Design of a novel anterior cruciate ligament prosthesis

by

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ABSTRACT

Injuries to the anterior cruciate ligament (ACL) are extremely common (approximately 100,000 every year in the US) and result in greatly reduced mobility; although several surgical procedures have been devised to address this condition, they are far from being completely satisfactory. The golden standard is currently represented by tendon autografts which, however, result in considerable donor site morbidity. An ideal solution would be to use effective, off-the-shelf permanent prostheses: however, all such devices proposed to date have proved highly disappointing, because of poor long term stability and biocompatibility, and unphysiological mechanical behavior. To address both concerns a novel prosthetic device has been developed, employing crimped NiTi superelastic wire bundles. To achieve near-physiological mechanical behavior, the fiber geometry resembles (on a much larger scale) that of the collagen fibrils that naturally make up the ligament, using as a starting point the Comninou-Yannas crimped-fiber model. NiTi (a superelastic alloy of titanium and nickel) has been tested and employed in a variety of biomedical settings and its excellent wear and biocompatibility characteristics make it a superior candidate for this application; the relevant literature has been reviewed and assessed. A detailed design for such prosthesis has been proposed, and a proof-of-principle model of the fiber geometry built and tested. The results obtained to date are encouraging and further testing, with a NiTi prototype should be carried out to validate our proposed design.

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1.Introduction and rationale of the investigation

The anterior cruciate ligament (ACL), that originates from the tibial plateau just medial and anterior to the tibial eminence, provides 85% of the total restraining force to anterior translation of the tibia. An ACL tear is a common injury that occurs in all types of sport: epidemiological studies estimate that approximately 1 in 3000 individuals sustains ACL injury each year in the United States [1,2]. This figure corresponds to an overall injury rate approaching 100,000 injuries annually, and, as the physically active percentage of the population increases, this figure is bound to rise, as well.. Until the introduction of arthroscopic surgery in the 70's, there were essentially no remedies for an ACL tear. Given the seriousness of the injury, that can severely restrict the motility of the patient, several therapies have been devised, aimed either at suturing or substituting the broken ligament. In the latter case, the grafts are either autografts or synthetic prostheses. Although autografts, usually taken from the patellary tendon, represent the gold standard, are associated with donor site morbidity, increased complexity of the operation itself, and unphysiological mechanical characteristics[3,4]. Sythetic prosthese designed ab-initio for ligament replacement could overcome such problems; however, all attempts made so far have been highly disappointing, due either to fracture/fatigue problems or particle release [5,6,7,8]. The purpose of this investigation was to devise and assess the feasibility of a novel type of permanent ACL prosthesis that takes advantage of the peculiar properties of NiTi alloys.

2.Method of approach

Since its very inception this investigation was meant to be above all a literature-review study, aiming at assessing the feasibility of a particular strategy for the replacement of human ACL before having to perform any actual experiments in the lab. Though this approach was dictated to a

large extent by financial constraints, it allowed us to take advantage of the wealth of data already available in the literature, and limiting to a minimum the number of questions we would still need to answer through ad-hoc experiments. Furthermore, it gave us greater freedom in pursuing different strategies, comparing different materials, before committing to a final design.

The first part of our research focused on understanding the structural and mechanical properties of the ACL, as well as its mechanical role in the knee during the different phases of motion. Secondly, the current therapeutic approaches to ACL reconstruction were reviewed, both the use of allografts and synthetic prostheses. The analysis of previous models of synthetic prostheses, and of the defects that lead to them being withdrawn from clinical use, was particularly instructive in shaping our goals for a novel design. In particular, all previously designed prostheses presented insufficient tribological characteristics,eventually leading to mechanical failure, and, even before that, unnatural stiffness, typically several times that of native ACL, leading to gait and back problems. Therefore, we wanted to design a prosthesis with both superior resistance to wear and more physiological mechanical properties.

The excellent tribological characteristics of NiTi alloys, combined with their exceptional biocompatibility immediately recommended it as a leading candidate for this use. Furthermore, as several models have been proposed [9,10,11] to explain collagen properties on the basis of fiber coiling and "waviness", we realized that the stiffness of the prosthetic construct could be altered, and the behavior of the native ligament mimicked, by altering the shape of the NiTi fibers composing it. Because of its simplicity and efficacy, the Yannas-Comninou model [9] was used as a starting point.

It was then essential to review the massive available literature concerning NiTi biocompatibility in vitro, in animal models, as well as in clinical applications, to see if we could

conclude that it would be safe in this application, too. The data gathered strongly suggests it, and in a later chapter we propose experiments that would definitively settle the issue. A similar approach was taken with regard to NiTi alloys wear resistance, the other essential feature for the success of the proposed prosthesis. A prototype was then designed, and tests on the proposed fiber geometry were carried out employing bundles of sinusoidal thin copper wires.

We then proposed a set of further experiments that would allow a more conclusive investigation regarding the clinical potential of the proposed device.

3.ACL Physiology

In order to correctly mimic the human ACL, the extensive literature surrounding it was reviewed; the data collected was at times hard to fit into a coherent framework because of the wide range of testing protocols, formats, and units employed (for example, N/mm vs. Mpa), as well as the exceptional variability of the object of study, human ACL, according to age, size, and weight, making the estimate of 'average" values somewhat arbitrary[11,12,13,14]. For safety reason, the ultimate tensile strength of the ligament has been taken to be 2200N, which is the upper bound for a young, healthy ligament in any study[14]. On the microscale, the ligament appears composed on axially oriented collagen fibrils, assembled in fascicles, that, in turn are organized in several bundles. On the macroscale, three major structures, or bundles can be identified, a posterolateral bundle (PLB) and two anteromedial bundles(AMB).

The PLB has an (average) modulus of approximately 160 MPa and a maximum stress of 18MPa, compared to values of 280and 28 MPa for the AMB[13]. The two sets of bundles exert different functions in knee kinematics, the PLB being mainly responsible for rotational stability in flexion and the AMB for rotational stability in extension; moreover, depending on knee flexion angle, the two bundles have unequal contributions to load transfer across the knee joint.

4.Synthetic prostheses

Over the years, there has been a wealth of synthetic substitutes for the ACL being proposed, both as permanent replacement devices, and as assistive, orthotic, devices. Though it can be claimed that they fulfill the orthotic niche quite nicely[15], until now all attempts at developing a successful synthetic prosthesis have failed.

Table 1: selection of proposed synthetic prosthesis and their description[5,7,8]

Commercial name	***Description***	***Material***
Stryker	4-6 woven tapes in tubular shell	PET/PP
proflex	15 concentric tubular braids of 32 yarn	PET
Lygeron	6 ribbons in a woven tube	PET
Kennedy-Lad	Braided narrow ribbons	PP
Leeds-Keio	mesh	PET
ABC Surgicraft	24 braided narrow ribbons wrapped at ends	PET
Ligastic	Tubular knit with polyurethane shell	PET
Raschel	Knitted structure rolled into tubular shape	UHMWPE
Braided PHP	Double concentric tubular braids	UHMWPE
Ligaid	Twisted cord braids wrapped at ends	PAA
Gore-Tex	24 braids of 3 yarns wrapped at the end	PTFE

Two modes of failure were evident: mechanical failure, in which the implant simply broke or became detached[5,7], and failure via inflammation and osteolysis induction[7], because of particles generated as the prosthesis wore down. In particular, SEM observations of recovered fibers revealed that abrasion of the textile fibers as a result of yarn-on-yarn and/or yarn-on-bone contact was a common phenomenon to almost all models[6,7], and was possibly the primary cause of prosthetic failure. Torsional and flexural fatigue of the fibers was also observed [7]. The collagenous infiltration present in certain prosthesis didn't act as a budding regenerated ligament, but rather showed a random, scarlike structure and, if anything, caused deterioration and fraying

of the textile fibers by infiltrating among them and disrupting their organized pattern[6]

Overall, the expexted lifespan of these prosthes is limited to a few years in the best of cases, with up to 80% failing at 5 years post surgery [16] and even less in groups that subject their knee to substaintial strains such as athletes or soldiers [17].

5.NiTi

5.1General characteristics

The first succesfull shape memory alloy based on an almost equiatomic mixture of Nickel and Titanium was discovered in the 1960's by Buehler and colleagues at the Naval Ordnance Laboratory (hence the name Nitinol) By the early 70's [18], its first medical applications were being explored. NiTi shape memory alloys can exist in two different temperature-dependent crystal structures (phases) called martensite (lower temperature) and ustenite (higher temperature, or parent phase). Several mechanical properties of the material change according to the phase: martensitic NiTi is soft and ductile, stress-induced martensitic (superelastic) NiTi is highly elastic, while austenitic NiTi is strong and hard, similar to pure titanium. The term superelasticity refers to the ability of NiTi to return to its original shape after a substantial deformation. This is based on stress-induced martensite formation: the application of an outer stress causes martensite formation at a higher temperature than normal, accommodating the imposed deformation. When the stress is released, the martensite transforms back into austenite and the speciment returns to the original shape. This mechanism allows to sustain elastic deformations (up to 8%) several times greater than normal metals, and is considered essential to NiTi's exceptional fatigue and wear resistance, highly desirable properties in a material employed in aligament prosthesis.

Table1: selected mechanical properties of NiTi, Stainless Steel and Titanium[19]

Material	*Austenitic NiTi*	*Martensitic NiTi*	*Stainless Steel*	*Titanium*
Ultimate tensile Strength (Mpa)	800-1500	103-1100	483-1850	540-740
Tensile yield Strength (Mpa)	100-800	50-300	190-1213	390
Modulus of Elasticity (Gpa)	70-110	21-69	190-200	105-110
Elongation at failure (%)	1-20	60	12-40	16

5.2Biocompatibility

The primary characteristic of any material destined to be implanted permanently in the human body is biocompatibility, therefore the early focus of my research has been to review the available literature concerning NiTi biocompatibility. Of particular concern was the possible release of Ni, of known toxicity and carcinogenicity, following implant surface corrosion and degradation. Though the studies by en large presented NiTi as an extremely safe material for medical application, considerable disparities were observed in corrosion resistance and citotoxicity depending upon surface preparation of the samples. The studies conducted can be divided into three broad categories: in vitro studies, studies conducted in animal models, and a posteriori analysis of clinical outcomes; i will briefly summarize the most important ones in each category, and then describe surface treatment and sterilization techniques which hold promise for further improving the suitability of NiTi for medical use.

5.2.1In vitro studies.

The first step toward establishing the biocompatibility of NiTi is customarily carried out in vitro, with cells grown on, or near, the substrate under scrutiny; cell proliferation , cell morphology and enzymatic activities are then assayed, and compared to a control population. A selection of in vitro cytotoxycity studies is summarized in table 2

Table 2: selected assessments of in vitro citotoxicity of NiTi alloys [20,21,22,23,24,25,26,28,29]

Cell type	*Assay used*	*Assessment of biocompatibility*
Prim. Murine splenocytes	proliferation	good
L132, HEMP	proliferation, viability	moderate, inferior to Ti
Rat fetal lung fibroblasts	proliferation	good
Prim. Human fibroblasts	proliferation	good
L929	Morphological evaluation	good
Prim. human epithelial cells	Morphological evaluation	good
Prim. Human fibroblasts	Proliferation	good
Prim human fibroblasts	proliferation	good, comparable to Ti
Osteosarcoma cells (MG-63, SAOS-2) prim. human osteoblasts (HOB), murine fibroblasts (3T3)	Proliferation, morphological examination	good
Prim. human epithelial cells	Enzymatic activity	good

5.2.2In vivo studies

Since the early 70's, a variety of animal studies have been conducted to test both the biocompatibility of NiTi alloys and the efficacy of the devices constructed from it.

Table 3 selected in vivo assessment of NiTi biocompatibility [30,31,32,33,34,35,36]

Animal model	*Target tissue*	*Assessment of*	*Biocompatibility evaluation*
rabbit	muscle	histocompatibility	good
rat	muscle	histocompatibility	good

Animal model	*Target tissue*	*Assessment of*	*Biocompatibility evaluation*
Guinea pig, rabbit. mice	skin	Sensitization, irritation, systemic toxicity	good
rat	bone, periosteum	histocompatibility	good
rabbit	oral mucosa	genotoxicity	good
rabbit	tendon	histocompatibility	good
dog	bone	histocompatibility	good
rat	dermis	histocompatibility	good
rabbit	bone	histocompatibility	good

5.2.3 Clinical implants

However, the ultimate test for a material's usefulness as an implant constituent comes from clinical experience: over the years, several devices have been approved by the FDA and have seen widespread clinical use in the US. The first device to be approved was the Simon Nitinol Filter, used to treat pulmonary embolism[37]. The filter was inserted as as a straight thin wire via the catheter used normally in angiographic diagnosis; upon reaching the lumen of the vena cava and sensing body temperature, it reverts to its original complex filter shape, trapping any circulating thromboemboli. A similar approach is followed by the vastly successful self-expandable NiTi stents: the low-temperature (thin) stent is inserted into the narrowed artery, where it heats and expands, dilating the lumen. Thousands of such devices have been implanted since the late nineties and in all the studies reviewed [38,39,40] no significant problem emerged linked to the use of NiTi as a permanent implant. Further applications of NiTi stents have been found, and approved by the FDA, in gastroenterology (for the treatment of biliary strictures both benign and malign, [41]), as well as in urology[42]. However,most of our data regarding long-term implantation of NiTi constructs comes from the fields of orthopedics and orthodontics. In orthopedics, NiTi has been

used with success as memory-shape fixation devices[43,44,45]. In orthodontics, it has established itself as the premiere brace material[46,47].

5.3Fatigue behavior

Since the ligament prosthesis will be subjected to an estimated 3-4 million cycles per year, one fundamental characteristic of the material to be taken into consideration during the design process is fatigue resistance. In particular, because of the nature of the loading in the physiological setting, it is important to take into consideration both pull-pull and bending/torsion fatigue tests. The considerable literature available in this regard suggests a safe value of approximately 0.5% strain, at temperatures similar to that of the body [48,49,50].

5.6Wear and corrosion resistance

NiTi alloys have been reported to have exceptional wear and corrosion resistance properties (up to two orders of magnitude less wear than steel or titanium)[51,52], particularly after surface-hardening treatments, such as plasma source ion (especially nitrogen, oxigen and argon)[53,54,55,56,57] implantation. Ion implantation is particularly suited for surface modification of NiTi alloys because it is carried out at near-room temperature, without altering the peculiar mechanical properties of the material. Furthermore, the modified surface layer is compositionally graded, so that there is no distinct interface with the bulk material, preventing the risk of delamination. Increasing wear and corrosion resistance, in turn, would further increase NiTi biocompatibility . There is, however, a lack of specific, quantitative data (particle generation and particle size) for wire-wire contact, as well as for NiTi surfaces sliding in a physiologically lubricated environment. Such questions should be addressed with ad-hoc experiments.

5.7 Sterilization

Finally, an important consideration was the possibility for NiTi wires (subjected to a

variety of surface treatments) to be sterilized via common methods without substantial degradation or alteration of their mechanical behavior or biocompatibility. Of the methods reviewed in the literature, ethylene oxide sterilizations seems the most satisfactory [58,59].

6.The Yannas-Comninou model

In order to ensure the clinical effectiveness of the prosthesis, it is important to try and match as closely as possible the ACL's native mechanical properties. In Particular, a relatively soft, viscoelatic material capable of high life cycles at high strain rates has to be mimicked using a relatively stiff, linear-elastic material, much less amenable to high strains. To accomplish this, we turned to a model developed by Yannas and Comninou [9] deriving the observed properties of ACL from the peculiar crimped, or sinusoidal, architecture of the single, relative stiff and linear-elastic collagen fibers. In a nutshell, the high apparent, macroscopic strain (given by the change in length over the original length) observed is due to a "flattening" of the fiber, which only undergoes a much less pronounced microscopic strain

Following Yannas and Cominou derivation, we wish to establish a simple mathematical relationship between the geometrical parameters of a sinusoidal fiber (of the form $y = a \sin bx$) and its apparent strain under a given stress. We consider the stress (σ) only in the direction of the fiber (denoted by X in the usual x,y,z coordinate system), so that

(1) $\sigma(x) = E\varepsilon(x)$,
(2) $\sigma(y) = \sigma(z) = \tau(xy) = \tau(xz) = \tau(yz)$,

where E is Young's modulus and τ the shear. The strains then are

(3) $\varepsilon(x) = (1/E)[\sigma(x) - \nu(\sigma(y) + \sigma(z)] = \sigma(x)/E$
(4) $\varepsilon(y) = (1/E)[\sigma(y) - \nu(\sigma(x) + \sigma(z)] = -\nu\sigma(x)/E$
(5) $\varepsilon(z) = (1/E)[\sigma(z) - \nu(\sigma(x) + \sigma(y)] = -\nu\sigma(x)/E$
(6) $\gamma(xy) = \gamma(xz) = \gamma(zy) = 0$

If we denote by I the moment of inertia of the wire, a its wave amplitude and b the frequency, we can use equilibrium and geometric compatibility constraints to derive a constitutive equation [] relating the stress in the fiber and the apparent uncrimping, denoted by α

$$(7)\sigma(x) = E\alpha - [(Ea^2*b^2)/4]*[\Lambda(\Lambda+2)/(\Lambda+1)^2],$$

where $\Lambda = A\sigma(x)/b^2*R^2$

However, we are only interested at small levels of stress and microscopic strain, so that $\Lambda<<1$. We have then:

$$(8)\Lambda(\Lambda+2)/(\Lambda+1)^2 \cong 2\Lambda$$

Substituting and rearranging, we then obtain,

$$(9)\ \sigma(x)= [E*R^2/(R^2 + 2a^2)]*\alpha.$$

$[E*R^2/(R^2 + 2a^2)]$, then is the effective stiffness of the wire, that can be altered by adjusting the wire thickness and wave amplitude, under the condition that $\Lambda<<1$.

7.The design

Mimicking the original ligament, the prosthesis will be composed of two bundles, an anteromedial (AMB) and a posterolateral (PLB)one, similar in size, orientation, and mechanical characteristics to the ones in the ACL. Their rest lengths would be 10cm for the posterolateral bundle and 85 mm for the anteromedial bundle, with corresponding stiffnesses of 160 and 280 Mpa. The different stiffnesses will be obtained by altering the crimp angle, and wave amplitude/radius ratios of the fibers in the two bundles. For wires 0.5 mm in diameter, commonly available in medical grade for orthodontic applications, with a Young's modulus of approx. 40GPa, this would translate into wave amplitude of 2.8 and 2.1 mm respectively, with a wavelength of 10mm. Note that with these parameters even the reported maximum stresses in the

two bundles would cause a material strain substantially less then the threshold (0.5%) indicated in the literature as safe for virtually infinite lifetime. The fibers will be connected to two terminal bone attachment points either via crimping or plasma welding. To insure fixation, instead of the current bone-plug method, devices similar to those used for dental implants could be used, taking advantage of the shape-memory behavior of the NiTi .

Pretensioning is an essential aspect of the implantation of current artificial ligaments, highly influential on the prostheses effectiveness, and would be greatly facilitated by the memory-shape behavior of NiTi: the prosthesis could be implanted (cold) in an elongated state and would tend to shorten as it reaches body temperature, generating a predetermined force level.

8.Proof of principle testing

As we were unable to obtain sinusoidal NiTi wire, we employed bundles of sinusoidal copper wire (made up by 10 1 mm wires) to test the effect of fiber geometry upon apparent stiffness and elasticity. 3 sets of such bundles, characterized by different values of amplitude:radius ratios (1:1, 3:1, 5:1, 10:1) where tested in elongation, and compared with a bundle made up of straight wire. As they were subjected to the same load, the respective apparent stiffness values could be obtained from the different macroscopic deformations. As we can see from the graphs below, the simple model we employed describes fairly well the material behavior at low strains

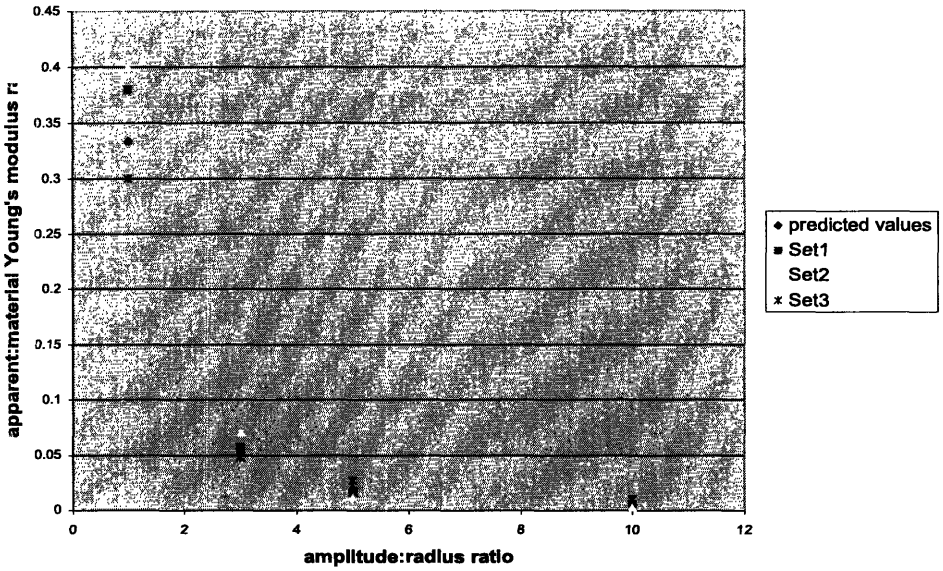

Figure 4: predicted and experimental ratios of apparent stiffness to young modulus vs. fiber r/A ratio.

9.Conclusions

The proposed artificial prosthesis for repair of the anterior cruciate ligament holds promise as a considerable improvement upon available ACL replacements, both autografts and synthetic prostheses, in terms of long-term performance, patient recovery of articular function, as well as ease of use. Although laboratory testing of the proposed design is still needed in order to fully characterize the behavior of the prosthesis prior to animal testing, the use of a well-established material and mechanical model has allowed a fast development of the original idea. A thorough review of the available literature has underlined the exceptional properties of nickel-titanium alloys for this particular application, with regard to both biocompatibility and tribological properties. Experiments that should be carried out to further validate the idea depend upon the realization of a proof-of-principle prototype made with sinusoidal NiTi wires; though fairly expensive, it's a service performed commercially by several companies, such as Guelph Wire Products or medical valley LLC. Such prototype should then be subjected to in vitro testing of mechanical properties,

wear resistance and particle generation, possibly in a simulated environment mimicking the in-vivo conditions. In this regard, the technology developed for the testing of total knee replacement prostheses would prove very valuable and should be easily adaptable.

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