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WOUND HEALING OF TENDON — II. A MATHEMATICAL MODEL*

BRUCE GOLDIN,† WALTER D. BLOCK and J. RAYMOND PEARSON

Departments of Physical Medicine and Rehabilitation, Nutrition and Mechanical Engineering, The University of Michigan, Ann Arbor, Michigan, U.S.A.

Abstract – A mathematical model for healing tendon was developed reflecting correlations of biomechanical and biochemical factors. The model provided values for the physical and mechanical property changes during isometric thermal denaturation utilizing differences associated with treatment and length of healing period, along with the selected biochemical covariates of hydroxyproline, protein, and hexosamine concentration levels. Application of the biochemical values to the model estimated the physical and mechanical property changes of both the wounded and control tendon when the property changes between the two groups were small. When property differences were large, the wounded group was predictable for all property changes except dry tendon weight. The model showed the fifth healing day to be different from the other healing periods supporting the observation that day 5 was the shortest possible test day. Significance of the modeling approach to tendon healing is discussed.

INTRODUCTION

Gross and microscopic studies indicate that a particular sequence of events take place in a healing tendon or ligament (Mason and Shearon, 1932; Fernando and Movat, 1963; Clayton *et al.*, 1968). Structural and chemical changes occur in collagen during this process (Edwards and Dunphy, 1958; Jackson, 1958). Dunphy and Udupa (1955) ascribed the healing pattern into a productive or substrate phase where mucopolysaccharide and soluble protein precursors form, lasting for about five days; and a collagen phase beginning at about the fifth day and lasting until completion of healing. Mechanical property development accompanies the latter fibrogenetic period (Howes *et al.*, 1929; Dunphy and Udupa, 1955; Geever *et al.*, 1965; Hamilton *et al.*, 1970; Williams and Harrison, 1977), modified during maturation with age related changes (Lin and Sterling, 1968; Schubert and Hamerman, 1968; Viidik, 1969; Bihari-Varga and Biro, 1971). Restoration of form and function depend on the relative composition and orientation of the tissue protein, the extent of cross-linking, and the particular pattern of acid mucopolysaccharides (Gustavson, 1956; Jackson, 1958; Delaunay and Bazin, 1964; Milch, 1965; Bryant and Weeks, 1967; Harkness, 1968; Munro *et al.*, 1970; Biro and Bihari-Varga, 1972).

Unimpaired mechanical property development depends on a precisely timed and located sequence of degradation and synthesis of cellular elements allowing proper assembly and modification in the desired environment. The recovery of the connective tissue framework may be synthesized in its original form or may be laid down in excess with a resultant keloid, or when repair is inadequate, resulting in atrophy (Kellgren, 1955; Lapiere, 1973). The collagen diseases of rheumatic fever, rheumatoid arthritis, scleroderma, dermatomyositis, and periarteritis nodosa are debilitating disorders evolving from a defective inflammatory response (Gross, 1974). Aging or the degenerative process in collagen is affected by quantitative alterations in the mucoid, polysaccharide, and collagen content with a coarser fibrillar organizational pattern (Kellgren, 1955).

Characterization of the mechanical properties of healing wounds with the unique properties encompassed within the developing chemical structure of collagen has not been addressed. Studies on the mechanical behavior of healing wounds have been generally separate from those delineating quantitative biochemical changes. Concurrent biomechanical and biochemical studies exemplified by Dunphy and Udupa (1955), Geever *et al.*, (1965), Biro and Bihari-Varga (1972) and Sadiq *et al.* (1973) and elucidated in the literature review of Viidik *et al.* (1972) and the review article by Harkness (1968) have involved comparisons based on the appearance, rate, duration, and time sequence of the property event. Correlation of the structural and mechanical properties of collagen during reconstruction and repair to establish constitutive equations describing its behavior needs to be undertaken. Mathematical descriptions of the stress–strain history law of uninjured and unpathological collagenous tissue in simple elongation has drawn the bulk of attention (Fung, 1972).

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†Present address: Department of Orthodontics, The University of Connecticut Health Center, School of Dental Medicine, Farmington, Connecticut 06032.

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The purpose of this investigation was to describe the wound healing process of tendon using selected biochemical properties of the constituent polypeptides of the structural protein to ascertain tissue physical and mechanical properties and to correlate these empirical data to develop a constitutive equation. Experiments reported earlier in Goldin *et al.* (1980) were designed to quantify the collagen formation and the quality of cross-linking in healing tendon by physical measurements and mechanical testing utilizing thermal denaturation with simultaneous analysis of the protein and ground substance.

MATERIALS AND METHODS

Complete details of the methodology have been given elsewhere (Goldin *et al.*, 1980) and will be described here only briefly. Thirty-two adult male New Zealand rabbits ranging in age between 20–24 weeks, weighing between 2.9 and 3.8 kg, were used for the experiments. Following a two week acclimatization, the animals underwent a tendon splint surgical procedure performed on the paw extensor digitorum communis tendons. Alignment of the severed tendon ends was maintained by the application of this teflon support. The extensor tendon from the fifth phalanx remained intact to serve as the control.

Animals were assigned to one of five groups, represented as the post-surgical sacrifice interval 5, 7, 9, 11 or 13 days. The number of animals in each group was 8, 7, 6, 5, and 6, respectively.

Careful dissection was utilized to remove the extensor tendons and afterward, cut to a standard length of 5.0 cm, splint facing up. The splint was removed by cutting the sutures prior to physical measurement.

Cross-sectional area measurements were determined on the wounded and/or normal sections of tendon using the polar shadow amplitude machine employed by Ellis (1969) with 2.4 mm slit width. Specimen contours were later reconstructed as described by Ellis (1969).

Isometric thermic denaturation was determined using the material testing machine outlined in Goldin *et al.* (1980). The specimen was mounted in the test apparatus with two clamps, the proximal end of the tendon placed in the upper clamp. After immersion in a 25 × 100 mm culture tube filled with 25 ml, 40°C physiological saline, the bath temperature surrounding the tendon was allowed to rise at a rate of 2°C per minute to 65°C. An approximate 980 dyn load was applied to the tendon by lowering the moveable lower clamp and was monitored and, if necessary, adjusted to maintain the tendon in tension as the bath temperature increased and until thermal contraction commenced. The experiment was concluded when an appreciable decrease in tension was recorded with increasing temperature past maximal tension. After the bathing medium cooled it was reconstituted to 25.0 ml and stored at − 20°C for later biochemical study. The tendon specimen was dehydrated under vacuum for week, weighed, and frozen at − 20°C for later biochemical study.

Biochemical assays were conducted on the physiological saline bath of each tendon following isometric thermal denaturation and the individual vacuum dried wounded and control tendons. The method of Lowry *et al.* (1951) was used to assess protein concentration levels, Kivirikko *et al.* (1967) for hydroxyproline, Bitter and Muir (1962) for uronic acid, and Blix (1948) for hexosamine determined at a photometric wavelength of 540 mμm. The dry tendon was biochemically analyzed for hexosamine using the technique of Shetlar *et al.* (1972) prior to the Blix (1948) procedure.

Data analysis

Data from the tendons of both the left and right rabbit paws were pooled to yield mean control (intact) or experimental (wounded) tendon values for each animal. These individual animal mean values were again pooled to give 5, 7, 9, 11 and 13 day mean group values for the control and wounded animal tendons. Multiple linear regression analysis of the physical and mechanical property was performed on the biochemical property covariates and a set of dummy variables, treatment and time, which represented the analysis of variance model parameters. Dry tendon weight (mg) and tendon cross-sectional area (mm^2) were the dependent physical property variables. Shrink temperature, *Ts* (°C), slope of the isometric thermic denaturation curve between the load range of 5 and 15 kdyn (kdyn/°C), isometric thermic denaturation yield tension, *Ly* (kdyn), and maximum isometric thermic denaturation tension, *Lm* (kdyn), were the mechanical property dependent variables. The covariate biochemical independent parameters included hydroxyproline concentration (μmole/ml) or hydroxyproline concentration per unit dry tendon weight (μmole/g/ml) and the ratio of hydroxyproline concentration to protein concentration (μmole/μg), both of which were measured on the physiological saline bath surrounding the tendon during thermal denaturation, and hexosamine concentration (μmole/ml) or hexosamine concentration per unit dry tendon weight (μmole/g/ml) of the individual tendon specimens. Selection of the biochemical covariate terms depended on minimization of the error sum of squares in the analysis of variance. Model predictability was analyzed by means of least squares linear regression ($p < 0.05$) of the observed measurement of the physical or mechanical property contrasted with the predicted value. A multiple correlation of one, i.e. a 45° regression line, would be optimal model property estimation. The effects of treatment, time, and the influence of the biochemical covariates on the physical or mechanical property model were determined by the outcome of the ANOVA ($p < 0.05$) to test whether the regression coefficients for the variable terms were different from zero. The data base for the development

of the model is given in a previous publication (Goldin *et al.*, 1980).

Modeling

The mathematical analog suggested as a model for the physical and mechanical properties of tendon during the eight day interval between the fifth through the thirteenth healing day had the form:

$$P(i,j,k) = u + \sum_{i=1}^{2} a(i)X(i) + \sum_{j=1}^{5} b(j)Z(j) + \sum_{ij} \sum g(i,j)X(i)Z(j) + \sum_{k} d(k)C(i,j,k) + e(i,j,k)$$

where

$P(i, j, k)$ was the actual physical or mechanical property for the ith treatment, jth wound healing time, with kth biochemical determinations.

u was a constant representing an overall deviation from a zero base point, i.e. an intercept value.

$a(i)$, $b(j)$, $g(i, j)$ were constant coefficients due to the effects of treatment (i), time (j), and the two-way interaction of treatment (i) and time (j).

$d(k)$ were constant coefficients of the kth biochemical components.

$C(i, j, k)$ were the actual measured biochemical quantities considered to affect the physical or mechanical property.

$e(i, j, k)$ were random quantities due to chance factors. The difference between the actual property P and its best estimator was due to this error term, which included other factors not considered as variables in the model.

and for the $X(i)$ and $Z(j)$ dummy variables:

$X(1) = 1$ control group
$= 0$ otherwise
$X(2) = 1$ wounded group
$= 0$ otherwise
$Z(1) = 1$ time 1, i.e. fifth healing day
$= 0$ otherwise
$Z(2) = 1$ time 2, i.e. seventh healing day
$= 0$ otherwise
$Z(3) = 1$ time, 3, i.e. ninth healing day
$= 0$ otherwise
$Z(4) = 1$ time 4, i.e. eleventh healing day
$= 0$ otherwise
$Z(5) = 1$ time 5, i.e. thirteenth healing day
$= 0$ otherwise.

The multiple linear regression model was a two factor, treatment and time, $2X5$ crossed design, two treatment groups, intact or wounded, and five healing time periods, with biochemical covariate terms. The first three summated terms,

$$\sum_{i} a(i)X(i), \quad \sum_{j} b(j)Z(j),$$

and

$$\sum_{ij} \sum g(i,j)X(i)Z(j)$$

were qualification statements as to which treatment and point in time one preferred to predict. They were constant terms added to or subtracted from the physical or mechanical property prediction depending on the particular ith treatment and jth time period chosen. To solve uniquely for the treatment and time coefficients, the following assumptions were made:

$$\sum_{i=1}^{2} a(i) = 0$$

$$\sum_{j=1}^{5} b(j) = 0$$

$$\sum_{i} g(i,j) = 0 \quad \text{for all } j$$

$$\sum_{j} g(i,j) = 0 \quad \text{for all } i.$$

The biochemical components, $C(i, j, k)$ were independent variables (covariates) considered to influence, and used for estimating the physical or mechanical property. They were specific concentration values measured for the kth biochemical property in the i, jth treatment time category. The magnitude of the effect of the biochemical components on the physical or mechanical property prediction was adjusted with terms relating to particular treatment and time effects.

RESULTS

A. Physical properties

Dry tendon weight model. The dry tendon weight multiple linear regression model utilized hydroxyproline concentration and the ratio of hydroxyproline concentration to protein concentration as the covariate biochemical properties. Figure 1 shows the observed dry tendon weights plotted against the predicted model values. The model showed significant regression with a multiple correlation coefficient of

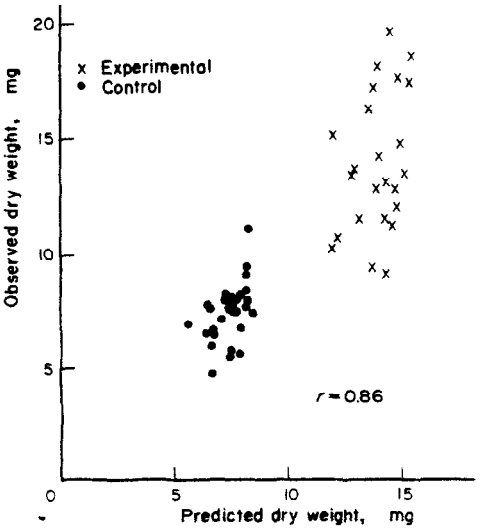

Fig. 1. Dry tendon weight multiple linear regression model, observed vs predicted model values.

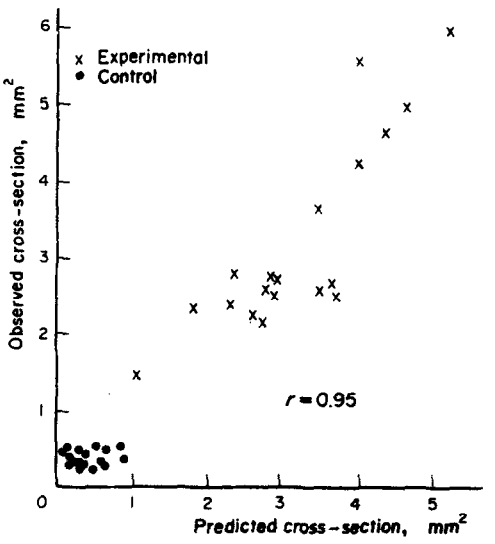

Fig. 2. Tendon cross-sectional area multiple linear regression model, observed vs predicted model values.

0.86, indicating 73% of the original dry tendon weight variance was explained by the systematic factors or variables in the model, namely, treatment effects, time effects, and biochemical effects. Analysis of variance indicated the biochemical properties chosen for this model had a small overall effect in predicting dry tendon weight. A significant treatment effect was shown and evidenced by the different cluster patterns seen in Fig. 1. The model predicted higher dry tendon weights for the wounded group than for the control group. Utilization of the model parameters separated on the control group tendons showed significant correlation ($r = 0.51$), the wounded group, however, showed poor model predictability. The dry tendon weight estimate was not influenced by healing time, indicating trends shown for the control group or the wounded group dry weight were consistent across the five time periods.

Tendon cross-sectional area model. The covariate biochemical properties selected for this model were hydroxyproline concentration, hexosamine concentration, and the ratio of hydroxyproline concentration to protein concentration. Figure 2 shows the observed tendon cross-sectional area plotted against the predicted model values. The model showed significant regression with a multiple correlation coefficient of 0.95, indicating 91% of the original tendon cross-sectional area variance was explained. Analysis of variance disclosed that both hydroxyproline and hexosamine concentration levels had a significant influence on the magnitude of the developed tendon cross-sectional area. Higher concentration values of hydroxyproline and hexosamine increased the prediction of tendon cross-section. A significant treatment effect on tendon cross-section was indicated by the model and observed by the cluster pattern in Fig. 2. There was distinct separation between the control and wounded groups, observed values greater than 1 mm² being characteristic of the wounded group. Prediction of tendon cross-sectional area using the model parameters separated by treatment was significant for the wounded group ($r = 0.85$), the control group showed poor model predictability. The model estimate of tendon cross-sectional area was not influenced by healing time, indicating trends shown for either the control or wounded groups were consistent across all five time periods.

B. Mechanical properties

The independent biochemical parameters employed throughout each of the mechanical property models were hydroxyproline concentration per unit dry tendon weight, hexosamine concentration per unit tendon weight, and the ratio of hydroxyproline concentration to protein concentration.

Shrink temperature model. Figure 3 shows the observed *Ts* plotted against the predicted model values. The model showed significant regression with a multiple correlation coefficient of 0.65, indicating 42% of the original *Ts* variance was explained by the systematic factors or variables in the model. Analysis of variance indicated that the biochemical properties chosen for this model had a small overall effect in predicting *Ts*. No treatment effect was predicted by the model as shown by the extensive overlap of the data from both the wounded and control tendon groups in Fig. 3. Correlation coefficients for the shrink temperature model separated on the control group was 0.43 and for the wounded group 0.77. Predictions at time 1, fifth healing day, showed significant effects on the model, differing from the other time periods.

Model for the slope of the isometric thermic denaturation curve. Figure 4 shows the observed de-

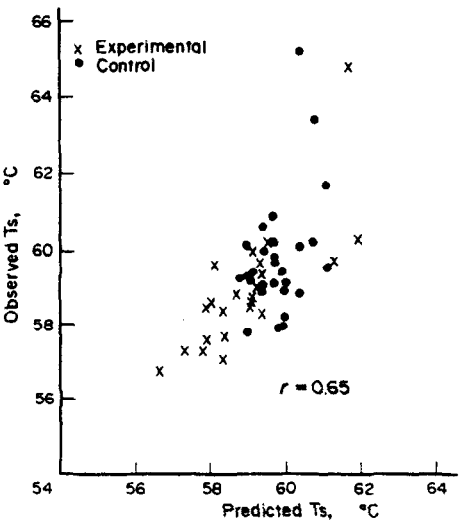

Fig. 3. Shrink temperature (*Ts*) multiple linear regression model, observed vs predicted model values.

naturation curve slopes plotted against the predicted values. The model showed significant regression with a multiple correlation coefficient of 0.84, indicating 71% of the original denaturation curve slope variance was explained by the variables in the model. Analysis of variance disclosed that hydroxyproline concentration per unit dry tendon weight had a significant role in determining the slope of the isometric thermic denaturation curve. Increased levels of hydroxyproline decreased the model prediction, i.e. a negative regression coefficient. A significant treatment effect on the model prediction of the denaturation curve slope was indicated. Prediction values for the wounded group were higher than the control group with the denaturation curve slope clustered at values greater than 2.50 kdyn/°C. When the model was separated by treatment only the wounded group showed significant regression ($r = 0.77$). The time 1 healing period, fifth day, was found to be different from the other prediction periods; at all other time periods treatment alone was necessary to estimate the denaturation curve slope.

Maximum thermic tension–thermic yield tension model. The mechanical property modeled, indicated as maximum thermic tension–thermic yield tension, was for *Lm* of the control tendon group or *Ly* of the wounded tendon group. Refer to the study presented in Goldin *et al.* (1980) for a description of the difference between the mechanical properties of the two treatment groups.

Figure 5 documents the observed tension values contrasted against the predicted model values. The model showed significant regression with a multiple correlation coefficient of 0.66, indicating 43% of the original *Lm* or *Ly* variance was explained by the variables in the model. Analysis of variance disclosed that the biochemical parameters of hydroxyproline and hexosamine were significant in determining *Lm* of the control group or *Ly* of the wounded group. Increased values of hydroxyproline decreased model prediction of tension as a consequence of a negative regression coefficient. The opposite was indicated for hexosamine concentration. No treatment effect was observed in the model as shown by the extensive overlap from both the wounded and control groups in Fig. 5. Correlation coefficients of the model separated on the control group predicting *Lm* was 0.53, the wounded group *Ly* was 0.77. Time 1, fifth healing day, again differed from the other time periods.

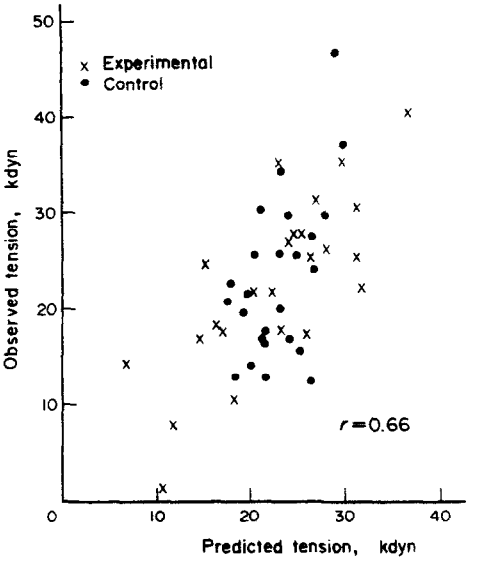

Fig. 5. Maximum thermic tension–thermic yield tension multiple linear regression model, control group *Lm* or experimental group *Ly*, observed vs predicted model values.

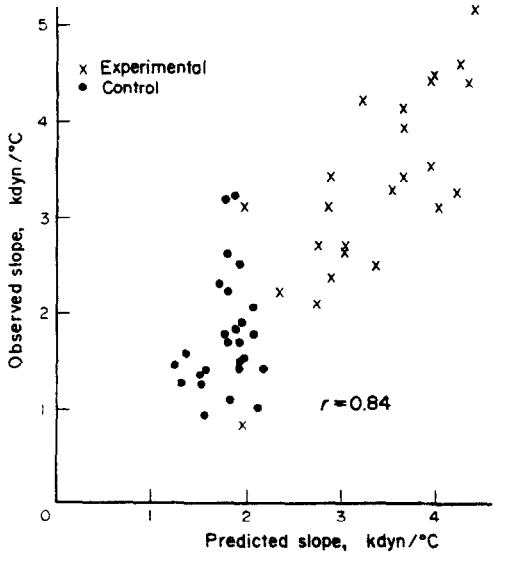

Fig. 4. Denaturation curve slope multiple linear regression model, observed vs predicted model values.

Maximum isometric thermic denaturation tension model. Figure 6 shows the observed *Lm* plotted against the predicted values. The model showed significant regression with a multiple correlation coefficient of 0.77, indicating 59% of the original *Lm* variance was explained by the variables in the model. Analysis of variance indicated that the biochemical property parameters chosen for this model had a small overall effect in predicting *Lm*. A significant treatment effect was observed in the model. Prediction values for the wounded group were higher than the control group with *Lm* clustered at values greater than 30 kdyn as shown in Fig. 6. Separation of the model parameters by treatment indicated significant regression ($r = 0.76$) of only the wounded group. Time 1, fifth healing day, was significantly different from the remaining healing periods, model estimation of the control or wounded group *Lm*, therefore, depended on whether time 1 was the chosen prediction period. At all other time periods treatment alone was necessary to predict *Lm*.

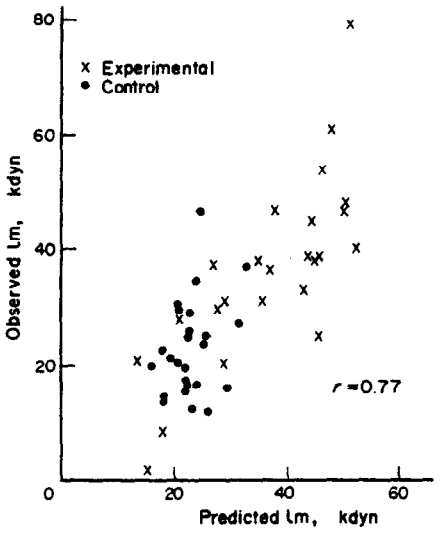

Fig. 6. Maximum thermic tension (*Lm*) multiple linear regression model, observed vs predicted model values.

DISCUSSION

The mathematical model developed for the physical and mechanical properties of healing tendon during a period from the fifth through thirteenth post-surgical day reflected the correlation of biochemical and biomechanical factors. The biochemical components were specific concentration values of either hydroxyproline, hexosamine, or both, for a selected treatment-time category, the magnitude of the effect on the physical or mechanical property prediction being adjusted with terms relating to treatment and time. Use of the ratio hydroxyproline concentration to protein concentration as a biochemical covariate normalized hydroxyproline concentration levels of tendon samples for the actual percentage incorporation into collagen. A subject factor due to the tendons from both the wounded and control groups being obtained from the same animal was ignored. Its effect was assumed small in comparison to treatment and time.

In general, the proposed model predicted the physical and mechanical property values of both the wounded and control tendon groups quite well when treatment effects on these properties were small. When treatment effects were large, the predicted model values were usually best for the wounded tendon group because of the wounded tissue physiochemical state with its resultant higher values measured for collagen and the acid mucopolysaccharides. The time 1 healing period, fifth post-surgical day, was shown by the model to be different from the other four healing periods with non-zero coefficients for the time 1 and interaction 1 terms in most physical and mechanical property prediction. Since all fifth healing day wounded tendon group data were limited with mechanical property results having large variance, the model supported the observation that day 5 was the shortest possible healing test day using the tendon splint surgical technique.

The dry tendon weight model was accurate only for the control tendon group because of pronounced treatment differences between it and the wounded tendon group, the only exception to the generalization mentioned above. Treatment differences and the lack of a healing time effect were supported by the data. Since the model prediction was based on uniform dry tendon weight over a 5.0 cm length specimen, it was not unreasonable for poor predictability for the wounded group. New tissue formed on a wounded group tendon encircled only 30% of the 5.0 cm specimen length and yet, contributed to 70% to 97% of the additional dry weight compared to its corresponding control group tendon. This may explain why no biochemical covariate was found to influence the dry tendon weight. Hexosamine concentration levels were not included in the model because its inclusion nullified the treatment effect.

The tendon cross-sectional area model demonstrated the treatment effect and the lack of healing period influence as observed in the data. Since the wounded tendon group had its cross-sectional area measurement ascertained about the gap region, which was the approximate center of an encompassed tissue mass occupying 30% of the total specimen length and the focal point of collagen and acid mucopolysaccharide formation, the tendon cross-sectional area model was consistent in its prediction of values for only this group. Hydroxyproline and hexosamine concentration levels were valuable indicators for model prediction of tendon cross-sectional area. The effect of each was to increase model values, indicative of fibrogenesis of regenerating tendon.

Model estimates of *Ts* were not affected by treatment indicating that its values for both the wounded and control tendon groups were not different from one another, and verified in the data. The time 1 or fifth healing day effect was shown by the model. *Ts* data from the wounded tendon group in the previous study were higher at the fifth day of healing when compared to its respective control group, inconsistent with the other healing periods and the progression of hydrogen bond formation. Hydroxyproline concentration levels did not influence the model prediction of *Ts*, in agreement with Chvapil and Jensovsky (1963) who felt shrink temperature was not the only factor determining the variation of physiochemical structural stability of collagen during the aging process. Hexosamine concentration levels also had little influence on the model. However, despite the inability to find better biochemical components for use in model prediction, the model was useful for estimation of *Ts* for both tendon groups.

The denaturation slope model estimated the rate of change of the developing isometric contraction force with increasing temperature during thermal denaturation. Treatment differences noted in the model

support the previous observations. The inverse proportionality between hydroxyproline concentration and the model prediction of the slope of the denaturation curve may be attributed to the immaturity of the regenerated tissue with its high level of collagenous activity. Wounded tissue with a haphazard fibrillar arrangement and a low number of effective intermolecular covalent bonds would have high salt solubility. Its rate of contraction would, and shown in the previous study relative to cross-sectional area, be slower compared to one with a more developed anatomical configuration having a greater potential incidence of molecular collisions.

The lack of a treatment effect noted in the maximum thermic tension–thermic yield tension model was observed in the data from the previous study. As a consequence, model prediction of the control group *Lm* was obtainable as well as the wounded group *Ly*. The influence of hydroxyproline and hexosamine concentration levels on the model was in agreement with the biosynthesis of collagen measured as hydroxyproline content and of the acid mucopolysaccharides measured as hexosamine content, and their observed increase coincident with tensile strength during the first two weeks of healing (Dunphy and Udupa, 1955; Bryant and Weeks, 1967; Biro and Bihari-Varga, 1972). Tensile strength, like the maximum isometric thermic denaturation tension, also ascertained the extent of intermolecular covalent bonding. Studies conducted on maximum isometric thermic denaturation tension (Brocas and Verzar, 1961; Boros-Farkas and Everitt, 1967; Takacs and Verzar, 1968) and neutral salt-soluble collagen measured as hydroxyproline concentration dissolved in Ringer at 65°C (Verzar, 1964; Takacs and Verzar, 1968; Everitt *et al.*, 1970) were implied to both estimate the extent of collagen covalent bonding and, hence, the biological age of the animal. The model for the control group *Lm* centralized this interrrelationship. Lower hydroxyproline concentration levels caused an increase in the model prediction of thermic tension (maximum/yield) for the tendon groups, consistent with higher tension values resulting from increased numbers of intermolecular covalent bonds. The model for the control group *Lm* supports work of Hruza and Hlavackova (1963). They found that a decrease in the extractability of hydroxyproline from rat skin with age was concurrent with a rise in the nonextractable part of the mucopolysaccharide in rat skin and tail tendon.

Lm values for the wounded tendon group were predicted by the corresponding tension model. As a consequence of the treatment effect, low biochemical concentration levels for the control group tendons resulted in its poor model predictability. Predictions of the control group *Lm* were best accomplished using the maximum thermic tension–thermic yield tension model. Treatment differences shown by the model and in the observed data diminished the effect of hydroxyproline and hexosamine in predicting model values of *Lm*. The studies by Dunphy and Udupa (1955), Bryant and Weeks (1967), Biro and Bihari-Varga (1972) and Sadiq *et al.* (1973) on wounded collagenous tissue, however, support their inclusion in the model.

CONCLUSIONS

A mathematical description of the wound healing process using the biochemical properties of the constituent polypeptides of the structural protein to ascertain the tissue mechanical properties during the first two weeks of tendon healing seems to provide a valuable tool to relate parameters of tissue composition to structure and function. The multiple linear regression model chosen was a basic first step in studying constitutive equations of the wound healing process. Since correct mechanical resistance of the collagen fibers depends on all, or most, of the chemical properties, an analog could aid in the proper maintenance of normal tissue growth by monitoring the intricate process of remodeling, and may allow a proper prescription of therapies to increase the precisely timed formation of biochemical constituents to accelerate the wound healing process. Gross (1974) indicated that surgeons already are using *cis*-hydroxyproline in tendon repair to interfere specifically with scarring and adhesions. Monitoring the biochemical concentration levels at the wound site would give predictions of the mechanical property at that particular moment in time. Abnormal connective tissue pathology, caused by defective chemical reactions leading to impaired mechanical properties, could be described using modeling techniques. In this way the genesis of the disease and its progression may be more fully elucidated. Pharmacological manipulation of collagen biosynthesis and deposition could be included as model covariate terms. These alterations may possibly regulate interactions between enzymes working on different parts of the macromolecular substrate to mediate the proper conformational change. The modeling technique might also be applied to determine systematically the variation of mechanical properties with physical and chemical factors, nutritional state, aging, the affect of one wound on another, location in the body, function of the organ, and resting and exercise.

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NOMENCLATURE

Ts	Shrink temperature, °C
Ly	Thermic yield tension, kdyn
Lm	Maximum thermic denaturation tension, kdyn.