not being biologically active in inducing ovulation.

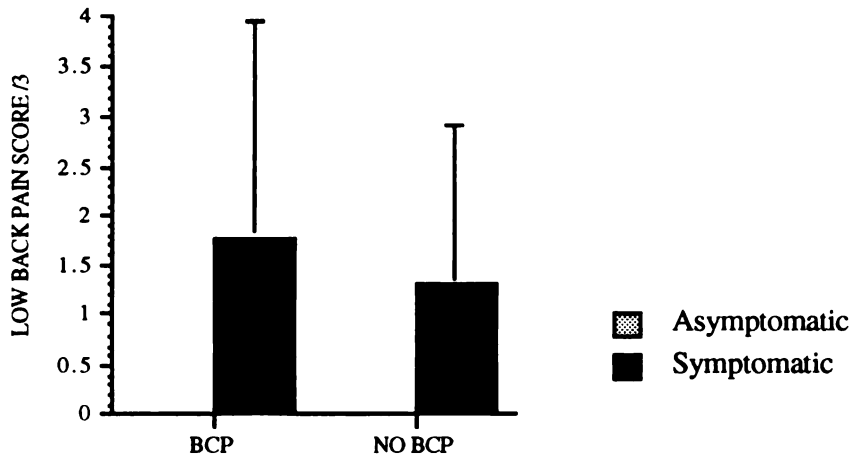

Figure 6: Histogram of mean (+ S.D.) low back pain score in the four subgroups.

Table V: Numbers of subjects in the SB and AB groups using different oral contraceptives and the active ingredients in each of these drugs.

Oral Contraceptive	Number of Subjects (N)		Active Ingredients	
	SB (9)	AB (14)	Estradiol	Progestin / Other
Demulen	0	4	ethinyl estradiol, 0.035 mg.	ethynodiol diacetate, 1 mg.
Modicon	0	1	ethinyl estradiol, 0.035 mg.	norethindrone, 0.5 mg
Ortho 777	3	6	ethinyl estradiol, 0.035 mg.	norethindrone, .5;.75;1 mg
Orthocept	1	0	ethinyl estradiol, 0.030 mg.	desogestrel, 0.15 mg.
Orthocyclen	1	1	ethinyl estradiol, 0.035 mg.	norgestimate, 0.15 mg.
Triphasil	4	2	ethinyl estradiol, 0.035 mg.	norethindrone, .5;.75;1 mg

B. CLINICAL TMJ FINDINGS

The clinical TMJ examination involved the determination of severity of pain and its location in the TMJ and surrounding structures, range of motion and joint sounds. The mean TMJ pain score out of a maximum possible of 10 was 1.78 for the SB group followed by 1.32 for the SN group (Fig. 7). These values compared with a mean pain score of 0 for both asymptomatic groups which resulted in a statistically significant difference between the SB-AB groups (P = 0.0016) and the SN-AN groups (P = 0.0013) (Table IV). Assessment of

the range of motion measured as passive opening and larger of the laterotrusive movements of the two TMJs revealed no significant differences between the 4 groups (Fig. 8a and b).

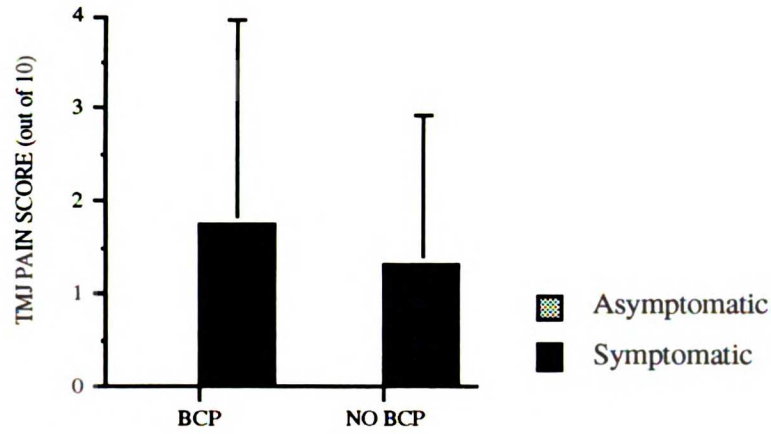

Figure 7: Histograms for mean (± S.D.) TMJ pain score reported by subjects in the four subgroups.

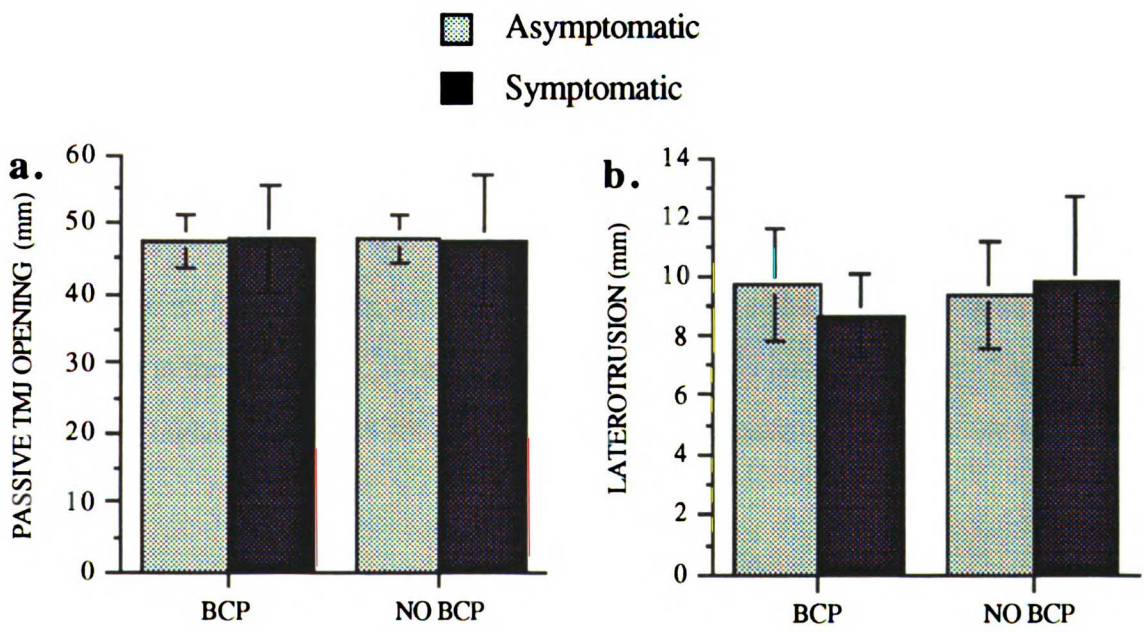

Figure 8: Histograms of mean (± S.D.) passive TMJ opening (a) and laterotrusion (b) in the four subgroups.

Table VI: Statistical analysis by ANOVA comparing clinical TMJ findings between various groups.

	ANOVA (P)	Intragroup Comparisons		Intergroup Comparisons	
		AB-AN	SB-SN	SB-AB	SN-AN
TMJ Pain	.0002	N.S.	N.S.	.0016	.0013
Range of motion: Opening	.9944	N.S.	N.S.	N.S.	N.S.
Laterotrusion	.6725	N.S.	N.S.	N.S.	N.S.

N.S. = not statistically significant

Table VII: Percent of subjects in each group demonstrating various TMJ sounds.

TMJ Sounds	SB (N=9)	SN (N=25)	AB (N=14)	AN (N=18)
No click (%)	0	8.0	42.9	44.5
Opening or closing click (%)	33.3	20.0	14.3	33.3
Reciprocal click (%)	44.4	44.0	42.9	0
Non-reproducible click (%)	22.2	28.0	0	22.2
Crepitus (%)	55.5	44.0	0	0

Table VII lists the findings of joint noises in the four groups. Many of the subjects displayed positive results in more than one category, i.e. an individual may exhibit crepitus +/- some form of click. There were no subjects in the SB group and only 8% in the SN group with no click. However, 42.9% of AB and 44.5% of AN demonstrated no clicks. The percentage of per group with each type of click was roughly similar in all groups, except that no reciprocal clicks were found in the AN group and no non-reproducible clicks were present in the AB group. The percent of subjects with positive crepitus findings are significantly higher in SB (55.5%) and SN (44%), compared to 0 in the asymptomatic groups.

C. RADIOGRAPHIC TMJ FINDINGS

The quantitation of morphologic changes in the TMJ detected by corrected tomograms demonstrated substantially higher levels of condylar flattening, erosions and osteophyte formation in the two symptomatic groups as compared to the two asymptomatic groups

(Fig. 9a,b,c,d and Table VIII). Statistical analysis by ANOVA revealed significantly higher scores for erosions and osteophytes in the SB than in the AB group (P = 0.012 and 0.013, respectively) (Table IX). Similarly, the SN group had significantly higher scores than the AN group for condylar flattening (P < 0.0001), erosions (P = 0.014) and osteophytes (P = 0.038). No significant differences in these three variables were noted between the two symptomatic groups (SB vs. SN) or the two asymptomatic groups (AB vs. AN).

Condylar rotation determined by superimposition of the condyles in the open and closed positions revealed significantly greater degree of rotation in the AB group than in the SB group (P = 0.012) or in the AN group (P = 0.030) (Table VIII). However, condylar rotation was not significantly different between the SB and SN groups or the SN and AN groups.

Table VIII: Mean (± S.D.) scores and percent of individuals with positive findings for morphologic changes and mean (± S.D.) condylar rotation observed in corrected tomograms.

Radiographic Findings		SB (N=9)	SN (N=25)	AB (N=14)	AN (N=18)
Flattening:	Mean Score (SD)	1.11 (1.05)	1.24 (.97)	0.50 (.85)	0.10 (.32)
	Percent affected (%)	66.7	76	33	10.5
Erosion:	Mean score (SD)	1.22 (1.48)	0.76 (1.30)	0.14 (.54)	0.0 (0)
	Percent affected (%)	44	28	14	0
Osteophytes:	Mean Score (SD)	0.67 (1.12)	0.40 (.71)	0.0 (0)	0.0 (0)
	Percent affected	33	28	0	0
Condylar rotation in degrees (SD)		21.17 (4.72)	25.35 (8.23)	28.71 (5.72)	23.47 (6.30)

Table IX: Statistical analysis by ANOVA comparing radiographic findings between various combinations of groups.

	ANOVA (P)	Intragroup Comparisons		Intergroup Comparisons	
		AB-AN	SB-SN	SB-AB	SN-AN
Flattening	.0002	N.S.	N.S.	N.S.	<0.0001
Erosions	.0073	N.S.	N.S.	0.013	0.014
Osteophytes	.0153	N.S.	N.S.	0.012	0.038
Condylar rotations	.1642	0.030	N.S.	0.012	N.S.

N.S. = not statistically significant

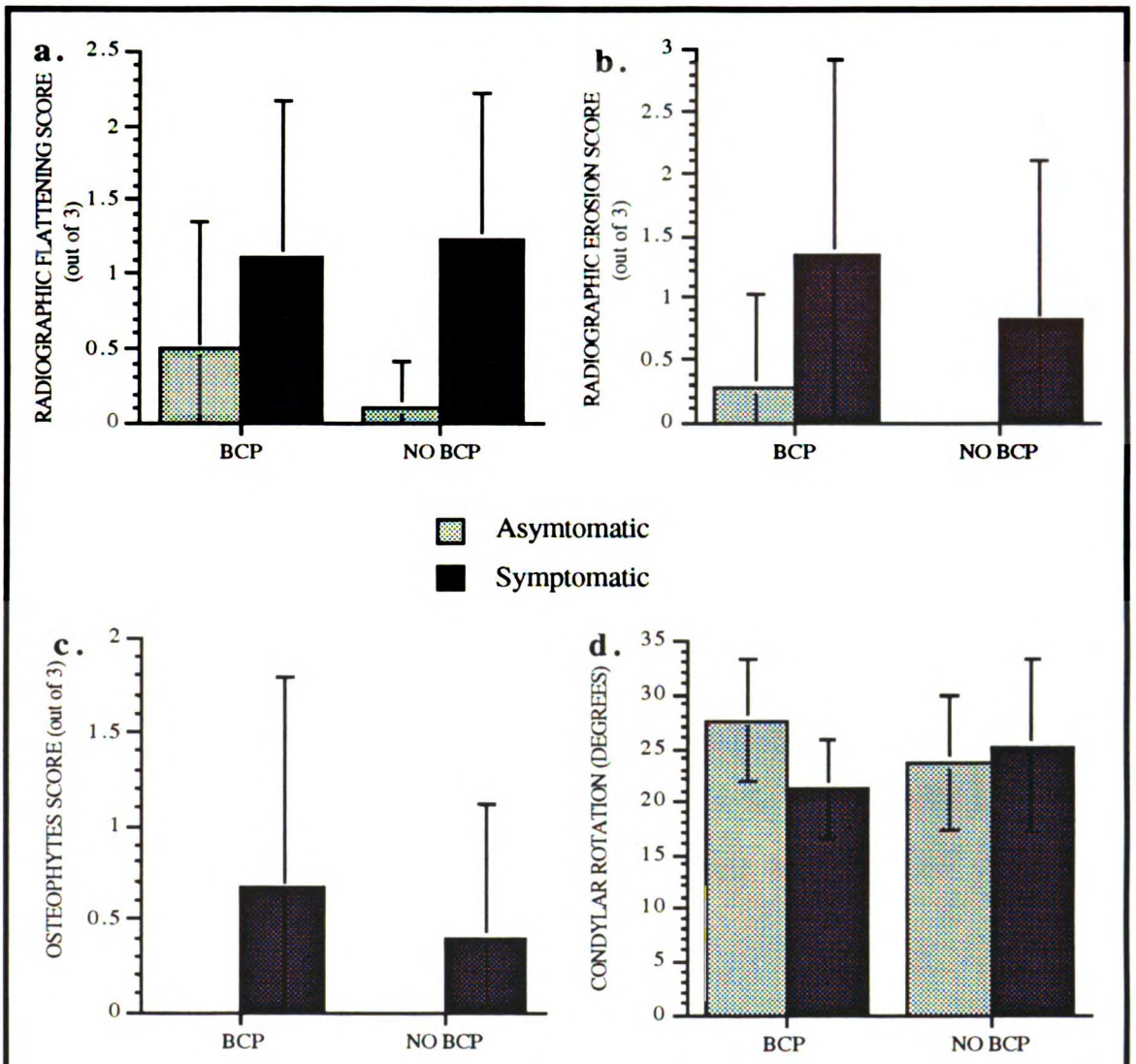

Figure 9: Histograms of mean (± S.D.) scores for condylar flattening (a), erosions (b), osteophytes (c) and condylar rotation (d) in the four subgroups.

D. SYSTEMIC HYPERMOBILITY

Because an assessment of generalized joint flexibility may provide insights into potential pathogenesis of TMJ disease, systemic hypermobility was assessed by examining the wrist, fifth digit, elbow and knee joints. The combined data from these joints was also used to determine a composite flexibility score. While data from the fifth digit, elbow and

knee joints provided an angular measurement of flexibility, that from the wrist was based on the presence or absence of hypermobility.

Findings on wrist flexibility show that SN is the only group in which a higher proportion of individuals have increased hypermobility, while AN group is the only one in which a greater proportion of subjects show normal levels of flexibility. Additionally, within the different groups a general trend of decreasing flexibility was noted for the fifth digit, elbow and total flexibility score with the SB group having the greatest flexibility followed by the SN, AB and AN groups (Fig. 10 and Table X). In the knee joint, a similar trend was also observed but the SN group had the highest flexibility followed by the SB, AN and AB groups. However, none of the hypermobility scores from individual joints or the total flexibility score were significantly different between the SB and SN groups or between AB and AN groups (Table XI). Similarly, no significant differences were noted between the SB and AB groups for any of these hypermobility indices. In contrast, the elbow joint ($P = 0.024$) and knee joint ($P = 0.034$) were significantly more flexible in the SN than the AN groups. This resulted in a significantly higher total flexibility score in the SN than the AN group ($P = 0.009$).

Table X: Percent of individuals demonstrating hypermobility in the wrist, and the mean (± S.D.) angular measures of fifth digit, elbow and knee joint flexibility. The mean (± S.D.) of total flexibility score is also provided.

Joint Flexibility (Normal value)	SB (SD)	SN (SD)	AB (SD)	AN (SD)
Wrist (% positive)	44.00	56.00	50.00	41.00
Fifth digit (< 90°)	98.00 (13.70)	104.38 (15.43)	109.46 (15.26)	111.17 (14.48)
Elbow (>10°)	8.06 (3.78)	7.68 (3.56)	6.17 (4.31)	4.97 (3.72)
Knee (> 10°)	6.94 (3.83)	8.54 (4.32)	4.65 (3.65)	5.89 (3.64)
Total flexibility score (/8)	3.44 (2.01)	3.32 (2.17)	2.00 (2.18)	1.72 (2.35)

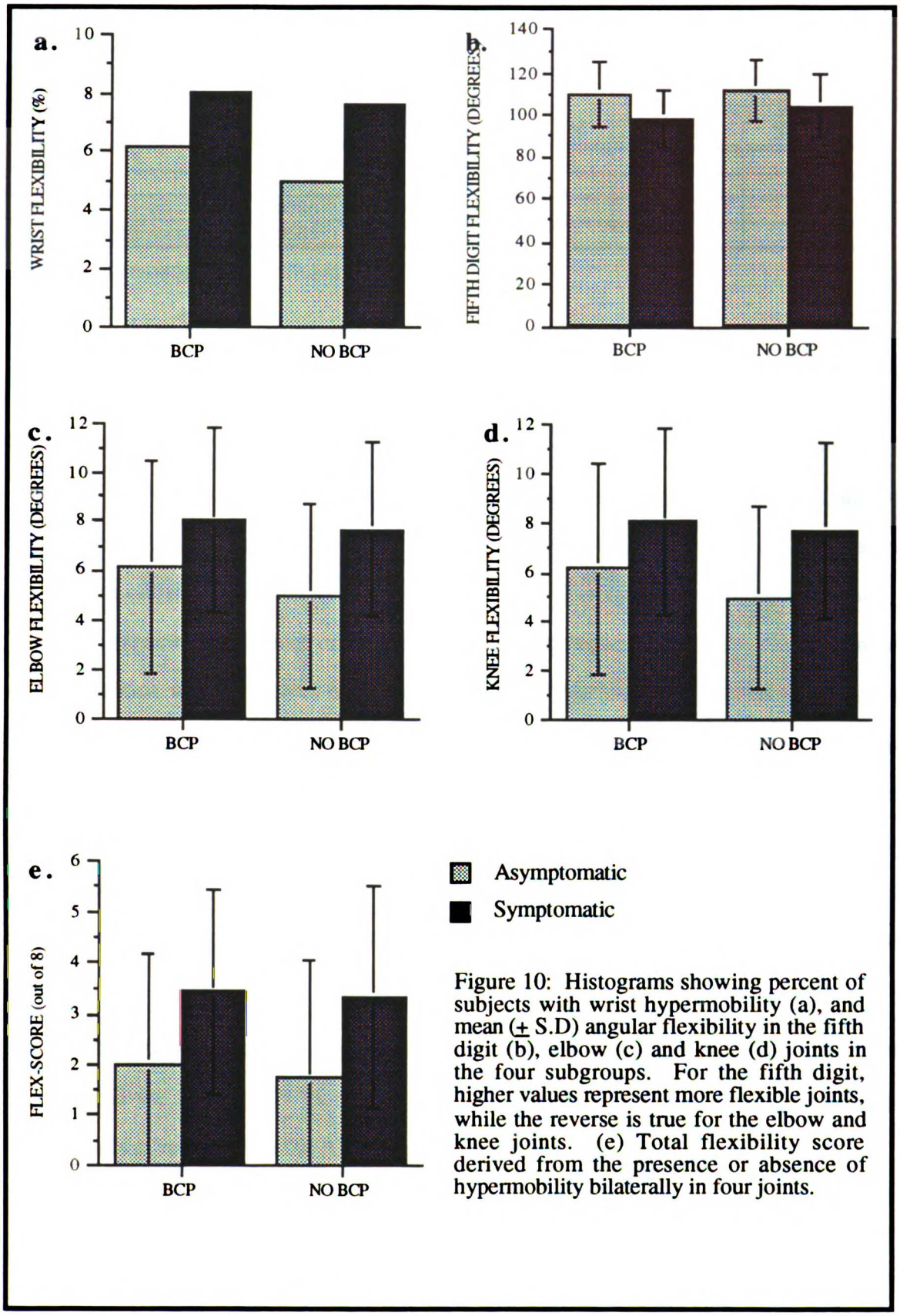

Figure 10: Histograms showing percent of subjects with wrist hypermobility (a), and mean (± S.D) angular flexibility in the fifth digit (b), elbow (c) and knee (d) joints in the four subgroups. For the fifth digit, higher values represent more flexible joints, while the reverse is true for the elbow and knee joints. (e) Total flexibility score derived from the presence or absence of hypermobility bilaterally in four joints.

Table XI: Statistical analysis by ANOVA comparing flexibility values in 3 regions and the total flexibility score between various combinations of groups.

	ANOVA (P)	Intragroup Comparisons		Intergroup Comparisons	
		AB-AN	SB-SN	SB-AB	SN-AN
Fifth digit	.1415	N.S.	N.S.	N.S.	N.S.
Elbow	.0889	N.S.	N.S.	N.S.	.024
Knee	.0286	N.S.	N.S.	N.S.	.034
Total flexibility score	.0583	N.S.	N.S.	N.S.	.009

N.S. = not statistically significant

E. SERUM β-ESTRADIOL AND RELAXIN LEVELS

The estrogen assay which measures the levels of circulating endogenous β-estradiol demonstrated significantly lower levels of this hormone in both groups of individuals on oral contraceptives (SB and AB) as compared to the subjects in their respective comparative groups not utilizing oral contraceptives (SN and AN) (Tables XII and XIII; Fig.11a,b). This is an expected result since oral contraceptives act by reducing the levels of endogenous estradiol which would result in individuals using oral contraceptives demonstrating lower levels of endogenous estradiol. The difference in β-estradiol levels between the oral contraceptive users and non-users emphasizes the need to compare the SB group with the AB group and the SN group with the AN group for this particular variable in order discern the potential role of estradiol in TMJ disease. Such a comparison, however, revealed no significant differences in the levels of endogenous β-estradiol between these two pairs of groups.

Measurement of the hormone relaxin demonstrated no significant differences between SB vs. SN, SB vs. AB and SN vs. AN groups. However, the AB group had significantly lower levels of relaxin than the AN group ($P = 0.048$).

Table XII: Mean (± S.D.) of serum β-estradiol and relaxin levels.

Hormone	SB (N = 9)	SN (N = 25)	AB (N = 14)	AN (N = 18)
Mean β-estradiol (SD)	33.48 (44.47)	104.19 (67.22)	20.22 (9.71)	112 (40.09)
Mean Relaxin (SD)	17.69 (26.30)	21.14 (33.69)	12.00 (17.44)	33.75 (33.70)

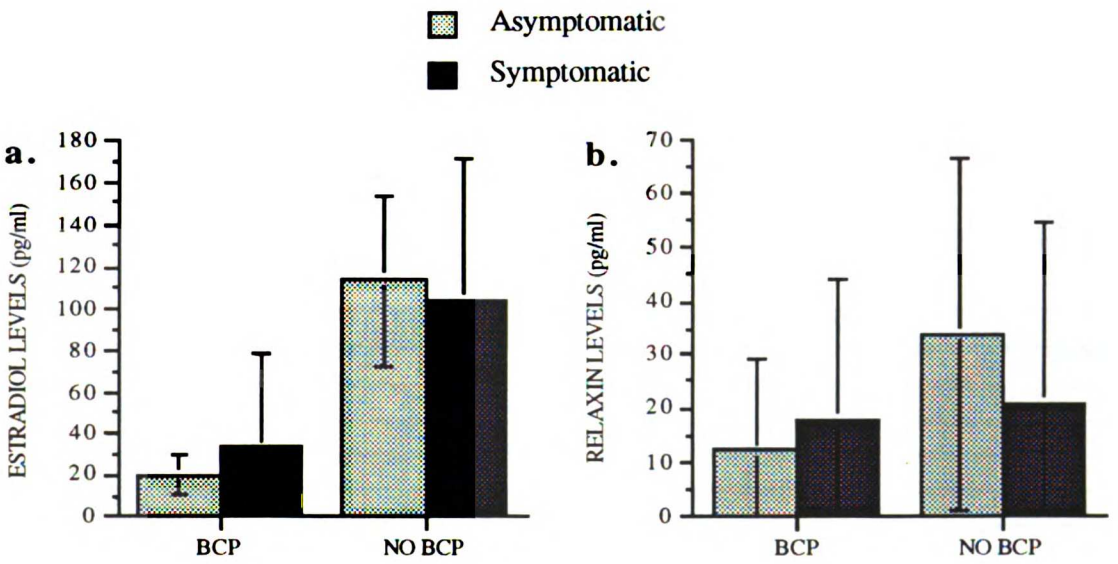

Figure 11: Histograms of mean (± S.D.) serum levels of β-estradiol (a) and relaxin (b) in the four subgroups.

Table XIII: Statistical analysis by ANOVA comparing hormone levels between various combinations of groups.

Hormone	ANOVA (P)	Intragroup Comparisons		Intergroup Comparisons	
		AB-AN	SB-SN	SB-AB	SN-AN
β-estradiol	<.0001	< 0.0001	< 0.001.	N.S.	N.S.
Relaxin	.2184	0.048	N.S.	N.S.	N.S.

N.S. = not statistically significant

F. ASSIGNMENT OF SUBJECTS BY TMJ DIAGNOSIS

Since the symptomatic patients in our sample represent a heterogeneous group of individuals, the groups were reclassified into recognized diagnostic categories derived from

objective clinical and radiographic observations. This classification resulted in redistribution of all the subjects in the SB and SN groups into those with a positive history of TMJ disease, presence of arthralgia or osteoarthrosis or osteoarthritis. Additionally, all subjects in the AN group satisfied the original and radiographic criteria of having no detectable TMJ disease. However, 1 of the 14 individuals in the AB group demonstrated radiological evidence of osteoarthrosis which included Grade 2 flattening and was reassigned to this group (Table XIV).

Table XIV: Distribution of subjects into categories of TMJ disease as determined by objective clinical and radiographic criteria.

Diagnosis	SB (N = 9)	SN (N = 25)	AB (N = 14)	AN (N = 18)
No TMJ disease	0 (0%)	0 (0%)	13 (93%)	18 (100%)
Positive history	2 (22.2%)	5 (20%)	0 (0%)	0 (0%)
Arthralgia	3 (33.3%)	12 (48%)	0 (0%)	0 (0%)
Osteoarthrosis	2 (22.2%)	2 (8%)	1 (7%)	0 (0%)
Osteoarthritis	2 (22.2%)	6 (24%)	0 (0%)	0 (0%)

G. ASSOCIATION OF SYSTEMIC VARIABLES WITH TMJ DISEASE

Following redistribution of subjects into various categories of TMJ disease, we sought to examine whether significant differences existed between these four groups and those showing no discernible TMJ disease in the quantitative measures of systemic hypermobility or hormone levels. Also included in these comparisons were the variables of condylar rotation as a measure of TMJ flexibility, and low back pain.

1. Overall TMJ Diagnosis vs. Systemic Joint Hypermobility

The group with osteoarthritis (OAitis) demonstrated the lowest (most flexible) mean for fifth digit flexibility (Fig. 12a and Table XV). Significant differences were found in fifth digit flexibility between the OAitis group and the history only group (P = 0.027), arthralgia

group (P = 0.040) and the no disease group (P = 0.004). Similarly, the elbow flexibility was significantly higher in the OAitis group than in the history only group (P = 0.039), arthralgia group (P =0.008) and no pathology group (P < 0.001) (Fig. 12b). There was also a significant difference in elbow flexibility between the osteoarthrosis (OAosis) group and the group with no disease (P = 0.010). For the knee joint, the OAitis group demonstrated the highest mean flexibility (Fig. 12c). Knee hypermobility was significantly higher in the OAitis group then in the group with no pathology (P = 0.025), as well as in the history only group then in the no disease group (P = 0.040). Finally, the OAitis group had significantly higher total flexibility score than the history only group (P = 0.028), arthralgia group (P = 0.010) and no disease group (P < 0.001) (Fig. 12d). For condylar rotation, significant differences were observed only between the OAitis group and the arthralgia group (P = 0.027), as well as the no disease group (P = 0.020). The OAitis group also experienced the most low back pain overall, while the no pathology group experienced the least. Significant differences were noted between the no pathology group and OAosis group (P = 0.021), OAitis group (P = 0.001) and arthralgia group (P = 0.002) for low back pain. Tables XV and XVI summarize the mean values and statistical comparisons for the above variables.

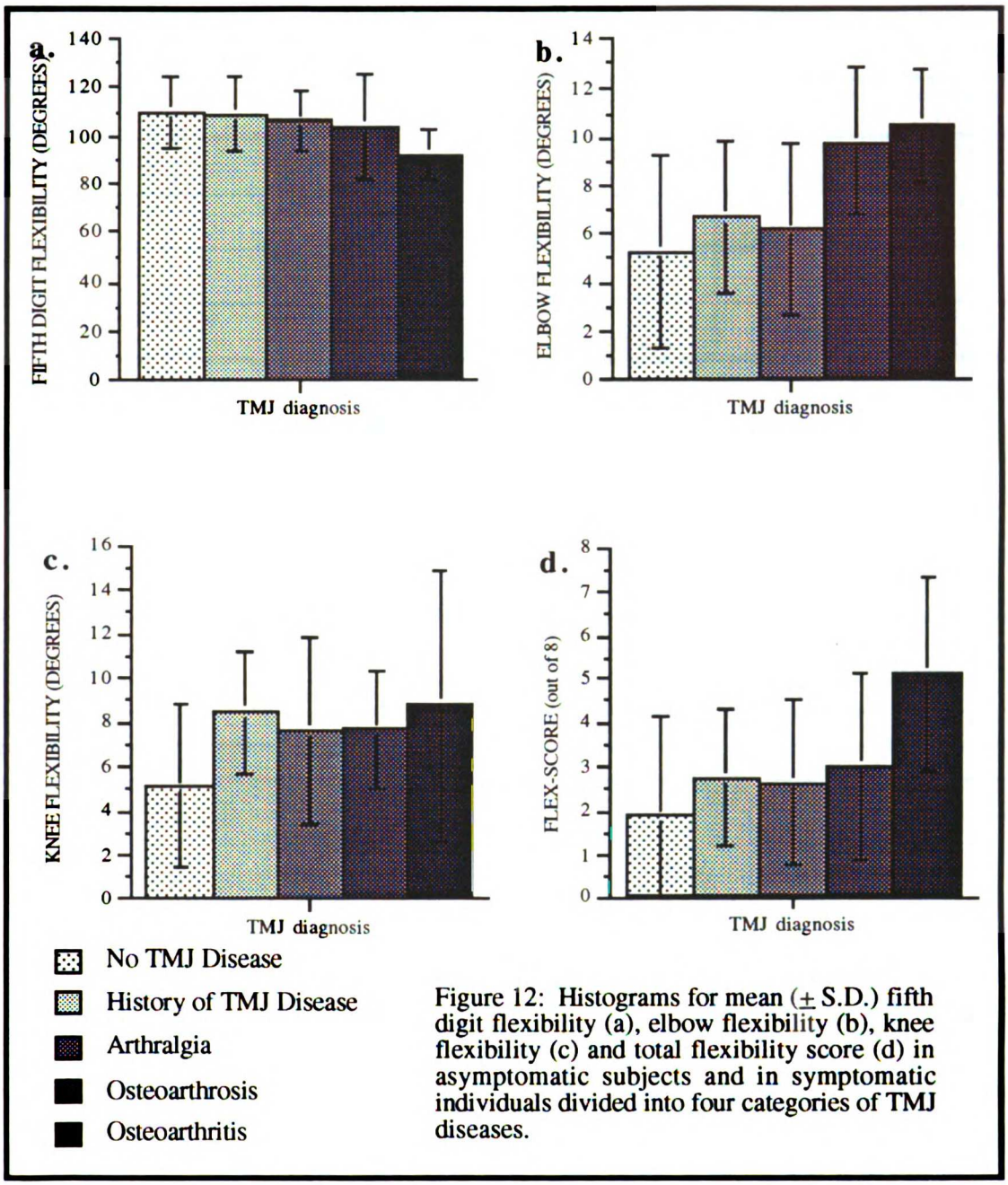

Figure 12: Histograms for mean (± S.D.) fifth digit flexibility (a), elbow flexibility (b), knee flexibility (c) and total flexibility score (d) in asymptomatic subjects and in symptomatic individuals divided into four categories of TMJ diseases.

Table XV: Mean (± S.D.) of flexibility parameters in subjects with no TMJ disease and those with various categories of TMJ disease.

Flexibility Parameter	No TMJ Disease (SD)	Positive History (SD)	Arthralgia (SD)	Osteoarthrosis (SD)	Osteoarthritis (SD)
Fifth digit	109.42 (15.14)	108.75 (15.37)	105.82 (12.46)	103.60 (21.50)	92.12 (10.60)
Elbow	5.27 (3.96)	6.75 (3.16)	6.21 (3.46)	9.80 (3.03)	10.50 (2.32)
Knee	5.18 (3.65)	8.50 (2.73)	7.64 (4.21)	7.70 (2.64)	8.81 (6.12)
Total flexibility score	1.87 (2.27)	2.75 (1.58)	2.64 (1.87)	3.00 (2.12)	5.13 (2.23)

Table XVI: Statistical comparison of measures of systemic flexibility between groups with no discernible TMJ disease and those with various categories of TMJ disease.

Flexibility Parameter	Pos. hx vs. OA-osis	Pos. hx vs. OA-itis	Pos. hx vs. arthr	Pos. hx vs. no dz	OA-osis vs. OA-itis	OA-osis vs. arthr	OA-osis vs. no dz	OA-itis vs. arthr	OA-itis vs. no dz	arthr vs. no dz
fifth digit	N.S.	.027	N.S.	N.S.	N.S.	N.S.	N.S.	.040	.004	N.S.
elbow	N.S.	.040	N.S.	N.S.	N.S.	N.S.	.010	.008	.0005	N.S.
knee	N.S.	N.S.	N.S.	.04	N.S.	N.S.	N.S.	N.S.	.025	N.S.
flex-score	N.S.	.028	N.S.	N.S.	N.S.	N.S.	N.S.	.010	.0002	N.S.
condylar rotation	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	.027	.020	N.S.

2. *Overall TMJ Diagnosis vs. Hormone Levels*

The levels of β-estradiol (Figure 13a) and relaxin (Figure 13b) were also compared between the no disease and 4 disease groups. While relatively high levels of both hormones were observed in the groups with positive history of TMJ disease and osteoarthritis, none of the groups demonstrated any significant differences in the serum concentrations of these hormones when evaluating the subjects on and not on oral contraceptives combined (Tables XVII and XVIII). However, since the levels of β-estradiol are significantly lower in subjects on oral contraceptives than in subjects not on oral contraceptives, these groups were separated for further analysis for differences in β-estradiol levels between the various diagnostic groups. Significantly higher levels of β-estradiol were observed only in the OAosis versus the arthralgia groups (P = 0.0082) and the OAitis versus the no disease

group (P = 0.0101) for individuals on oral contraceptives (Tables XIX and XX and Fig. 14).

Table XVII: Mean (± S.D.) of b-estradiol and relaxin in subjects with no TMJ disease and those with various categories of TMJ disease.

Hormone	No TMJ Disease (SD)	Positive History (SD)	Arthralgia (SD)	Osteoarthrosis (SD)	Osteoarthritis (SD)
β-estradiol	77.45 (58.71)	81.75 (76.92)	74.52 (60.89)	47.40 (40.35)	110.00 (76.60)
Relaxin	25.28 (30.95)	40.38 (23.34)	20.99 (19.77)	15.00 (12.11)	43.30 (56.43)

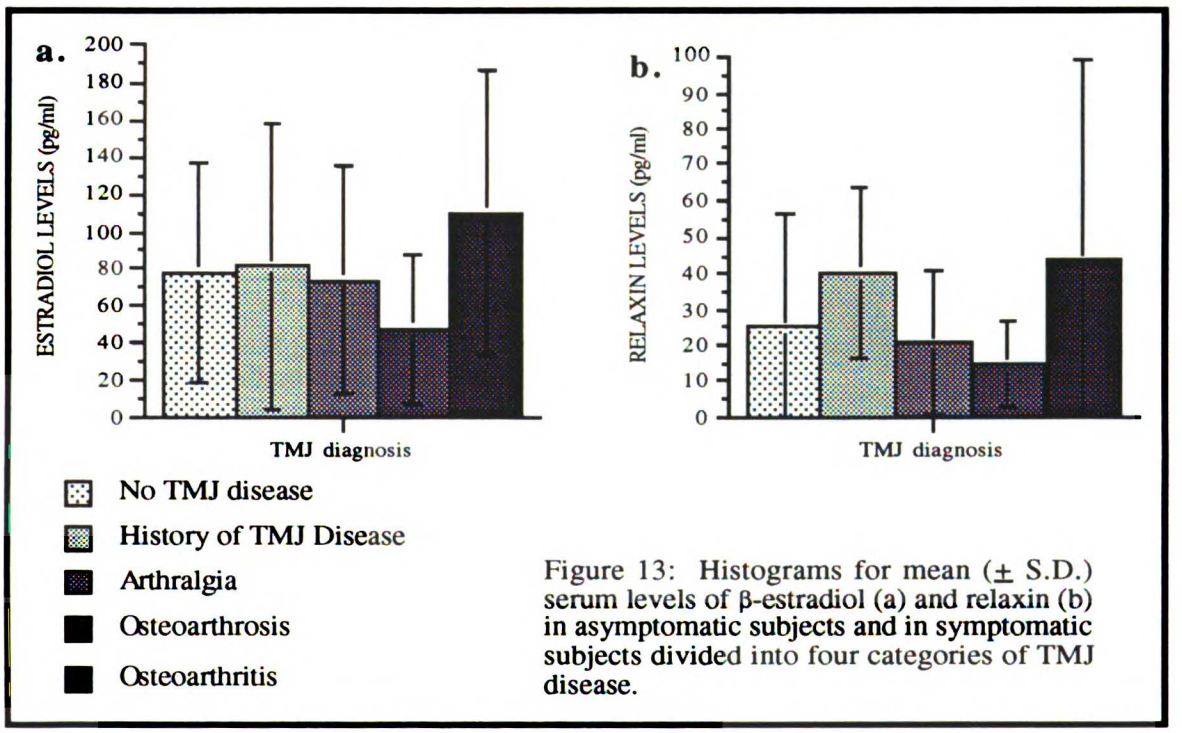

Figure 13: Histograms for mean (± S.D.) serum levels of β-estradiol (a) and relaxin (b) in asymptomatic subjects and in symptomatic subjects divided into four categories of TMJ disease.

Table XVIII: Statistical comparison of β-estradiol and relaxin levels between groups with no discernible TMJ disease and those with various categories of TMJ disease.

Hormone (ANOVA P)	Pos. history vs. OAosis	Pos. history vs. OAitis	Pos. history vs. arthr	Pos. history vs. no disease	OAosis vs. OAitis	OAosis vs. arthr	OAosis vs. no disease	OAitis vs. arthr	OAitis vs. no disease	arthr vs. no disease
β-estradiol (P= 0.5125)	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
Relaxin (P= 0.3118)	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	.N.S.	N.S.	N.S.

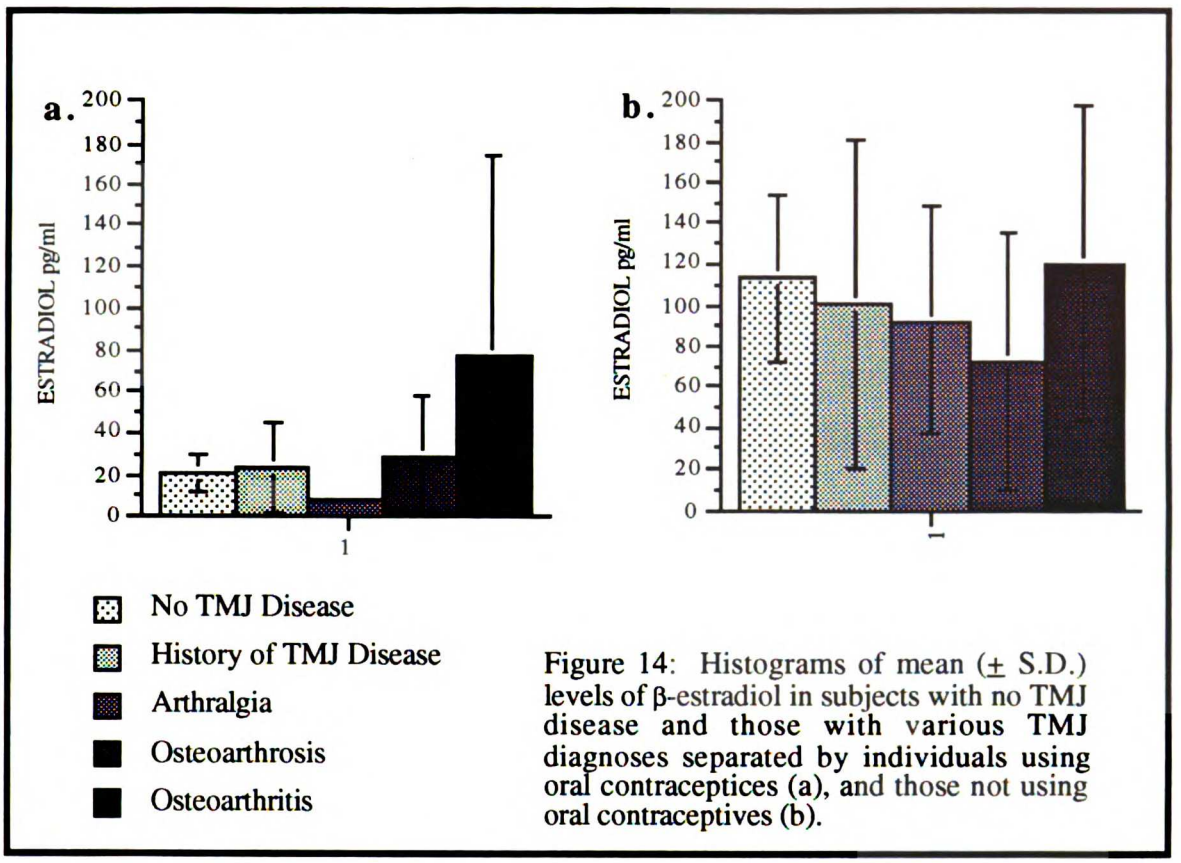

Figure 14: Histograms of mean (± S.D.) levels of β-estradiol in subjects with no TMJ disease and those with various TMJ diagnoses separated by individuals using oral contraceptices (a), and those not using oral contraceptives (b).

Table XIX: Means (± S.D.) for β-estradiol levels in different TMJ diagnosis groups separated by individuals using or not using oral contraceptives.

Hormone	No TMJ Disease (SD)	Positive History (SD)	Arthralgia (SD)	Osteoarthrosis (SD)	Osteoarthritis (SD)
β-estradiol: no bcp	113.33 (40.81)	101.08 (79.97)	92.77 (55.76)	72.50 (62.93)	120.83 (76.35)
β-estradiol: bcp	20.97 (9.27)	23.75 (21.57)	7.60 (0.53)	29.00 (17.52)	77.50 (95.46)

Table XX: Statistical comparisons with ANOVA for β-estradiol levels in different TMJ diagnosis groups separated by individuals using or not using oral contraceptives.

Hormone	Pos. history vs. OAosis	Pos. history vs. OAitis	Pos. history vs. arthr	Pos. history vs. no disease	OAosis vs. OAitis	OAosis vs. arthr	OAosis vs. no disease	OAitis vs. arthr	OAitis vs. no disease	arthr vs. no disease
β-estradiol : no bcp	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
β-estradiol: bcp	N.S.	N.S.	N.S.	N.S.	N.S.	0.0082	N.S.	N.S.	0.0101	N.S.

IV. DISCUSSION

In this study, we demonstrated that systemic joint laxity is increased in individuals with TMJ disease. It was the first to determine that an objective TMJ diagnosis, derived by radiographic and clinical evaluation, is associated with the degree of joint laxity. It was also the first to investigate the potential association of relaxin and estrogen with TMJ disease.

Several factors impacted upon the validity of the results obtained. While adequate numbers of subjects were recruited for the symptomatic and asymptomatic groups, it became apparent that these groups should be further divided into those using oral contraceptives and those not using oral contraceptives. This division substantially reduced the group sizes, making it inadequate to derive meaningful statistical conclusions for several variables. Nevertheless, while serum levels of relaxin and β-estradiol were not significantly different between the SB and AB groups or the SN and AN groups, significantly higher levels of systemic flexibility were observed in the SB and SN groups as compared to their respective controls.

Several other variables were dependent upon personal assessment and may be called to question. The criteria for inclusion as an individual with a symptomatic TMJ dictated that an individual either is currently experiencing TMJ pain or had a history of an open or closed lock. The validity of this information is dependent upon both the subject's understanding and memory of such an event.

The parameter of low back pain was evaluated since relaxin levels have been positively correlated with painful sacroiliac joints (Wreje et al., 1995). It was interesting to find significant differences in reports of low back pain severity between the symptomatic and asymptomatic groups and agree with those of Hagberg (1991). The mean score for low

back pain was highest in the SB group, although not significantly higher than that in the SN group. However, caution should be exercised in interpreting these results since an individual experiencing TMJ pain may be more likely to report low back pain than would a participant with an asymptomatic TMJ.

Assessment of TMJ pain demonstrated significantly higher pain levels in both symptomatic groups than in their respective controls. The information on TMJ pain was determined from subjects responses and was also was utilized in the formulation of the TMJ diagnoses. Joint pain was graded by the participant, so the results depend not only upon each participant's honesty and lack of bias, but also their individual pain thresholds. Another variable to consider in arriving at these diagnoses is the cyclic nature of TMJ symptoms, which vary during the course of the disease.

No significant differences were found between any of the groups for linear jaw opening or excursive movements. On first consideration, one may expect an increased linear range of TMJ motion in individuals with greater joint laxity. This lack of significant differences between the symptomatic and asymptomatic groups in the range of motion of the TMJ may be explained by the fact that laxity of the TMJ ligament may predispose an individual to dislocation, resulting in inflammatory and/or physical limitation of jaw opening. Furthermore, presence of alterations in tissue morphology or configuration in a diseased joint may further limit movements. Therefore, as indicated previously (Westling, 1990), values obtained from clinical TMJ mobility testing are not expected to provide an accurate representation of TMJ mobility in symptomatic patients because of limitations on TMJ function due to pain, reflex splinting or physical blockage by the disc.

We utilized a radiographic technique for determining condylar rotation as a measure TMJ hypermobility. The concept of TMJ hypermobility was first introduced to the dental literature by Schultz (1947), who noted its association with symptoms of TMD. Clinically and radiographically, TMJ hypermobility has been diagnosed when the condyle passes

beyond the articular eminence during translation (Katzberg et al., 1982). It has been proposed that although joint laxity is not evident in the TMJ by linear assessment, it mat be evident by measuring the angular rotation of the mandible. Pullinger et al. (1987) proposed a method to measure angular rotation without using radiographs. The present study utilizing corrected tomograms to measure angular differences in the condyle in the closed and open positions, demonstrated the highest condylar rotation in AB group while the SB had the lowest condylar rotation . Condylar rotations may be decreased in the symptomatic individuals for the reasons described above for linear mandibular movements.

There were no distinct trends of occurrence of opening / closing clicks amongst the groups. Reciprocal clicks were seen in 44% of the symptomatic groups, 42.9% of the AB group and 0% of AN. It is conceivable, once again, that hormonal differences from the oral contraceptives may account for the substantial differences in TMJ sounds between the AB and AN, but this concept requires further study for validation. Crepitus was noted in 55% of the SB group, 44% of the SN group and 0% of both control groups.

One may assume that the symptomatic group would show substantially more radiographic evidence of bony remodeling than the control group. However, both cadaver and radiographic studies utilizing a control group show that bony changes occur in a sizable percentage of the asymptomatic population (Lubsen et al, 1985; Solberg et al, 1985). Ericson and Lundberg (1968) found that 44% of 80 consecutively treated dental patients had undergone radiographic TMJ changes. The symptomatic groups had significantly more flattening than the control groups. In our study, 44.5% of asymptomatic participants exhibited some radiographic evidence of condylar flattening. The AN group had zero incidence of erosion. The group with the highest percentage affected by osteophytes was SB, followed closely by SN . That no osteophytes were found in either control group contradicts the findings of Ericson and Lundberg (1968), who found the incidence to be as high as 29%. The potential association between oral contraceptive use and radiographic TMJ findings were not conclusive except in the case of condylar erosions which

demonstrated a greater severity in both oral contraceptive groups than in their respective non-contraceptive groups. However, even this difference was not statistically significant.

Several variables may decrease the systemic laxity measured in a joint. One factor is the dominant side of an individual which usually has more muscular tone and thus the resultant laxity is less (Westling, 1993). Another factor is history of trauma to a joint. Finally, laxity in a joint may vary depending upon the time of day. To circumvent the first two variables, measurements were made bilaterally in all joints and the value from the more flexible side was used for statistical analysis. The logistics of controlling the timing of testing was not feasible in this study. In the wrist evaluation, the SN group displayed the most laxity, while the AN group displayed the least. This is in concert with the findings of Bates et al. (1984), who found a significant relationship between wrist laxity and internal derangement of the TMJ. The fifth digit was significantly more flexible in the symptomatic group. Again, the SB group demonstrated the most laxity. Ericson and Lundberg (1968) found significant correlations between radiological changes in the TMJ and in finger joints. Beighton et al. (1973) found a positive correlation between laxity of the fifth digit and generalized joint laxity. The symptomatic group was also found to be most flexible in the elbows. This finding also agrees with that of Ericson and Lundberg (1968), who found significantly more elbow laxity when TMJ internal derangement was present. Of the four subgroups, SB again had the most elbow laxity. The SN group demonstrated significantly more knee laxity than its asymptomatic groups. It is noteworthy that the majority of participants in the SB group reported a history of knee trauma, most frequently involving the anterior cruciate ligament, which may help explain the lower laxity of this joint in this subgroup. Also of significance is the fact intra-tester reliability of the lower extremities has been shown to be less accurate than that of upper extremities (Boone, 1978). Finally, the total flexibility score was found to be significantly higher in the symptomatic groups, with SB again scoring the highest. These findings are in agreement with those of Westling

(1993), Buckingham (1991) and Harkins et al. (1985) and contradict those of Dijkstra (1992).

As mentioned earlier, the difficulty in interpreting findings from previous studies arises from the disparity in definitions of TMJ disease. We have standardized the classification of TMJ diseases by utilizing objective definitions with proven intra-rater reliability which combine findings from TMJ history, joint pain and bony changes. The criteria for positive diagnoses are very conservative in order to err on the side of higher sensitivity. This may cause apparent discrepancies between findings from this study and other studies. While joint pain (arthralgia + osteoarthritis) was most predominant in the SN group (72% vs. 55.3% in SB), evidence of significant bony changes (osteoarthrosis + osteoarthritis) was more prevalent in the SB group (44% vs. 32% in SN). Only one participant from the control group had bony changes consistent with osteoarthrosis and none had arthralgia.

Assuming the theory is correct that systemic joint laxity predisposes to mechanical hyperextension of the condyle past its physiological limit, one may expect to see more internal derangement and remodeling in individuals with systemic joint laxity. The results from this study support this line of logic. The group of participants diagnosed with osteoarthritis also showed significantly higher means for fifth digit laxity, elbow laxity, knee laxity, total flexibility score and low back pain. They also experienced the least amount of condylar rotation during opening. This finding may suggest that this group had a correspondingly higher amount of condylar translation during opening.

For individuals not using oral contraceptives, the literature suggests that the mean estradiol level at day 24 is approximately 80-120 pg/ml. Of the groups not using oral contraceptives, SN's mean estradiol level was approximately 104 pg/ml, while the mean for AN was 111 pg/ml. The RIA for estradiol used in the present study specifically quantifies the endogenous levels of this hormone. Thus, in participants taking oral contraceptives, one would expect lower levels of endogenous estradiol, the amount being

suppressed by the exogenous estradiol in the oral contraceptive. Most participants' oral contraceptive formulation contained a daily dose of 0.035 mg. of ethinyl estradiol. For individuals using oral contraceptives, the mean amounts of circulating endogenous estradiol was 32 pg/ml in the SB group and 19 pg/ml in the AB group.

The data related to hormone levels is subject to substantial variation for several reasons. First, in the normal menstrual cycle the mid-luteal phase occurs on approximately the 24th day after onset of menstruation assumes a menstrual cycle that is exactly 28 days long. Since levels of these hormones vary substantially through the cycle, a slight difference in the length of the menstrual cycle may substantially impact on the serum levels of both β-estradiol and relaxin. Second, individuals using oral contraceptives may have peak levels of hormones day that differs from that of non-oral contraceptive users. It is also possible that the day of peak hormone levels in this group may be dependent on the type or regularity of oral contraceptive use, or on the day the oral contraceptive cycle commences. Third, circadian rhythms may affect hormone levels (Wreje et al., 1994). In this study, blood draws were performed at the time of day which was convenient for the parties involved and thus may provide variability in the results. These factors suggest the need for several modifications in experimental design for future studies including a careful monitoring by subjects of their menstrual cycle to determine the optimal day for retrieving blood, and a controlled use of oral contraceptives for more reliable results. However, despite these limitations, higher levels of β-estradiol and relaxin were observed in subjects with osteoarthritis than in asymptomatic controls or individuals with other TMJ diagnosis. Further studies should also evaluate not only the peak hormone levels, but also the baseline levels since this may provide insights into whether TMJ disease is associated with chronic increases in relaxin and / or β-estradiol rather than the peak levels evaluated in the present study.

Several additional unknowns also apply to an assessment of the effects on relaxin on joint disease. Most significantly, relaxin is a hormone which is known to have long-lasting

effects (Goldsmith, 1994). Therefore, the effects of relaxin on remodeling of joint tissues may have been initiated previously at a time when relaxin levels were higher and which have since returned to normal levels. Since the subjects are being assessed in substantially advanced stages of their diseases, it becomes difficult to confirm that these conditions were not initiated or perpetuated by increased hormone levels at a previous date. Another factor of importance is that relaxin exerts its effects locally in autocrine and/ or paracrine modes. Therefore, systemic levels of relaxin may not necessarily reflect local effects, particularly if specific tissues demonstrate a high responsiveness to this hormone. Our studies (Kapila et al., 1996) demonstrate that relaxin specifically induces the expression of collagenase and stromelysin in TMJ disc cells but not in synoviocytes, indicating that the matrix-degradative effects of this hormone may indeed be targeted to specific joint tissues. Finally, relaxin is known to function in an estrogen-dependent manner such that estrogen priming of cells increases their sensitivity to relaxin (Kapila et al., 1996). This occurs at least in part by causing an upregulation of relaxin receptors. If this were the case, only slight increases in levels of both β-estradiol and relaxin may be necessary to induce substantial lysis of joint tissues.

It has been found that women using oral contraceptives have a higher incidence of painful TMJ problems (LeResche et al, 1995). In this study, there were no significant differences between the TMJ diagnosis groups in hormone levels. However the osteoarthritis group demonstrated substantially higher levels of β-estradiol and relaxin than the control groups. In interpreting these data, one should consider additional information provided by *in vitro* experiments using relaxin + / - β-estradiol priming on TMJ disc cells. It was shown that the combined effects of relaxin and estrogen on induction of tissue degrading enzymes are greater than either of their singular effects (Kapila et al., 1995). Thus the matrix-degradative effects of these hormones are synergistic and may not be reflected by their values in isolation. Also, as mentioned earlier, these hormones may exert their actions in a

V. CONCLUSIONS AND CLINICAL IMPLICATIONS

While the diagnostic criteria presently in use provide an assessment of clinical status of the patient, the population of symptomatic subjects in our study probably represent a group with heterogeneous etiologies and pathogenesis. Thus, the factors which have been tested in this study may influence TMJ disease in some individuals but have no role in this disease in others. This limitation begs for a more definitive basis for the rational diagnosis of TMJ diseases. However, until such diagnostic criteria are available, studies such as the present one should rely on objective and controlled assessment of patients as used in our investigation. Despite the various limitations of a study of this nature, several conclusions were drawn from our investigation:

1) The symptomatic TMJ group defined by this study demonstrated significantly greater systemic joint laxity in the joints tested. In addition, the total flexibility score values were significantly greater in the symptomatic groups.
2) Despite the increased systemic joint laxity in symptomatic subjects, no differences were observed in jaw mobility between the symptomatic and asymptomatic individuals.
3) When the participants were separated by TMJ diagnostic categories, the osteoarthritis group demonstrated the highest degree of systemic joint flexibility, which was significantly greater than the group with no TMJ disease.
4) Although not statistically significant, the osteoarthritis group demonstrated the highest levels of relaxin and β-estradiol as compared to then the no disease or other TMJ diagnosis groups.
5) No conclusions could be drawn regarding the effects of oral contraceptives on TMJ disease since the sample sizes were not substantially large.

Armed with this information, as well as information which will hopefully be obtained in future studies, the clinician may be able to better anticipate which patients may experience TMJ problems and minimize treatments which may aggravate existing TMJ disease.

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VII. APPENDIX

APPENDIX 1

HEALTHY FEMALES

NEEDED

FOR STUDY OF TMJ (JAW JOINT)

DISEASE IN WOMEN

Volunteers are needed to explore the possible hormonal causes of TMJ problems in females of childbearing age.

Volunteer Criteria:

- Females, 13-40 years of age
- healthy
- no history of trauma to jaws

Participation Involves:

- health questionnaire (30 min)
- TMJ examination (30 min)
- flexibility testing in wrist, elbow and knee joints (30 min)
- drawing of blood (1 teaspoonful/4 ml) on day 10 of the menstrual cycle

TOTAL TIME = 2 hours

SUBJECTS COMPLETING THE STUDY WILL RECEIVE $50.00 .

To learn more about participating in this study, please call (415) 476-9011.

APPENDIX 2

UNIVERSITY OF CALIFORNIA, SAN FRANCISCO CONSENT TO PARTICIPATE IN A RESEARCH STUDY

The Role of Hormones in Temporomandibular Joint (TMJ) Disease in Women

A. PURPOSE AND BACKGROUND

Sunil Kapila, D.D.S., M.S., Ph.D. and Elana Peikoff, D.M.D., from the Department of Growth and Development, are conducting a study to help understand the causes of temporomandibular joint (jaw joint) problems in women. Because I am a healthy female between 13-40 years of age, I am being asked to participate in the study.

B. PROCEDURES

If I agree to be in this study, the following will happen:

1. I will complete a questionnaire regarding my age, number of pregnancies and history of pain in my joints. This should take about 30 minutes to complete.

2. I will be examined for flexibility in my jaw, wrist, elbow and knee joints. This will involve measuring the amount I can comfortably bend my little fingers backwards, bend my thumbs toward my forearm, extend my elbows, extend my knees, bend my upper body forward while my knees are straight and open my mouth. This testing should take approximately 30 minutes.

3. I will recieve a thorough examination of my jaw joints, the TMJ. This examination, used for research purposes, is commonly done for patients. This test usually lasts 30 minutes.

4. Twice in the month, approximately a teaspoonful (4ml.) of blood will be drawn from a vein in my arm for laboratory tests. Each blood draw should take about 15 minutes.

5. I may be withdrawn from the study without my consent if the researchers believe it is in my best interest, or if I fail to follow study procedures.

Participation in this study will take a total of about 2 hours over a period of 2 weeks.

All study procedures will be done at the Center for Temporomandibular Disorders and Orofacial Pain, in the School of Dentistry, U.C. San Francisco.

C. RISKS/DISCOMFORTS

1. Venipuncture: The risks of drawing blood include temporary discomfort from the needle stick, bruising and rarely, infection.

2. Confidentiality: Participation in research may involve a loss of privacy, but information about me will be handled as confidentially as possible. My name will not be used in any published reports about this study.

Treatment and Compensation for Injury:

If I am injured as a result of being in this study, treatment will be available. The costs of such treatment may be covered by the University of California, depending on a number of factors. The University does not normally provide any other form of compensation for injury. For further information about this, I may call the office of the Committee on Human Research at (415) 476-1814.

D. BENEFITS

I will not directly benefit from participating in this study. It is hoped that the information gained from this study will help the investigators learn more

about the cause of jaw joint problems in women, which may provide better methods to diagnose and treat this condition.

E. COSTS

I will not be charged for any of the study treatments or procedures.

F. REIMBURSEMENT

I will be reimbursed a total of $50.00 at my second visit for participation in the two sessions.

G. QUESTIONS

This study has been explained to me by Dr. Peikoff and my questions were answered. If I have any other questions about the study, I may call Dr. Peikoff at (415) 476-9011.

H. CONSENT

I have been given copies of this consent form and the Experimental Subject's Bill of Rights to keep.

PARTICIPATION IN RESEARCH IS VOLUNTARY. I have the right to decline to participate or to withdraw at any point in this study without jeopardy to my medical care.

If I wish to participate, I should sign below.

_____	_____
Date	Subject's Signature
_____	_____
Date	Person Obtaining Consent

APPENDIX 3

QUESTIONNAIRE

Please answer the following questions as accurately as possible.
If you don't understand a question, please ask for assistance.

1. Would you say that your health in general is:
1-excellent 2-very good 3-good 4-fair 5-poor

2. Would you say that your oral health in general is:
1-excellent 2-very good 3-good 4-fair 5-poor

3. Please complete the following:

Please circle the appropriate response for each of the following.

Key: N = Never had this condition P = Previously had this condition C = Currently have this condition

ARTHRITIS			
Rheumatoid	N	P	C
Gout	N	P	C
Osteoarthritis	N	P	C
Other: _____	N	P	C
ARTIFICIAL IMPLANTS			
Joint prosthesis	N	P	C
Pacemaker	N	P	C
Heart valve	N	P	C
BLOOD DISORDERS			
Bleeding tendencies	N	P	C
Anemia	N	P	C
Leukemia	N	P	C
ENDOCRINE (GLAND) DISORDERS			
Diabetes	N	P	C
Thyroid disease	N	P	C
EYE DISORDERS			
Glaucoma	N	P	C
Ocular herpes	N	P	C
HEADACHE			
Tension headache	N	P	C
Migraine headache	N	P	C
Unexplained headaches	N	P	C
HEART DISORDERS			
Coronary artery disease	N	P	C
Heart murmur	N	P	C
High blood pressure	N	P	C
WOMEN			
Are you pregnant?	No	Yes	

KIDNEY, URINARY DISORDERS			
Kidney disease	N	P	C
Bladder infections	N	P	C
LIVER DISEASE			
Hepatitis	N	P	C
Cirrhosis	N	P	C
LUNG DISORDERS			
Asthma	N	P	C
Emphysema	N	P	C
Lung cancer	N	P	C
MUSCLE DISORDERS			
Muscle tension	N	P	C
Muscular dystrophy	N	P	C
Frequent muscle spasms	N	P	C
NERVE DISORDERS			
Cerebral palsy	N	P	C
Epilepsy	N	P	C
Neuralgia	N	P	C
Multiple sclerosis	N	P	C
Stroke	N	P	C
Parkinson's disease	N	P	C
STOMACH, INTESTINAL DISORDERS			
Ulcers	N	P	C
Colitis	N	P	C
OTHER CONDITIONS			
Osteoporosis	N	P	C
Psychological difficulties	N	P	C
Tumors or malignancies	N	P	C
Venereal disease	N	P	C
Radiation treatment	N	P	C
Other _____	N	P	C

Have you ever been seriously injured? ☐ Yes ☐ No (If so, please complete this section).

1. Cause of injury:	Approx. date of injury
Description of injury:	
Amount of recovery: ☐ Complete ☐ More than half. ☐ Less than half.	Time to recover
2. Cause of injury:	Approx. date of injury
Description of injury:	
Amount of recovery: ☐ Complete ☐ More than half. ☐ Less than half.	Time to recover
3. Cause of injury:	Approx. date of injury
Description of injury:	
Amount of recovery: ☐ Complete ☐ More than half. ☐ Less than half.	Time to recover

Surgical History

How many major surgeries have you had? _____ Please describe (last surgery first):

1. Reason for surgery:	Approx. date of surg.
Description of surgery:	
Amount of recovery: ☐ Complete ☐ More than half. ☐ Less than half.	Time to recover
2. Reason for surgery:	Approx. date of surg.
Description of surgery:	
Amount of recovery: ☐ Complete ☐ More than half. ☐ Less than half.	Time to recover
3. Reason for surgery:	Approx. date of surg.
Description of surgery:	
Amount of recovery: ☐ Complete ☐ More than half. ☐ Less than half.	Time to recover
4. Reason for surgery:	Approx. date of surg.
Description of surgery:	
Amount of recovery: ☐ Complete ☐ More than half. ☐ Less than half.	Time to recover

4. Have you ever been told that you have a hormone abnormality?
0-no 1-yes

5. Have you ever been pregnant?
0-no 1-yes

6. If yes, how many times?
1-once 2-twice 3-more than three times

7. How many times have you given birth?
0-never 1-once 2-more than once

8. Are you currently taking birth control pills?
0-no 1-yes

9. Do you think that you have hyperflexible joints?
0-no 1-in some joints 2-in many joints

10. Have you ever had a dislocated joint?
0-no 1-yes

11. Have you had pain in the face, jaw, temple, in front of the ear, or in the ear in the past month?
0-no 1-yes
[IF NO PAIN IN THE PAST MONTH, SKIP TO QUESTION 22]

12. How long ago did your facial pain begin for the first time?
_____ months or _____ years

13. Is your facial pain persistent, recurrent, or was it only a one-time problem?
1-persistent 2-recurrent 3-one-time

14. Have you ever gone to a physician, dentist, chiropractor, or other health professional for facial ache or pain?
1-no 2-yes, in the last 6 months 3-yes, more than 6 months ago

15. How would you rate your facial pain on a 0 to 10 scale at the present time, that is right now, where 0 is "no pain" and 10 is "pain as bad as it could be"?

NO PAIN										PAIN
0	1	2	3	4	5	6	7	8	9	10

16. In the past 6 months, how intense was your worst pain, rated on a 0 to 10 scale, where 0 is "no pain" and 10 is "pain as bad as it could be"?

NO PAIN PAIN

0 1 2 3 4 5 6 7 8 9 10

17. In the past 6 months, on the average, how intense was your pain rated on a 0 to 10 scale where 0 is "no pain" and 10 is "pain as bad as it could be"? [That is, your usual pain at times you were experiencing pain].

NO PAIN PAIN

0 1 2 3 4 5 6 7 8 9 10

18. About how many days in the last 6 months have you been kept from your usual activities (work, school, or housework) because of facial pain?

_____ days

19. In the past 6 months, how much has facial pain interfered with your daily activities rated on a 0 to 10 scale where 0 is "no interference" and 10 is "unable to carry on any activities"?

NO INTERFERENCE UNABLE TO CARRY ON ANY ACTIVITIES

0 1 2 3 4 5 6 7 8 9 10

20. In the past 6 months, how much has facial pain changed your ability to take part in recreational, social and family activities where 0 is "no change" and 10 is "extreme change"?

NO CHANGE EXTREME CHANGE

0 1 2 3 4 5 6 7 8 9 10

21. In the past 6 months, how much has facial pain changed your ability to work (including housework) where 0 is "no change" and 10 is "extreme change"?

NO CHANGE EXTREME CHANGE

0 1 2 3 4 5 6 7 8 9 10

22. Have you ever had your jaw lock or catch so that it won't open all the way?

0-no 1-yes

23. If yes, was this limitation in jaw opening severe enough to interfere with your ability to eat?

0-no 1-yes

24. Does your jaw click or pop when you open or close your mouth or when chewing?
0-no 1-yes

25. Does your jaw make a grating or grinding noise when it opens and closes or when chewing?
0-no 1-yes

26. Have you been told, or do you notice, that you grind your teeth or clench your jaw while sleeping at night?
0-no 1-yes

27. During the day, do you grind your teeth or clench your jaw?
0-no 1-yes

28. Does your jaw ache or feel stiff when you wake up in the morning?
0-no 1-yes

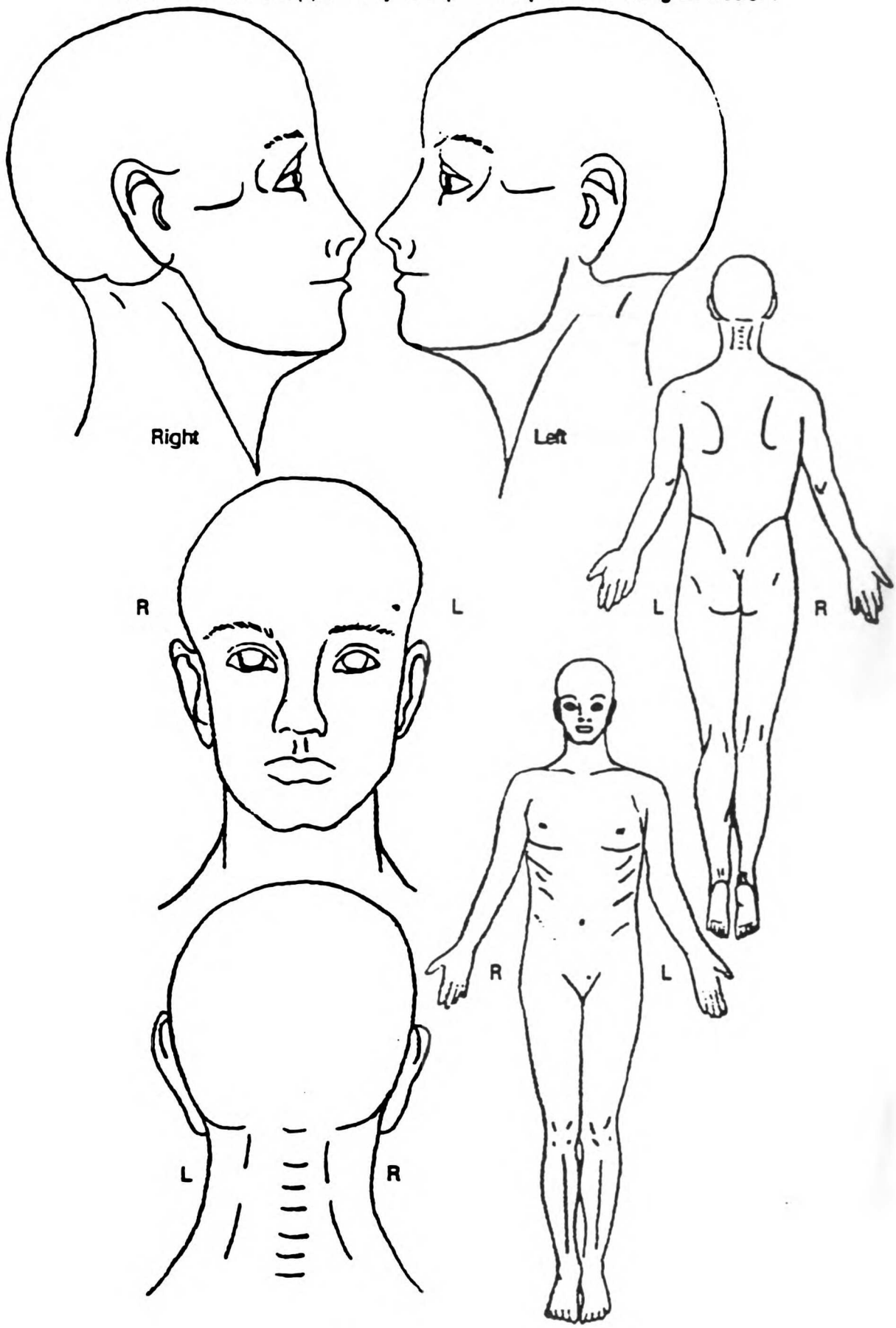
29. Do you have noises or ringing in your ears?
0-no 1-yes

30. Does your bite feel uncomfortable or unusual?
0-no 1-yes

31. What activities does your present jaw problem prevent or limit you from doing?

	NO	YES
a. chewing	____	____
b. drinking	____	____
c. exercising	____	____
d. eating hard foods	____	____
e. eating soft foods	____	____
f. smiling/laughing	____	____
g. cleaning teeth	____	____
h. yawning	____	____
i. swallowing	____	____
j. talking	____	____

32. Please mark the area(s) where you experience pain on the diagrams below.



33. In the last month, how much have you been distressed by:

	not at all	a bit	quite a bit	extremely
a. headaches	_____	_____	_____	_____
b. fainting or dizziness	_____	_____	_____	_____
c. feeling low in energy	_____	_____	_____	_____
d. thoughts of death or dying	_____	_____	_____	_____
e. poor appetite	_____	_____	_____	_____
f. crying easily	_____	_____	_____	_____
g. pains in the lower back	_____	_____	_____	_____
h. feeling lonely	_____	_____	_____	_____
i. worrying too much about things	_____	_____	_____	_____
j. feeling no interest in things	_____	_____	_____	_____
k. nausea or upset stomach	_____	_____	_____	_____
l. soreness of muscles	_____	_____	_____	_____
m. trouble falling asleep	_____	_____	_____	_____
n. trouble getting your breath	_____	_____	_____	_____
o. numbness or tingling in parts of your body	_____	_____	_____	_____
p. feeling hopeless about the future	_____	_____	_____	_____
q. overeating	_____	_____	_____	_____
r. sleep that is restless or disturbed	_____	_____	_____	_____
s feelings of worthlessness	_____	_____	_____	_____
t. feelings of guilt	_____	_____	_____	_____

34. When were you born? Month _____ Day _____ Year _____

35. Which of the following groups best represent your race?
1-Eskimo or American Indian
2-Asian
3-African American
4-Caucasian
5-Other (Please specify) _____

36. What is the highest level of school that you have completed?
0-none
1-Elementary School 1 2 3 4 5 6 7 8
2-High School 9 10 11 12
3-College 13 14 15 16 17 18+

37. What is your marital status?
1-never married
2-married
3-separated
4-divorced
5-widowed

38. Which best represents your household income during the last 12 months?
0-$14,999 ____
$15,000-$24,999 ____
$25,000-$34,999 ____
$35,000-$49,999 ____
$50,000 or greater ____

THANK YOU FOR YOUR PARTICIPATION. YOUR ANSWERS WILL BE CONSIDERED CONFIDENTIAL INFORMATION.