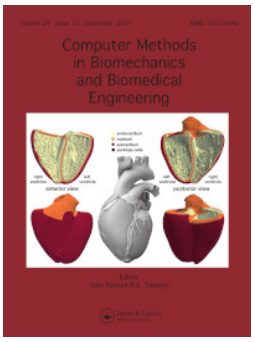

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Sensitivity analysis of the knee ligament forces to the surgical design variation during anterior cruciate ligament reconstruction: a finite element analysis

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ABSTRACT

The purpose of this study is to understand the effect of essential surgical design parameters on collateral and cruciate ligaments behavior for a Bone-Patellar-Tendon-Bone (BPTB) anterior cruciate ligament reconstruction (ACL-R) surgery. A parametric finite element model of biomechanical experiments depicting the ACL-R surgery associated with a global sensitivity analysis was adopted in this work. The model parameters were six intraoperative variables, two-quadrant coordinates of femoral tunnel placement, femoral tunnel sagittal and coronal angles, graft pretension, and the joint angle at which the BPTB graft is tensioned (fixation angle). Our results indicated that cruciate ligaments (posterior cruciate ligament (PCL) and graft) were mainly sensitive to graft pretension (23%), femoral tunnel sites (56%), and the angle at which the surgeon decided to fix the graft (14%). The collateral ligaments (medial and lateral) were also affected by the same set of surgical parameters as the cruciate ligaments except for graft pretension. The output data of this study may help to identify a better role for the ACL-R intraoperative variables in optimizing the knee joint ligaments' postsurgical functionality.

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KEYWORDS
ACL reconstruction; surgical variability; ligaments behavior; finite element model; global sensitivity analysis

1. Introduction

Approximately 250,000 anterior cruciate ligament ruptures occur annually with a cost of treatment exceeding $2 billion, among which mostly incurred for surgical reconstruction (Prodromos 2007; Gianotti et al. 2009; Bates and Hewett 2016; Wiggins et al. 2016). The primary goals of anterior cruciate ligament reconstruction (ACL-R) are to restore the knee's stability and reinstate healthy functional activity (Nakamura et al. 2017). However, some studies have demonstrated that the successful recovery of standard joint movement patterns during dynamic or static activities is hardly achieved (Bush-Joseph et al. 2001; Lewek et al. 2002; Papannagari et al. 2006; Stergiou et al. 2007; Tashman et al. 2007; Webster and Feller 2011; Zabala et al. 2013; Signorelli et al. 2016; Zaffagnini et al. 2016). The failure to restore normal movement would influence both the joint active-passive response as a whole and the mechanical role of the remaining intact components, such as collateral and cruciate ligaments, with a high likelihood of increasing the rate of postsurgical revision or failure (Klimkiewicz et al. 2000; Strobel et al. 2001; Liow et al. 2003; Fujimoto et al. 2004; Mesfar and Shirazi-Adl 2006; Shimokochi and Shultz 2008; Gianotti et al. 2009; Hart et al. 2009; Iriuchishima et al. 2010; Norris et al. 2012; Richter et al. 2018; Svantesson et al. 2019).

Alteration of the medial collateral ligament (MCL) and lateral collateral ligament (LCL) mechanical responses because of concomitant injuries or abnormal postsurgical loading have been recognized as a strong predictor of the risk of ACL-R revision within the first 2 years postoperatively (Liow et al. 2003; Halinen et al. 2006; Hart et al. 2009; Hamrin Senorski et al. 2018; Svantesson et al. 2019). This reported evidence of a positive correlation between the alteration of the collateral ligament response (because of traumatic injuries), specifically the MCL, and the rate of ACL-R postsurgical revision and failure may be attributed to the irregular loading conditions of the

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reconstructed joint. The irregular loading conditions may be mediated by surgical parameters such as femoral tunnel attachment sites and tunnel orientations, graft pretension, angle of fixation, or the patients' specific parameters such as joint geometry and postsurgical muscle activation patterns (Schroeder 2014).

Furthermore, several arthroscopic observations of failed ACL-R grafts showed that the grafts were strained due to impingement against the lateral bundle of the posterior cruciate ligament (PCL) (Strobel et al. 2001; Simmons et al. 2003; Fujimoto et al. 2004; Nishimori et al. 2007; Iriuchishima et al. 2010; Noyes 2012; Nakamura et al. 2017). These observations suggested that surgical parameters like femoral tunnel placement and graft pretension were responsible for this altered mechanical contact (impingement) between the graft and the PCL, resulting in high graft cyclic tension (Simmons et al. 2003; Fujimoto et al. 2004). However, the relative contributions of the surgical variables to the cruciate ligaments interaction following an ACL-R remain unclear.

To investigate the sensitivity of the joint ligament forces to the surgical alteration of the bone-patellar-tendon-bone (BPTB) ACL-R procedure, a systematic computational approach was employed in this study. Within the adopted framework, several ACL-R models along with a calibrated and validated healthy model (Dhaher et al. 2010; 2016; Adouni et al. 2019) were used to identify the effect of femoral sagittal and coronal orientations, vertical and horizontal locations of the femoral tunnel, fixation angle and graft pretension on collateral (MCL and LCL) ligaments, and cruciate ligaments (graft and PCL) force patterns as estimated during an isolated task (axial compression). The sensitivity analysis framework is advantageous because of the multifactorial nature of the problem. Consequently, it is hypothesized that ligament and ACL graft forces are altered by changes in the surgical design parameters.

2. Methods

The finite element (FE) model of the knee joint employed in this study consists of all relevant soft tissues. A detailed explanation of the FE model was presented in the supplementary materials and our prior works (Dhaher et al. 2010; Schroeder 2010, 2014; Adouni et al. 2019), and only a brief overview will be described here. The knee model includes three bony structures – tibia, femur and patella, and their articular cartilage layers, menisci, six principal ligaments (i.e. collaterals LCL/MCL, cruciate ACL/PCL and medial/lateral patellofemoral ligaments MPFL/LPFL), the patellar and quadriceps tendons (PT, QT). The adopted FE model incorporates the collagen networks and solid matrix with depth-dependent variations of properties within the structures of cartilage and ligament (Weiss and Gardiner 2001; Bi et al. 2006) (Figure 1a1) (*for detailed description, please see the supplementary materials section*). This model was updated with additional features, while some changes developing the parametric FE model of biomechanical experiments depicted the ACL reconstruction surgery (Salehghaffari and Dhaher 2014, 2015) (Figure 1a2). The model parameters were six intra-operative variables, four femoral tunnel geometrical properties (tunnel sites and orientations), and two graft specifications (graft pretension and the joint angle at which the graft initially tensioned) (Figure 1b) (please see the supplementary materials section). Five steps were sequentially implemented to achieve the surgical simulation – (1) the proximal bone plug was placed inside the femoral tunnel, aligned with the tunnel axis; (2) with the proximal bone plug constraint to rotate and slide about the femoral tunnel axis, the distal bone plug was placed and fixed in the tibial tunnel; (3) the tibia was flexed to a given fixation angle; (4) with the tibia free in all degrees of freedom, the proximal bone plug was pulled along the axis of the femoral tunnel using a given pretensioning force; and (5) the joint was fully extended, and the surgical simulation was completed (Figure 1c). Details on the models (healthy and ACL-R) and surgical simulations are given in our prior investigations (Dhaher et al. 2016; Adouni et al. 2019).

Articular cartilage was considered as a hierarchical hyper-elasto-plastic composite material. This model was built based on a multilevel multiplicative decomposition of the deformation gradient combined with the rule of the mixture (Adouni and Dhaher 2016; Adouni et al. 2019). A transversely isotropic hyperelastic material model assumed to be nearly incompressible was employed for the ligaments where the material model was driven by an uncoupled representation of the strain energy function defined by Limbert and Middleton (2004). The menisci were considered transversely isotropic, linearly elastic, homogeneous material (Adouni et al. 2019). A 0.001 g/mm^3 density was assigned to all soft tissues (Penrose et al. 2002), whereas the rigid bony segments were assigned to a density of 0.002 g/mm^3 (Hoffer 1983). A detailed description of the properties of the assigned materials is given in the supplementary materials section and our prior published

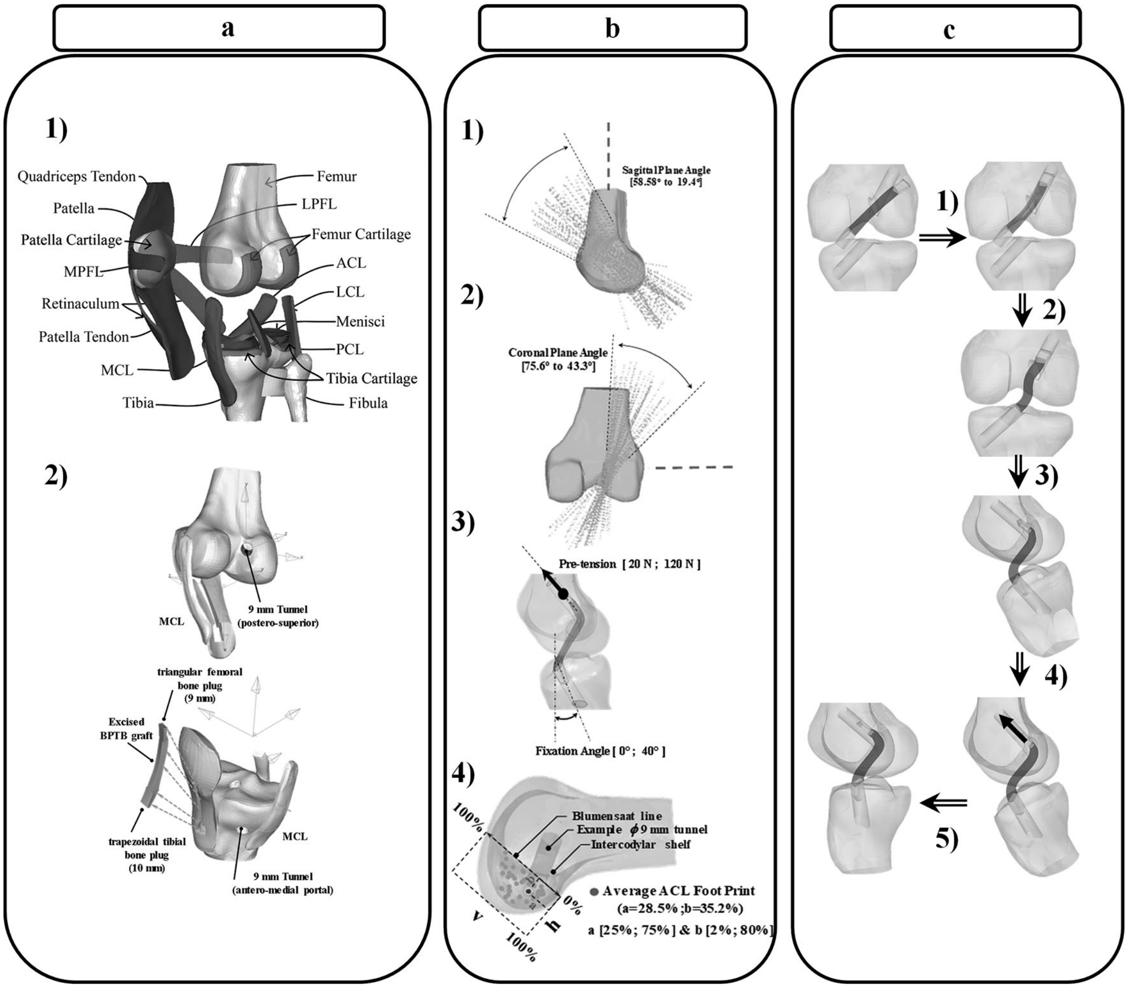

Figure 1. (a1) Posterior view of the finite element model representing the knee joint. The FE model consisted of all bones, all relevant ligaments, articular cartilage and menisci were included. (a2) an updated version of the FE knee model with the key surgical features used to mimic the ACL-R procedure; (b1) femoral tunnel sagittal plane angle, (b2) femoral tunnel coronal plane angle, (b3) graft pretension and the angle of fixation, (b4), tunnel placement following the quadrant method; (c) different ACL-R surgical simulations steps (Step 1 to 5). Details on the FE and ACL-R models and the reference of the considered range of variation of the surgical parameters can be found in Dhaher et al. (2016).

Table 1. Range of variation for each surgical parameter.

Ranges	Sagittal angle (°)	Coronal angle (°)	Horizontal quardant coorinate (h%)	Vertical quardant coorinate (v%)	Fixation angle (°)	Tensioning force (N)
Lower bound	19	43	2	25	0	20
Upper bound	59	75	80	75	40	120

Tunnel placement (location of the tunnel centers), the sagittal and coronal orientations, fixation angle, and tensioning force (see Figure 1).

investigations (Dhaher et al. 2010; Adouni and Dhaher 2016; Adouni et al. 2019; Faisal et al. 2019).

A global sensitivity analysis, based on the variance decomposition (Saltelli et al. 2010), was adopted to investigate the contribution of surgical parameters (fixation angle, graft pretensioning force, horizontal and vertical femoral tunnel locations, sagittal and coronal femoral tunnel orientations) to the uncertainty of the ACL-R knee four principle ligaments forces (graft or anterior cruciate ligament (ACL), posterior cruciate ligament (PCL), lateral and medial collateral ligaments (LCL and MCL)) under 1000 N of axial compression with fully extended knee joints. The main reasons for choosing the 1000 N of compression for our loading conditions were the observed similarity with the joint's load under single-leg standing activity (Harrison et al. 1994; Noyes 2012) and the reported observations informing that cruciate ligament (graft/PCL) impingement occurs when the knee is in full extension (Strobel et al. 2001; Fujimoto et al.

2004). The sensitivity analysis requires several executions of the ACL-R model with varying sets of surgical parameters. To alleviate the computational cost associated with the multiple FE model simulations (each FE model simulation may take between 12 and 14 hours), a radial basis function (RBF) has been used as a mapping between the considered surgical parameters and the knee ligament forces (reducing the simulation time to a couple of seconds) (for more details, please see the supplementary materials section). The smallest error of this approximation was achieved through 48 training points. Reasonable bounds for the surgical parameters relative to data reported in a large body of the literature were also employed (Dhaher et al. 2016) (Figure 1b) (Table 1). Hence, the contributions of a set of input parameters (6 surgical design parameters) to the uncertainty in response output (knee ligament forces) can be quantified by ranking the parameters based on the output variance when one of the parameters is fixed to its true value (the value of the surgical parameter that may lead to a ligament force almost equal to the force produced before the deficiency of the ACL). The expectation of all possible values of the input parameters was considered here to circumvent the unknown true value of the surgical parameters (input parameters). Based on the above description, equation (1) has been used to determine the sensitivity indices (Saltelli et al. 2010):

$$\begin{cases} S_i = \dfrac{V(E(YX_i))}{V(Y)} \\ S_{ij} = \dfrac{V(E(YX_i, X_j)) - V(E(YX_i))}{V(Y)} \\ \vdots \\ \sum_i S_i + \sum_i \sum_{j>i} S_{ij} + \ldots + S_{12\ldots6} = 1 \end{cases} \quad (1)$$

where S_i and S_{ij} … are the first and the subsequent orders of sensitivities, X is the input parameters, Y is the output, and $V()$ and $E()$ are variance and expectation operators, respectively.

3. Results

5 out of 48 models experienced an LCL force within 10% of the LCL force observed in the healthy model under the same boundary condition (Figure 2a). These models were characterized by a range of anterior location of the femoral tunnel (Figure 1b4) varying from 32 to 60%, lower tunnel sagittal orientation (19° to 25°), and midrange of the angle of fixation (18° to 28°). The force increased remarkably – reaching 59 N – with an increased angle of fixation (35° and up), that was associated with a low graft pretension (lower than 50 N), more superior tunnel location (22 to 31%), and higher tunnel coronal orientation (62° to 71°). However, most of the simulated designs have been characterized by a decrease of 18 ± 4 N in the LCL force (37 models) when compared with the

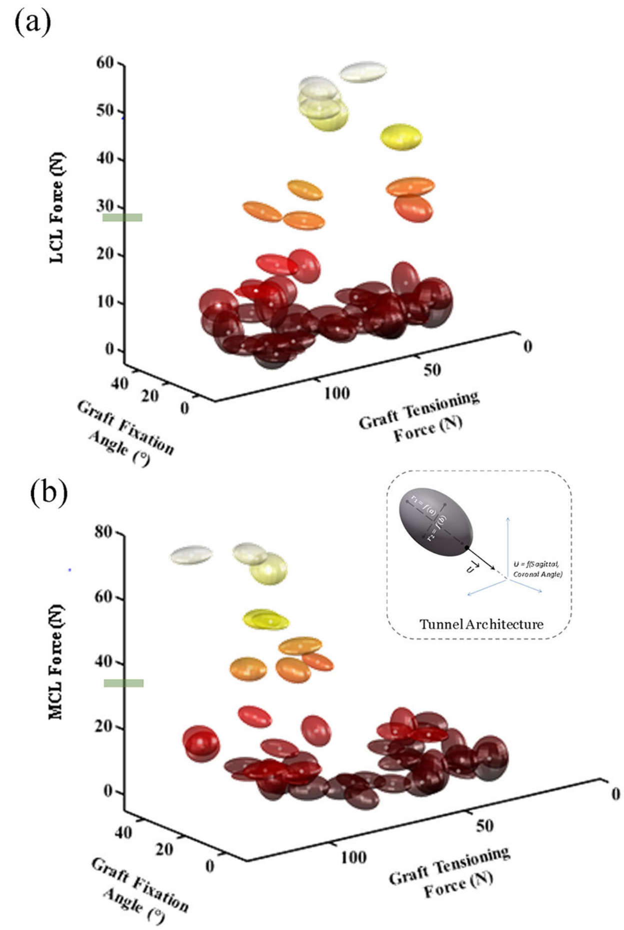

Figure 2. The collateral ligament forces of all 48 ACL reconstruction models during an axial compression of 1000 N applied at full extension; a) lateral collateral ligament force (LCL), b) medial collateral ligament force (MCL). The shadow green line corresponds to the ligament force obtained from the healthy knee model under the same boundary conditions. Note that the x and y axes in the figures represent two surgical parameters (fixation angle and graft pretensioning force). Data points are represented in the gray dots located at the center of the ellipsoids in these figures. The ellipsoids associated with each of the data points represent the corresponding tunnel architecture. In this figure, the tunnel architecture is expressed in the form of an ellipsoid (see the inset) for which the principal direction is the three-dimensional direction of the tunnel and the size of the minor and major dimensions of the ellipsoid are in function of the quadrature coordinates of the tunnel placement (see Figure 1).

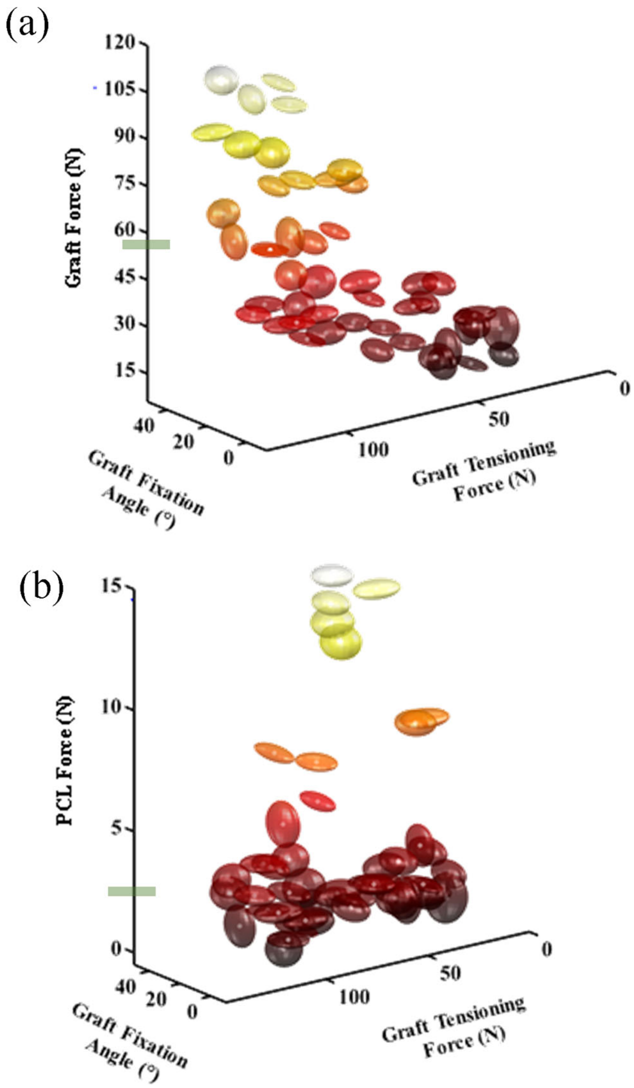

Figure 3. The cruciate ligament forces of all 48 ACL reconstruction models during an axial compression of 1000 N applied at full extension; a) graft force, b) posterior cruciate ligament force (PCL). The shadow green line corresponds to the ligament force obtained from the healthy knee model under the same boundary conditions.

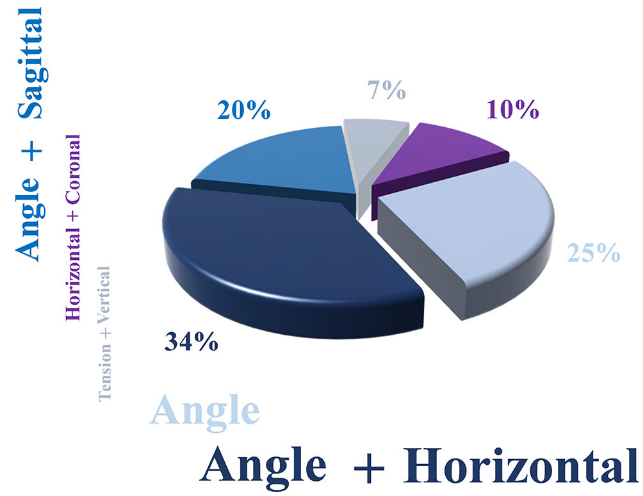

Figure 4. Pie chart representing the sensitivity indices computed based on the meta-model estimate for the lateral collateral ligament force (LCL) in response to axial compression. A graphical representation of the sensitivity indices of the identified surgical parameters to the corresponding outcome was represented by the shown word cloud (**Angle**: Angle at which the graft is fixed, **Horizontal**: Horizontal femoral tunnel locations, **Vertical**: Vertical femoral tunnel locations, **Tension**: Graft pretension, **Sagittal**: Sagittal femoral tunnel orientation, **Coronal**: Coronal femoral tunnel orientation). The color and the size of these words are consistent with pie chart colors and distribution percentage. Sensitivity indices less than 1% were not displayed.

intact model. The horizontal placement of the femoral tunnel and the angle at which the graft was fixed accounted for most of the variance of the LCL force (59%), followed by the combined action of the angle of fixation and the sagittal tunnel orientation (20%) (Figure 4).

A higher graft pretension, higher superior-posterior tunnel location, and higher fixation angle (29° to 38°) were the common surgical parameters responsible for the substantial increase of the MCL force (almost twice) observed within 5 surgical designs (Figure 2b). Only 3 surgical models exhibited an MCL force within 10% of the MCL force computed with the intact model. The fixation angles of these three models were 32°, 28° and 37° with pretension forces of 101 N, 86 N, and 69 N, respectively. The tunnel properties consisted of sagittal (40°, 19°, and 21°) and coronal (60°,52°, and 68°) tunnel angles, respectively. MCL force was mainly sensitive to the individual or combined variation in the femoral tunnel locations (53%) (Figure 5). The rest of the MCL force variance was explained first by the fixation angle and its combined action with the vertical tunnel location (24%) and second by the graft pretension (15%).

We also compared the computed graft force to the ACL force (56 N). 12 surgical designs increased the graft force by reaching almost double for certain models (∼108 N) (Figure 3a). The most common characteristics between these surgical designs were the high graft pretension (60 N and up) and the high angle (25° and up) at which the graft was fixed. In addition to the previous characteristics, a coronal tunnel orientation varying between 55° and 61° with a mid-range of tunnel location led to reproduce the ACL force with a difference that was not exceeding 15%. Tunnel locations and graft pretension accounted for the most significant portion of the graft force variance (56%, 33% tunnel locations, and 23% graft pretension) (Figure 6). The fixation angle was the next most crucial factor and accounted for 14% of the

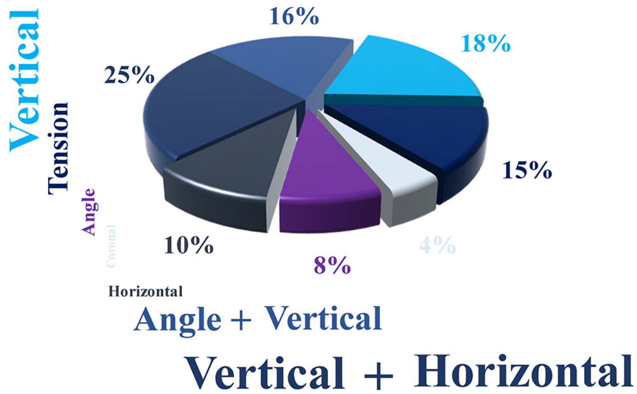

Figure 5. Pie chart representing the sensitivity indices computed based on the meta-model estimate for the medial collateral ligament force (MCL) in response to axial compression. A graphical representation of the sensitivity indices of the identified surgical parameters to the corresponding outcome was represented by the shown word cloud. Sensitivity indices less than 1% were not displayed.

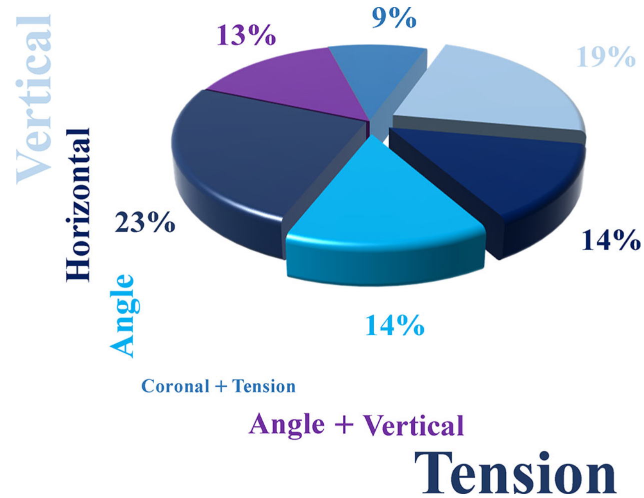

Figure 6. Pie chart representing the sensitivity indices computed based on the meta-model estimate for the graft force in response to axial compression. A graphical representation of the sensitivity indices of the identified surgical parameters to the corresponding outcome was represented by the shown word cloud. Sensitivity indices less than 1% were not displayed.

variance. Finally, the PCL was slack with the majority of simulated designs (Figure 3b).

4. Discussion

Our examination indicated that the combined or individual action of the femoral tunnel locations, the graft pretension, and the angle at which the graft was fixed accounted for most of the estimated variance of the four principal ligaments forces found in the knee joint. Collateral ligament (MCL and LCL) responses were mainly affected by the location of the femoral tunnel and the fixation angle, and the cruciate ligaments (PCL and graft) were affected by the same surgical parameters, with a clear role of the graft pretension.

In all types of ACL-R treatment, including the technique adopted in this investigation (BPTB), 6% of the surgery revisions were performed because of the alteration of the functionality of the collateral ligaments (Klimkiewicz et al. 2000; Liow et al. 2003; Halinen et al. 2006; Shimokochi and Shultz 2008; Hart et al. 2009; Nakamura et al. 2017; Hamrin Senorski et al. 2018; Nagaraj and Kumar 2019; Svantesson et al. 2019). This mechanical alteration may be mediated by both surgical and patients' specific parameters, either individually or in combination (Plaweski et al. 2006; Nakamura et al. 2017). However, the interplay between collateral ligament outcomes and surgical design has not been well investigated. In our simulations, 4 out of the 5 models that were able to reproduce the LCL response within 10% of the intact case failed to restore the MCL force. These models led to a substantial increase in the MCL force in a range varying from 32% to 88%. In contrast, a considerable decrease of nearly 65% of the LCL force was observed in 2 out of the 3 models that were able to restore the MCL force. However, one design was able to restore both ligament forces. This model was mainly characterized by a tunnel located close to the ACL footprint (horizontal 30.5% and vertical 38.5%), a low tunnel sagittal orientation (19°), a high angle of fixation (28°) and graft pretension (86 N). Furthermore, this model was able to reproduce the knee joint stability during the Lachman test but with high compressive stress within the tunnel-graft interface (Dhaher et al. 2016). This high compressive stress represents a limitation that explains the higher calculated graft force within the surgical design during this investigation and earlier published studies (Segawa et al. 2003; Salehghaffari and Dhaher 2015; Dhaher et al. 2016). Our results indicated the complexity of the interaction between the ACL-R surgical design parameters and the ability of the surgery to restore the normal response of the collateral ligaments (regular response of the tissue in the case of an intact joint). This observation was supported by the results of the global sensitivity analyses, where a wider distribution of the MCL variance factors was observed as compared with the LCL results. The MCL force was more sensitive to the independent variance (Si) of the tunnel locations (vertical 18% and horizontal 10%), graft pretension (15%), angle at which the graft was fixed (8%), and coronal tunnel orientation (4%). However, the LCL force was more sensitive to the dependent variance (Sij), such as the combined action of the angle of fixation and the horizontal tunnel location (34%) or the sagittal tunnel orientation (20%). Yet, even with the observed high distribution of the causes of the variability of the collateral ligament forces, the femoral tunnel locations and the angle at which the graft was fixed remained the most significant contributors to the variance of the collateral ligament forces by almost 70% of the variance (Figures 4 and 5). We speculate that these two contributors should be treated with a certain degree of care with any ACL-R technique associated with concomitant untreated collateral ligaments injury (Halinen et al. 2006; Hamrin Senorski et al. 2018; Svantesson et al. 2019).

On the side of the cruciate ligaments, graft pretension was the main driver of the variance of the graft force by nearly 23%. The graft reaction was more sensitive to graft pretension during the Lachman test (28%) (Dhaher et al. 2016), an observation that confirms the variability of the sensitivity of the graft's response to the adopted activity (Schroeder et al. 2015). However, the alteration of the graft response did not affect the typical concluding agreement observed during prior computational and experimental investigations focusing on the importance of the initial graft tension on the postsurgical graft reaction (Mae et al. 2008; Salehghaffari and Dhaher 2015; Dhaher et al. 2016; Halonen et al. 2016). On the other hand, the variability of the graft force also depended on the femoral tunnel locations, specifically the vertical site (19%) rather than the horizontal one (14%). These computed results are consistent with the general conclusion, based on a few placement options, as reported by Markolf et al. (2002). The lower computed forces of the PCL with most of the adopted designs explain the lesser predicted stress (0.28 ± 0.08 MPa) on the interface of contact between the graft and the PCL. The result agrees with the outcomes of Iriuchishima et al. (2010) and Simmons et al. (2003), where a complete absence of graft-PCL impingement was observed at full joint extension, but it does not agree with Strobel et al. (2001). This contradiction could be explained by the limitation of the study of Strobel and colleagues to the specific case of ACL-R surgery, where the femoral tunnel was exceptionally located on a higher posterior-superior site of the internal femoral condyle. However, even with the current predicted data on the graft-PCL impingement, further research is needed to understand the variations of the graft-PCL impingement after the ACL-R under different frames of boundary conditions. Understanding this area of concern can be used to explain some instances of ACL-R failure or revision (Iriuchishima et al. 2010; Kropf et al. 2013).

The primary limitations of the current study were as follows. The biphasic-viscoelastic behavior of the ligaments, menisci and cartilage was not considered. However, it has been well documented that the soft tissue's transient response can be accurately captured either by a biphasic-viscoelastic analysis or equivalently by a nearly incompressible hyperelastic analysis (Ateshian et al. 2007). Despite the cycling loading and the remodeling process over time (Graf et al. 1994), the change in the graft structure after the surgery was not considered. The wide range of the considered graft pretensions (20 to 120 N) during this investigation may lead to a generalization of the graft's post-surgical states. A generalized parametric model of ACL-R surgery was examined instead of the subject-specific model. The posterior capsule, anterolateral capsule, and posterior oblique ligaments were not considered. Finally, only one joint loading scenario (axial compression) was simulated. Thus further investigations treating joint instability are required (Kim et al. 2015) to have a more reliable outcome.

In conclusion, we developed an in-silico synthesis of the effect of six major surgical design parameters on knee principal ligament outcomes (forces). One of the take-home messages from this study is that femoral tunnel locations, graft pretension, and the angle at which the graft is fixed play a significant role in optimizing the knee joint ligaments' postsurgical responses.

Author contributions

All authors have read and approved this submission; the first author carried out analyses, all authors participated in the definition, design, and development of the work, and finally, the manuscript was written by all authors.

Disclosure statement

No potential conflict of interest was reported by the authors.

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