TMD Rediscovered: A New Paradigm, part 2

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Part one of this two article series predominately dealt with temporomandibular disorder (TMD) as an infectious disease. [1]A substantial effort was made to highlight the important relationships and changes inherent in the vascular biology of inflammation which included activation of the hemostatic system. [2] While the activation of the coagulation system was clearly established in the previous article, the concept of thrombophilia as an independent cause in joint disease[3,4] was somewhat marginalized. Additionally, the global symptoms manifest in reactive arthritis were underscored to help the practitioner transition from the academic rigors of the underlying pathophysiology to the clinical diagnosis.

The goal of this article is to take the background information previously presented and provide a solid diagnostic investigative clinical protocol that can be utilized on a daily basis. The author's position in this article is to take the basic information and provide the clinician with an approach that has not been previously explored in dentistry. Clear clinical examples of how this platform works will be presented. Content details will be constrained so the reader can move forward on the clinical level. Adequate references and resources are provided to help the readership learn at their own pace. However, this discourse cannot serve as a complete program within the set limitations. Hopefully this article will function as a firm introduction to material and ideas which are complex and require a great deal of personal effort to begin to understand the relationships to the disease entities clinicians observe. There is not one disease entity which cannot be explored through the premise of this platform.

Prior to moving forward with this new segment, there were two questions posited in the first article: One, why does the gender bias exist on this platform? Second, if TMD had its origin as an occlusomuscular disorder, why would a splint work if an infection was at the core foundation?

The Gender Bias in TMD

The sex steroids have an immunomodulatory role with respect to autoimmunity, infection and inflammation. [5-8] Estrogen not only modulates the immune response, but has a clear role in bone biology controlling osteoclastogenesis through regulation of TNF-α. [9] [10,11] Thus, in bone regulation, adequate estrogen levels have a protective role. The effects of combined oral contraceptive use in association with 17-β-estradiol deficiency have been reported by Gunson *et al.* in connection with human temporomandibular joint condylar resorption. [12] Concordantly, treatment with progesterone and estradiol in animal models enhances the survival patterns of *Chlamydia trachomatis.* [13] Oral contraceptives can also promote acquired thrombophilia by reducing protein S and increasing blood viscosity by reducing fibrinolysis. Protein S is required as a cofactor of protein C to initiate the breakdown of clots. [14]

In the innate immune system, TNF-α, a proinflammatory cytokine, serves the function as a purposeful acute phase reactant to kill pathogens. [15,16] Sex steroids influence the cytokine network, having both an organ-specific and tissue-specific role. [17.18] As estrogen levels change during the estrous cycle or during pregnancy when estrogen and progesterone levels steadily increase during the gestational period, the immunomodulating effects are altered, creating a potential window of opportunity for infection. Lahita notes that the role of pregnancy in the

generation of autoimmune disorders is complex. [17] While symptoms of SLE (systemic lupus erythematosus) may be aggravated during pregnancy, [19] rheumatoid arthritis can remit. [7 20]

Herein is where the conundrum occurs with respect to the gender bias in TMD. When gated by estrogen, TNF-α activity is reduced creating a permissive environment for microbial invasion. As described by Roberts *et al.,* the role of the endocrine system in altering immune response to protozoans may have several biologic advantages. Certainly, fetal retention is enhanced as estrogen and progesterone levels rise and the immune response is dampened. However, the tolerance generated creates an opportunistic environment increasing the likelihood of microbial penetration and persistence. During the earlier course of pregnancy, when estrogen and progesterone levels are lower, a more volatile immune response is possible which may increase the ability to kill pathogenic aggressors, but is potentially damaging to the viability of the fetus and can result in spontaneous abortion. [21]

This concept is the basis for a very important question the author always asks during the interview with women who have children or have attempted to conceive. [22,23,24] They are asked to report spontaneous pregnancy loss, difficulty in getting pregnant, preeclampsia, or stillbirths. There are a significant number of positive respondents for this question, and it has become a very valuable marker for suspicion of thrombophilia and infection (particularly chlamydia or other sexually transmitted diseases).

Sex steroids have diverse functions controlling the expression of toll-like receptors, cytokines, and antibody production, and can affect the metabolism, progression and virulence of pathogenic organisms. [25 26]Sex hormones maintain a key role in bacterial cell-to-cell communication called quorum-sensing. The conversational language between microorganisms and host is called “inter-kingdom signaling.” Many of these signals can be beneficial in a

symbiotic relationship; however, signals can also be 'hijacked' by bacterial pathogens to initiate virulence factors. In addition to sex steroids, microorganisms can also sense "fight-or-flight" responses from the adrenergic system. Opportunity is the "Achilles Heel" for host invasion. The signaling may not only enhance virulence, but facilitate chemotactic recruitment and migratory pathways serving as a trafficking mechanism. [27-32]

Different organisms will flourish or perish depending on host resistance factors and the ability of the organism(s) to adapt and survive on an epigenetic platform. Estrogen and testosterone have opposing effects on plasma extravasation in the rat temporomandibular joint. [33] Musculotendinous stiffness and sensorimotor responses may have suboptimal protective roles with respect to joint stability during the ovulatory phase of the menstrual cycle, predisposing to injury. [34-37] (Note: Review reference #18 for more information on this topic.)

The sexual dimorphism associated with TMD may be among the most difficult questions to answer in a straightforward fashion. As unique biological entities, each individual carries a distinct signature; no one answer can satisfactorily fulfill all the demands of this topic.

Splint Therapy

Splint therapy poses a very thought-provoking question within the paradigm presented. The objective in answering this segment is not to question whether splint therapy can be effective, because it often alleviates symptoms, but to contest the common wisdom. There is not one authoritative article describing the changes induced in the vascular supporting structures of the human or animal temporomandibular joints during occlusal alteration procedures such as splint therapy. Further, no studies have been identified that comprehensively describe the flow dynamics of the arterial and venous drainage systems during normal function. Even anatomical

and histological reports are few in this area. Yet, there are many changes that can occur to the vascular system upon alteration. [38] The human temporomandibular joint has a rich venous plexus both anterior and particularly posterior to the condyle. [39,40] Upon opening, the venous plexus of the retrodiscal tissue volumetrically expands to fill the space vacated within the fossa, increasing the volume by approximately four to five times[41,42] with an increase in lumen size. During jaw gapes, the parotid gland moves into the space under the expanded retrodiscal vascular complex. The clearance, however, is dependent upon return of the condyle posteriorly during the intercuspal phase of occlusion to drain the system. [41]

Occlusal splints increase the vertical dimension and induce rotational changes in the ability of the condyle to achieve its destiny with respect to venous clearance. Initially the effects may be beneficial, allowing the arteries to stretch and inducing higher flow rates and thrombin shear forces. [43] However, with the inability to clear the venous system quickly enough to keep pace with the increased blood flow, the untoward effect is to develop a static venous backflow system leading to the detrimental Virchow's triad and a localized state of hypercoagulability. The initial changes in vascular permeability may have beneficial considerations in allowing the infiltration of cell lineages to help clear an infection, but the dark side of full-time or long-term splint therapy in contributing to joint breakdown may become apparent.

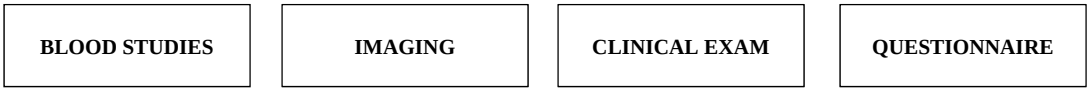
One such study was done by Fantini in a group of asymptomatic Class II orthodontic cases, whereby splint therapy was instituted for full-time wear to improve occlusal/condylar starting position and stability prior to the initiation of orthodontic care. Splints were worn 24 hours per day 7 days per week for an average of 7.8 months. The condylar displacement values in the raw data section were as high as 9.3mm in departure from starting position. [44] These

severe values would have resulted in a substantial anterior open bite on many of the participants due to degenerative changes in the condyle.

The author has one major rule of thumb. If I cannot load the joint statically or dynamically as instructed in my examination protocol, I will never make any type of occlusal splint.

The Key Elements In Clinical Diagnosis of TMD

The systematic approach to diagnosis of TMD is dependent on four categories:



Each category carries with it specific goals.

Blood Studies

The foundational principle of this category is predicated on the fundamental relationship between activation of the coagulation system and infection. The underlying mechanism consists of any entity that could potentially result in hypoxic or ischemic changes. Infections, therefore, will likely initiate changes in the hemostatic system that can be seen in blood studies. The basic questions that need to be answered within this class are:

1. Has the coagulation system been activated and are there markers present to confirm this?
2. Are there inherited or acquired markers for thrombophilia?
3. If an infection is at the root cause, can it be identified?
4. Is the patient immunocompetent?
5. Are there inflammatory markers present?

It is beyond the scope of this article to review all the blood tests and the rationale for prescribing such testing. Therefore, this discussion will focus on testing by category.
As reference sources, many commercial blood testing laboratories have a handbook they will provide to their clients upon request. For the coagulation section, Esoterix, now a subsidiary of LabCorp, has a "coagulation handbook" reference guide describing the tests offered, rationale, and a medical history screening protocol. The book can be purchased through Amazon. There are also many similar manuals available for purchase.

In evaluating whether the hemostatic system has been activated, the author traditionally orders the following tests as part of the initial routine screening to answer question #1:

- D-Dimer
- Fibrin Monomer
- Prothrombin Fragment 1.2
- Thrombin-Antithrombin Complex (TAT)
- Antithrombin III Activity
- Fibrinogen Activity
- Fibrinogen Degradation Products (FDP), Plasma
- Plasminogen Activity
- Acitvated Partial Thromboplastin Time (aPTT)
- PT with INR (Screening Test for Abnormalities of Coagulation Factors that are Involved in the Extrinsic Pathway)

The above tests are helpful markers in determining whether initiation of the coagulation cascade has occurred. [45,46] The D-Dimer and Fibrinogen Degradation Products are part of the fibrinolytic pathway and will often be elevated as a compensatory mechanism in the breakdown of clots and are useful indicators of the risk for venous thromboembolism (VTE). [47,48] If one or more of these tests are positive, the clinician will proceed to more comprehensive testing. However, many of these tests are often built into laboratory panels that can be ordered simultaneously as part of a comprehensive approach in reaching an earlier end point.

As part of the fibrinolytic pathway, elevated lipoprotein (a) and alpha-2-antiplasmin are pathway inhibitors to clot lysis, increasing the risk for VTE. [49,50]

- Alpha-2-antiplasmin
- Lipoprotein(a)

Protein C is part of the complex required to inactivate factor V and VIII in initiating the fibrinolytic component of the hemostatic system. Protein C requires protein S as a cofactor in order to accomplish this task. However, approximately sixty-five percent of protein S is normally bound to the C4b binding protein within the complement system, forming a bridge between the immune system and the coagulation system. Protein S has a higher affinity for C4b than protein C. During infection, the complement system is often activated and levels of C4b may rise, stealing protein S away from the anticoagulant activity of the protein C/protein S complex [51] creating a hypercoagulable state. [52] Oral contraceptives can also affect this complex and reduce protein S, [14] creating an imbalance between coagulation and fibrinolysis. [53]
To this end, the author always includes the following tests for the C4b binding protein:

- C4b Binding Protein, Serum
- C4b Binding Protein, Plasma

If positive results are obtained in the first set, then the answer to question #2 is sought: Does the patient have acquired or inherited thrombophilia? A powerful learning starting point for this area as it may pertain to joints and other structures is covered in all of these articles by Charles Glueck, MD, a renowned expert in this area. [3,4,54-69,70]

Tables 1-7 contain many of the tests that can potentially be ordered for patients. Tests for autoimmune profiles are not included. The tests are formatted for two commercial laboratories which accept most medical insurance plans so the author's patients will have minimal out-of-

pocket expenditures. In establishing whether there is an evidentiary trail of infection the author uses the selection options in Table 5 to answer question #3. Questions # 4 & 5 are addressed in Tables 6 and 7. *(Note: Due to space limitations Tables 1-7 can be found with this article online at DentalCEtoday.com)*

Imaging

If the patient has a TMD problem, as opposed to an orofacial pain condition, the author may refer the patient for MRI imaging subsequent to an examination. The MRI prescription is standardized. *(Note: A standardized MRI prescription of the TMJ can be found with this article online at DentalCEtoday.com).* Three computer discs are always ordered; one for the author, one for the patient, and one for an oral surgeon, if necessary. An online account is often beneficial to obtain quick results; however, many radiology practices are presently being consumed by larger conglomerates and hospitals requiring software, platform and password changes. Often, if one's computer is not dedicated to the radiology service, there can be conflicts between the existing programs in the computer and the network support. Traditionally, the clinician is the last to know such acquisitions have been made, making the transition difficult and frustrating.

The broad area of thrombophilia and hypofibrinolysis is referenced above. Antiphospholipid syndrome can be reviewed in these four articles. [71-74] The complement system is captured nicely by Glovsky. [75]

Clinical Examination for TMD

The clinical examination is part of the discovery process which has been paired with the anticipated findings on an MRI. The joint loading exam contains three modules; instructions are provided for module three and an interpretative guide for modules one, while the interpretation for two and three are combined. Each module has components designed for the specific purpose of evaluating each tissue area. *(Note: The modules can be found with this article online at DentalCEtoday.com).* The author does not seek to separate out the common view of muscle pain versus an intra-articular disorder. In this paradigm, the root cause is not occlusion, although certainly occlusion can be affected by joint disorders. The paradigm is fueled by inflammation which causes vascular changes and impedes oxygen delivery to the joint as an organ system. All disorders have an intra-articular component as well as disturbances in the surrounding structures. It is a given that muscles will be sore to palpation and the muscle component exists on the same platform.

If the joint(s) cannot be loaded statically or dynamically with load resistance and isometric testing, an MRI will be ordered. No treatment decisions are considered until the author views and interprets the images. All the surrounding structures are also palpated, including the vascular areas, muscle, lateral pole of the condyle, parotid and other salivary glands. All hard and soft tissues are evaluated and often an initial screening panoral radiograph is used.

Questionnaire

The author's questionnaire is very detailed and designed to provide a diagnostic advantage in assessing the associated risk indices for infection, thrombophilia, and VTE. There is a long list of symptoms and opportunity for environmental exposure risks assessing the chances for vector-borne diseases or sexually transmitted diseases. The questions asked are

often alienating and it is made very clear to my patients that I am non-judgmental and apologetic. The patient is asked about the number of sexual partners, if they have ever had an STD, if they have discharge from their genitals, urinary frequency or burning. A personal and family history is required in order to establish potential inherited traits that would lead me to genetic testing.

(Note: The complete questionnaire can be found with this article online at DentalCEtoday.com).

Putting Together the Elements of the Story

** indicates a substantial risk for thrombophilia.

Below are some case histories and support for the value of this paradigm. Case 1 is a full description with selective MRI images, freeze frames from arthroscopy and clinical photographs. Cases 2 and 3 will be brief descriptions and only partial disclosure.

Case 1

Patient: a 29 year old white, married female at time of the initial contact

Chief complaint: Pain in left TMJ with a visual analogue scale ranging from 4-9.

Symptoms on left side only:
- Pain on speaking, eating hard or soft foods
- Morning jaw stiffness
- Ear pain
- Jaw shifted toward left
- Pain upon opening
- Pain upon closing

Bilateral symptoms:
- Frontal Headache

IID: 18mm. with pain

Pain Description: Soreness

Temporal Aspects: Constant with fluctuations in intensity

Duration: 9 months at the current level but complains it has been present at reduced levels for 15 years

Personal Medical History: Hashimoto's thyroiditis, irritable bowel syndrome, mitral valve prolapse, asthma, hypermobile joint syndrome, heartburn, GERD, stress and past mononucleosis

Sexual partners: 1
- 2 children (normal) vaginal delivery
- 1 miscarriage **
- Bruises easily

Constitutional symptoms:
- Left knee pain
- Fatigue
- Skin Rashes (Negative)

Family History:
Mother: Hashimoto's thyroiditis, diverticulitis, osteopenia, back pain, celiac disease
Father: Prostate cancer, stomach cancer **
Sister: Bipolar, bulimic
Brother: Hashimoto's thyroiditis, undisclosed stomach problems
Maternal Uncle: Crohn's disease, Hashimoto's thyroiditis

Medications: Synthroid

Prior treatment: Part-time NTI provided by referring dentist for 9-10 months night wear only
Outcome: Partial initial positive response with relapse

Clinical exam:
- Slight partial anterior open bite
- All left side muscles of mastication extremely tender
- Right side lateral pole tender to palpation
- Right side masticatory muscles negative
- Inability to load left joint statically, dynamically with resistance, isometric resistance and contraction and load dependent with medium hard wax
- Working Side: Right Side
- Non-working (balancing side): Left Side
- IID: 18mm.

Initial Recommendations:
1. Testing for microbial pathogens
2. MRI TMJ
3. Referral to hematologist for thrombophilia profile (denied)

<u>Infectious disease findings</u>:
1. Epstein Barr Virus IgG (likely old illness)
2. Positive Lyme EIA early IgM

- Positive IgM Western Immunoblot meeting CDC criteria with 2/3 bands positive

Diagnosis: Lyme disease, treated by her physician with doxycycline 100mg. / b.i.d. for 6 weeks

MRI Findings Left Side:
1. joint effusions
2. soft tissue peri-capsular effusions
3. bone marrow lesion (edema)
4. displaced disc
5. effusion and stasis in retrodiscal tissue

Recommendations: Left Side Arthroscopy, eliminated splint therapy
1. Synovitis
2. Fibrosis

Outcome: 3 years later the patient is pain free without complaint

Case 1 Images: (Figures 1-6) *(Note: Complete images associated with this case can be found online with this article at DentalCEtoday.com)* THE ONLINE ARTICLE WILL BE MODIFIED TO INCLUDE ALL IMAGES NUMBERED IN SEQUENCE.)

Case 2
(Note: MRI images associated with this case can be found online with this article at DentalCEtoday.com).

This abbreviated case history is meant to demonstrate the associated elements of thrombophilia with degenerative joint disorders.

- 65 year old white female with right side TM joint pain.
- Medical history: Hashimoto's thyroiditis, hypertension, osteopenia, bulging discs in back, periodic muscle spasms in back, urinary irritation and frequent infections, allergies to dander.
    - Anemia, acne, arthritis, chronic nosebleeds, chronic post-nasal drip,
    - Family history of coronary heart disease and type II diabetes.**
    - Clogged ears, eating disorder, frequent urination, hypercholesterolemia.
    - Phonosensitivity
    - Varicose veins**
    - Irregular menses
    - Numerous lidocaine trigger point injections and steroids in back for lower back pain.
    - Left shoulder rotator cuff surgery.
    - Ophthalmic migraine**
    - Bone cyst left hip.
    - 1 miscarriage **
    - 1 sexual partner
- Medications: levothyroxine, Losartan HCTZ, OTC pain medications as needed
- **Thrombophilia profile:**

    - Anticardiolipin antibodies (+)
    - Homocysteine (+) elevated
    - MTHFR GENE MUTATION (+) A1298C/A1298C
    - PAI-1 GENE MUTATION 4G (single allele) intermediate VTE risk
    - Decreased Protein C activity
    - C4b binding protein (elevated) correlates with infection
- Diagnosis: Degenerative TM joint disease associated with thrombophilia, antiphospholipid syndrome, and likely infection of unknown source
- Recommendation: referral to rheumatologist and further testing for thrombophilia and infection. (denied)
- Clinical exam: inability to load test the right joint without pain in all tests
- Recommendation for right TM joint: Arthroscopy (accepted)
- Surgery performed and patient is asymptomatic 6 months post-surgery.
    - 4 months post-surgery judicious equilibration to MIP.

Case 3
(Note: MRI images associated with this case can be found online with this article at DentalCEtoday.com).

This last case is meant to show a patient with reactive arthritis. This is a 40 year old male single patient complaining of a dull ache in his left TM joint. The patient was able to accept static load force, but was uncomfortable during dynamic loading tests.
Symptoms: Headaches, neck aches, ear pain, and shoulder pain in addition to his TM joint (left). Stress, anxiety, stomach discomfort, carpal tunnel-like pain in wrists, ankles, knees, lower back pain, brain fog, fatigue, chronic rhinosinusitis, multiple phobias, OCD, psychiatric therapy, GERD and orthostatic hypotension.
The patient had been to multiple health care specialists and physicians and been given diagnoses such as chronic fatigue syndrome and fibromyalgia. During the course of treatment the patient described pain associated with prostatitis. Subsequently, the patient was diagnosed with:

- H. *pylori*
- Chlamydia *trachomatis*

This case is noteworthy because it was initiated prior to the development of this platform. The patient was treated with splint therapy and was doing quite well with his TM joint symptoms, but his constitutional symptoms worsened and ultimately he had to leave his job, collect disability and seek psychiatric care.

At time of treatment the patient's IID was 47mm. Subsequent to splint therapy and judicious coronoplasty he was able to open comfortably to 53mm. Upon periodic re-examination, his global symptoms seemed to have abated. It was at this time that the author had a consult with him and gathered some blood studies. Organisms were identified which contributed to his reactive arthritis, and he also disclosed that his physician had previously tested him for STD, *chlamydia trachomatis* and *H. pylori* and he was treated successfully. His TM joint-related symptoms had totally remitted. This occurred just subsequent to the author's care when his constitutional symptoms escalated.

This raises an important point. The author has four patients that have now been diagnosed with the chlamydia species. Traditionally, our profession has been taught to separate out muscular problems from intra-articular problems with the use of a dental appliance that will

increase the VDO and may redirect condylar position. The positive response may have no relationship to the underlying cause as demonstrated in this case, where the etiology of his joint complaints and global body symptoms were related to a reactive arthritis from chlamydia.

Conclusion

This article presents TMD as part of a complex disease model incorporating valuable diagnostic indicators and biomarkers that can be utilized beyond the traditional techniques. The approach allows the dentist to assume an investigative role that may be part of the first-line diagnosis in establishing an infective process, immune-incompetency or coagulopathy that will have a substantial impact on the well-being of the patient above the objectives of simple pain relief.

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