Comorbidity-related quality of life in anterior cruciate ligament insufficiency

A cross-sectional study involving 282 candidates for arthroscopic reconstruction

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Background and purpose Comorbidity-adjusted health-related quality of life (HRQoL) in anterior cruciate ligament insufficiency (ACLI) has not been assessed to date. A cross-sectional study was conducted to test the hypothesis that HRQoL in ACLI is comorbidity-related and differs from the Italian norm.

Methods 282 chronically ACL-insufficient candidates for arthroscopic reconstruction with or without meniscal and/or focal chondral lesions were studied. Knee function was evaluated with IKDC form, HRQoL with SF-36, and associated medical comorbidities with a self-administered questionnaire allowing calculation of a comorbidity index (CI). Patients were stratified according to CI into subgroup A (CI = 0) and subgroup B (CI > 0). The SF-36 profiles in the whole sample and in subgroups A and B were compared with the Italian norm.

Results Of the 282 patients, 82 had associated comorbidity and 200 did not. Patients with comorbidity were older and had a higher degree of knee laxity than patients without comorbidity. Distinctive SF-36 profiles were obtained after stratification by comorbidity and comparison with the age- and sex-matched norm. The SF-36 profile in subgroup A showed statistically significantly lower scores on the PF, RP, BP, and SF domains while the GH and MH domains were statistically significantly higher than the norm. Subgroup B showed statistically significantly lower scores than the norm for the PF, RP, BP, VT, SF and RE domains.

Interpretation Comorbidity-related HRQoL in ACL-insufficient candidates for arthroscopic reconstruction showed statistically significant differences from the norm. Comorbid illness acting as confounder should thus be controlled for when reporting SF-36 profiles, in order to avoid selection bias. Our findings may also be used as benchmark data for researchers investigating SF-36 profiles in ACLI.

Health-related quality of life (HRQoL) in patients with ACL injury has been investigated in a number of studies using the SF-36 without adjusting for associated comorbidity (Shapiro et al. 1996, McAlister et al. 2003). SF-36 profiles should, however, be controlled for medical comorbidities because comorbid illness would cause what has been referred to as a “background noise”, blurring the potential association between HRQoL and musculoskeletal disorders (Dunbar et al. 2004).

The aim of the present study was twofold: (1) to investigate the effect of chronic ACL insufficiency (ACLI) on HRQoL in candidates for arthroscopic reconstruction who were stratified by comorbidity and compared with the Italian norm, and (2) to establish benchmark data for HRQoL profiles in ACLI. The following hypotheses were tested: (1) that chronic ACLI modifies HRQoL in candidates for arthroscopic reconstruction, and (2) that HRQoL in ACLI is affected by associated comorbidities.
**Patients and methods**

We conducted a cross-sectional study on 282 ACL-insufficient patients (median age 28 (15–52) years, 235 men) who were admitted consecutively to our department from January 2004 through August 2006 with an indication for arthroscopic reconstruction. Patients had been examined in the outpatient practice by the senior author (VC) and had undergone a 6-month rehabilitation program, which started when joint inflammation related to knee injury had subsided.

Inclusion criteria were unilateral chronic ACLI with or without associated meniscal and/or focal chondral lesions and intact function of the opposite lower limb. ACLI was defined as being chronic if it persisted 6 weeks (Hacker 2003) or more after the patient had self-reported the first episode of major knee injury. Exclusion criteria were acute ACL tear, severe (Outerbridge grade III–IV) and diffuse chondral lesions, concomitant major (grade III) ligamentous injuries of the knee and/or fractures requiring surgery, and previous ACL reconstructive surgery. Patients with infectious, neoplastic, and rheumatic disease were also excluded. The indication for surgery was persistence of knee instability following rehabilitation in patients who were unwilling to change their activity level, or despite modification of activity.

The clinical diagnosis of ACLI was based on history, physical examination (positive Lachman and pivot-shift test), and assessment of tibial anterior translation (TAT) with KT-1000 knee ligament arthrometer (MEDmetric, San Diego, California) at 67 N, 89 N, and at maximal manual traction (MMT). TAT exceeding 10 mm or a side-to-side difference (SSD) of > 3 mm at MMT were suggestive of ACL tear (Bach et al. 1990). KT-1000 testing was performed by an experienced senior resident who was not involved in the study. Arthroscopy preceded autograft harvesting and was used to confirm the clinical diagnosis on the day of surgery.

All patients were administered the Italian validated version of the SF-36 (Apolone et al. 1997, Apolone and Mosconi 1998) and a comorbidity questionnaire on the day before surgery. The SF-36 is a self-administered questionnaire supplying an 8-scale profile of HRQoL (Ware et al. 1993). SF-36 scores were calculated according to published algorithms (Ware et al. 1995). The comorbidity index (CI) we used is derived from a self-administered comorbidity questionnaire (SCQ) that has been validated for use in clinical research (Sangha et al. 2003).

Knee function was assessed with the International Knee Documentation Committee (IKDC) Examination Form categorizing knee function into four groups: A (normal), B (nearly normal), C (abnormal), and D (severely abnormal) (Hefti et al. 1993). The IKDC form was completed by an experienced senior resident who was not involved in the study.

The study sample was stratified according to CI using a cut-off criterion: CI = 0 (subgroup A) and CI > 0 (subgroup B). Since use of norm-based scoring (Ware et al. 2000) has been recommended (Hjermstad et al. 1998, Zanoli 2006), differential SF-36 scores from the age- and sex-matched Italian norm were computed for each patient and the mean of the differences was calculated for the whole sample and for each subgroup.

**Statistics**

Mean and standard deviation (SD) of the SF-36 scores were calculated in order to supply summary data that can be used in research for intergroup comparison. Parametric testing using summary data has already been reported in the literature (McAllister et al. 2001). Mean differences from the age- and sex-matched norm (norm-based scoring) and the relevant 95% confidence limits (CLs) were computed using data from the Italian norm (Apolone et al. 1997). Confidence intervals not including zero conveyed statistical significance. Non-parametric tests (Mann-Whitney U test and contingency tables) were used to compare categorical and continuous variables when no assumption of normality was made. Age, KT-1000 measurements, and SF-36 scores were rounded up/down to the first integer digit. Two-sided significance level for hypothesis testing was preset at p < 0.05. We used dedicated software (StatsDirect version 2.5.7; StatsDirect Ltd., Cheshire, UK).

**Results**

200 patients were stratified into subgroup A (CI =
0) and 82 patients into subgroup B (CI > 0). Patients in subgroup B were generally older and had a higher degree of laxity (TAT and SSD) than those in subgroup A (Table 1). The most common type of comorbidity was back pain (Table 2).

The findings in the whole study sample indicate that chronic ACLI modifies HRQoL, and comorbidity stratification yielded distinctive SF-36 profiles in subgroups A and B. In particular, the SF-36 profile in subgroup A showed statistically significantly lower scores on the PF, RP, BP, and SF scales, while the GH and MH domains were statistically significantly higher than the norm. Subgroup B showed statistically significantly lower scores than the norm for the PF, RP, BP, VT, SF, and RE domains (Figure and Table 3).

Table 1. Variables in the whole study sample and in comorbidity-stratified subgroups of patients affected by chronic ACL insufficiency with indication for ACL reconstruction

| Variable                          | Whole group | Subgroup A (CI = 0) | Subgroup B (CI > 0) | P-value a |
|-----------------------------------|-------------|---------------------|---------------------|-----------|
| Age, median (range)               | 28 (15–52)  | 26 (15–52)          | 33 (15–51)          | < 0.001   |
| Gender, men, n (%)                | 235 (83)    | 167 (83)            | 68 (83)             | 1.0       |
| women, n (%)                      | 47 (17)     | 33 (17)             | 14 (17)             |           |
| CI, median (range) b              | 0 (0–9)     | 0 (0–0)             | 2 (2–9)             | < 0.001   |
| Meniscal tears, total, n (%)      | 152 (54)    | 110 (55)            | 42 (51)             | 0.5       |
| medial                            | 94 (62)     | 68 (62)             | 26 (62)             |           |
| lateral                           | 36 (24)     | 29 (26)             | 7 (17)              |           |
| both                              | 22 (14)     | 13 (12)             | 9 (21)              |           |
| Chondral lesions total, n (%) f   | 45 (16)     | 31 (16)             | 14 (17)             | 0.6       |
| grade I                           | 8           | 3                   | 5                   |           |
| grade II                          | 12          | 10                  | 2                   |           |
| grade III                         | 16          | 9                   | 7                   |           |
| grade IV                          | 9           | 9                   | 0                   |           |
| Meniscal plus chondral lesions, n (%) | 33 (12)  | 24 (12)             | 9 (11)              | 1.0       |

Discussion

It has been suggested that HRQoL should be routinely assessed in ACLI (Johnson and Smith 2001). Patient-oriented assessment in ACLI is also recommended because physician-based evaluation may introduce a positive bias (Roos 2001). The SF-36 has been shown to be a valid tool for HRQoL self-assessment in musculoskeletal conditions (Beaton and Schenitsch 2003).

Few papers have specifically addressed the issue of HRQoL in ACLI. Shapiro et al. (1996) recommended that SF-36 should be used for outcome assessment in order to enhance the value of ACL reconstruction to policy-makers and to third-party payers. McAllister et al. (2003) found that SF-36...
scores in elite collegiate athletes, with an ACL injury dating back 2–24 years and previously treated with an ACL reconstruction, were in almost all cases not significantly different from those of uninjured peers. Although these studies highlight the importance of using SF-36 for HRQoL evaluation in patients with ACL injury, their external and internal validity may be weakened by the fact that SF-36 profiles were not comorbidity-related.

We have not found any study investigating comorbidity-related HRQoL in a large sample of candidates for reconstruction because of chronic ACLI. We used explicit criteria for enrollment of patients and indications for surgery, and patient variables were detailed, which helps when assessing the representativeness of the sample.

Our study had four limitations, all related to the clinical selection process. Firstly, all patients were collected from the practice of one surgeon—which possibly reflected his attitudes and beliefs about ACL reconstruction. These have been shown to vary between surgeons (Marx et al. 2003). Secondly, selection bias could have arisen from the unbalanced case-mix with regard to gender, which, unlike that of Shapiro et al (1996) with a male-to-female ratio of 1.4, had a ratio of almost 5. We believe that gender imbalance reflects inequalities in sex-related participation in sports between coun-

Table 2. Type and frequency of medical conditions in 82 patients with comorbidity associated with ACL insufficiency

| Type of medical comorbidity | No. of patients |
|-----------------------------|----------------|
| **Single comorbidity**      |                |
| Back pain                   | 36             |
| High blood pressure         | 7              |
| Lung disease                | 5              |
| Ulcer or stomach disease    | 5              |
| Anemia or other blood disease | 3             |
| Liver disease               | 2              |
| Heart disease               | 2              |
| Migraine                    | 2              |
| Osteoarthritis              | 1              |
| Ulcerative rectocolitis     | 1              |
| Hypothyroidism              | 1              |
| **Subtotal**                | 65             |
| **Multiple comorbidities**  |                |
| Back pain plus lung disease | 5              |
| Back pain plus allergy      | 1              |
| Back pain plus anemia or other blood disease | 1 |
| Back pain plus ulcer or stomach disease | 1 |
| Back pain plus depression   | 1              |
| Back pain plus rotator cuff disease | 1 |
| Back pain plus anemia or other blood disease | 1 |
| Back pain plus high blood pressure plus lung disease | 1 |
| Lung disease                | 1              |
| Lung disease plus heart disease | 1 |
| Lung disease plus liver disease | 1 |
| Lung disease plus ulcer or stomach disease | 1 |
| High blood pressure plus ulcer or stomach disease | 1 |
| Depression plus sinusitis   | 1              |
| **Subtotal**                | 17             |
| **Total**                   | 82             |

The type of comorbidity is reported using terminology of the self-administered comorbidity questionnaire (SCQ) (Sangha et al. 2003). The SCQ lists thirteen defined medical conditions (closed-ended items: heart disease; high blood pressure; lung disease; diabetes; ulcer or stomach disease; kidney disease; liver disease; anemia or other blood disease; cancer; depression; osteoarthritis, degenerative arthritis; back pain; rheumatoid arthritis) and three medical diseases (open-ended items) that may be added by the patient. The SCQ requires that the diagnosis of the patient’s self-reported comorbidity has been made by a physician. 

The mean differences in SF-36 domain scores in subgroup A (n = 200, CI = 0) and in subgroup B (n = 82, CI > 0) from the age- and sex-adjusted Italian norm (Apolone et al. 1997). SF-36 domains scoring above or below the reference line represent scores that are higher or lower than the norm, respectively (see Table 3 for confidence limits and Discussion for the minimum clinically important difference attributable to statistically significant deviations from the norm). Domain legends: PF, Physical Functioning; RP, Role Physical (role limitations due to physical health problems); BP, Bodily Pain; GH, General Health; VT, Vitality; SF, Social Functioning; RE, Role Emotional (role limitations due to emotional health problems); MH, Mental Health.
tries. One survey has reported that 32% of males and 17% of females are engaged in sports in Italy, as opposed to 70% of males and 70% of females in Sweden (European Commission Directorate-General for Education and Culture 2005). Thirdly, including patients with meniscal and/or chondral lesions associated with ACLI could introduce a confounder because the resultant HRQoL would depend on both ACLI and joint lesions. However, joint lesions are often present in chronic ACLI and we believed that this would add to the representativeness of the sample. Lastly, selection bias could arise from the fact that not all individuals may seek medical care after ACL injury, and our sample of surgical candidates may represent those with worse HRQoL.

Stratification of patients by comorbidity revealed the confounding effect of comorbidity on HRQoL scoring. However, stratification resulted in imbalance because the subgroups differed regarding age and laxity (Table 1). Age itself is unlikely to have biased our results, as comorbidities increase with age; in any case, this factor was eliminated in norm-based scoring. Conversely, increased laxity might act as confounder, although the small magnitude of the difference in laxity is unlikely to have had any clinical significance. How one should interpret an imbalance in laxity remains speculative. It could relate to a greater length of time since injury, yet the use of cut-off criteria to define chronic ACL injury prevents correlation analysis. Also, it could be characteristic of elderly and comorbid patients requiring surgery for ACL insufficiency despite rehabilitation and modification of activity.

One debated issue regarding the interpretation of norm-based changes in SF-36 scores is the extent to which small statistically significant differences are actually of clinical importance (Walters and Brazier 2003, Brozek et al. 2006). Some authors have suggested a 5-point difference on the GH scale (Ware et al. 1993) while others have advocated ranges from 3.3 to 5.3 and from 7.2 to 7.8, respectively, on the PF and BP scales in hip and knee osteoarthritis (Angst et al. 2001), or from 3 to 5 points (Hays and Morales 2001). The problem is complicated by findings suggesting that the minimum clinically important difference (MCID) may be disease-related (Zanoli 2005). The results of our study should thus be interpreted by clearly distinguishing between statistical significance and

Table 3. SF-36 domain scores in the whole study sample and in comorbidity-stratified subgroups of patients affected by chronic ACL insufficiency with indication for ACL reconstruction

|                | Total n | PF          | RP          | BP          | SF-36 domain a |
|----------------|---------|-------------|-------------|-------------|----------------|
| Whole group    | 282     |             |             |             | SF-36 domain a |
| Mean (SD)      |         |             |             |             | SF-36 domain a |
| NBS b, mean    |         |             |             |             | SF-36 domain a |
| 95% CL c       |         |             |             |             | SF-36 domain a |
| Subgroup A (CI = 0) | 200 |             |             |             | SF-36 domain a |
| Mean (SD)      |         |             |             |             | SF-36 domain a |
| NBS b, mean    |         |             |             |             | SF-36 domain a |
| 95% CL c       |         |             |             |             | SF-36 domain a |
| Subgroup B (CI > 0) | 82  |             |             |             | SF-36 domain a |
| Mean (SD)      |         |             |             |             | SF-36 domain a |
| NBS b, mean    |         |             |             |             | SF-36 domain a |
| 95% CL c       |         |             |             |             | SF-36 domain a |

a PF: physical functioning; RP: role physical (role limitations due to physical health problems); BP: bodily pain; GH: general health; VT: vitality; SF: social functioning; RE: role emotional (role limitations due to emotional health problems); MH: mental health.

b NBS: norm-based scoring obtained by comparison with the Italian norm (Apolone et al. 1997). The age- and gender-matched SF-36 domain scores are expressed as difference from the mean equalling zero, with positive and negative values indicating higher and lower scores, respectively, than the norm.

c CL: confidence limits; confidence intervals not including zero indicate statistical significance.
the currently undetermined MCID of changes in SF-36 score in ACLI.

These limitations aside, ACLI in comorbidity-free patients would cause a negative perception of HRQoL with scores lower than the norm on the PF, RP, BP, and SF scales. The GH and MH domains scored statistically significantly higher than the norm (Table 3). Although any interpretation is conjectural, the indication for surgery in otherwise healthy young patients seeking medical care might represent a “selection bias” enhancing perception of HRQoL on these scales.

Our study indicates that relative to the age and gender-matched norm, chronic ACLI has an effect on SF-36 profiles, and that associated medical comorbidity is a confounder. Comorbidity should thus be controlled for when reporting SF-36 profiles in patients with ACLI, in order to avert this type of bias.

**Contributions of authors**

VC initiated data collection, designed the study, analyzed data, and commented on and corrected the draft manuscript. SL designed the study, collected and analyzed data, and wrote the draft manuscript. BDV collected and analyzed data, and commented on the draft manuscript. GZ analyzed data, and commented on and corrected the draft manuscript. No competing interests declared.

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