Porosity polymeric elastomers for repair and replacement of the knee joint meniscus
Groot, Jacqueline Hermina de

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SUMMARY

Since sporting activities increased in the recent years, there has been a substantial rise in incidence of meniscus injuries. Totally excising the meniscus (meniscectomy) results in degeneration of articular cartilage. Because the degree of degeneration is proportional to the removed part of the meniscus, nowadays, the method of choice is partial meniscectomy to preserve as much meniscal tissue as possible. Although the results improve compared to total meniscectomy, the stresses on the underlying cartilage are still higher and degeneration is not prevented. Therefore, many researchers have been developing new experimental techniques for the repair or replacement of a damaged meniscus. Due to the limited blood supply of the meniscus, healing is a problem. Only lesions in the outer 10-20% vascularized part of the meniscus can be repaired adequately by simply suturing (figure 1). When the lesions are situated in the avascular part of the meniscus there is no tendency for healing and no reliable surgical methods exist.

**Figure 1.** a: Normal meniscus. Only the peripheral rim of the meniscus (1) is vascularized throughout its attachments to the joint capsule (2) and the meniscal horns. The central two-thirds of the meniscal body is avascular (4). b: All lesions, longitudinal (1), transverse (2) or a combination of these two (3), that have a connection to the meniscal blood supply can heal spontaneously. c: Lesions located in the central part of the meniscus do not heal.

Chapter 1 describes the functions, structure and mechanical properties of the meniscus and gives an overview of different meniscal repair and replacement techniques. In the case of meniscal repair, reports on repair with meniscus-like tissue, fibrocartilage, are sparse and healing of only very small lesions was observed. Cryopreserved allografts or prostheses made of collagen, fiber teflon, carbon fibre reinforced polyester, polyurethane coated dacron often showed failure due to insufficient incorporation or due to a severe inflammatory response. There is thus still a need for new techniques to repair and replace the meniscus.
In this thesis porous polymeric elastomers are used for the repair and the replacement of the meniscus. Distinction has to be made between meniscal reconstruction and meniscal prosthesis. In the case of meniscal reconstruction only a small piece of material is implanted into a meniscus (figure 2). In the case of meniscal prosthesis, the meniscus is excised completely and removed by a total meniscal prosthesis.

The use of porous biodegradable PU/PLLA composites which served to make a connection between the synovial capsule and a meniscal lesion, has been previously shown to lead to healing of damaged tissue (figure 2). In the grafts, larger pores of 200-250 μm were dispersed in a denser matrix with pore sizes up to about 60 mm. Ingrowth of connective tissue and blood vessels and even areas with fibrocartilage were observed. These materials were prepared by a repeated dipcoating procedure or a modified saltcasting process but reproducibility of the materials has found to be a problem. In chapter 1 other available techniques to prepare porous polymers are described.

The aim of this study was optimization of the porous materials and gain insight into the influence of pore structure, porosity, mechanical properties and chemical structure of the materials on the healing of the lesions and ingrowth of meniscus-like tissue in the implant. An additional aim was to investigate whether porous polymeric elastomers could be used as meniscal prosthesis.

In chapter 2, porous different polyester(urethanes) are prepared using a combination of techniques: thermally-induced phase separation (TIPS) and salt leaching. For TIPS the polymer is dissolved into a solvent system. The solution is then cooled until the solvent is frozen. Next the solvent is sublimated under vacuum (freeze-drying) resulting in a porous polymer structure. The interconnected pores reach sizes in the range of 50 μm. Larger pores

Figure 2. a: A longitudinal lesion in the avascular part of the meniscus does not heal. b: After connection this lesion to the vascular periphery by using a second access defect, vascular tissue can reach the longitudinal lesion and healing can be observed. When the access defect is left open, both lesions are filled with fibrous tissue not resembling meniscal fibrocartilage. c: After implantation of a porous polymer in the wedge-shaped defect, healing with fibrocartilage is observed.
are obtained by salt casting. Therefore, the polymer solution is mixed with saccharose crystals (150-300 μm) which are washed out afterwards. The materials have a biporous structure containing macropores of 150-300 μm interconnected with micropores smaller than 50 μm. With this technique homogenous porous materials with a controllable and reproducible morphology could be prepared.

In chapter 3, PLLA-fibre reinforced PU/PLLA composites, PU/PLLA and PU foams with different porosity and pore structure are used for meniscal reconstruction in dogs. The polyurethane is based upon 4,4’-diphenylmethane diisocyanate (MDI) and an adipic acid/tetramethylene glycol polyester. The materials are prepared using the technique described in chapter 2. The healing process is initiated as a result of ingrowth of blood vessels and other cells into these porous materials. The PLLA fibres, used to reinforce the materials, retarded the degradation process and the ingrowth of fibrocartilaginous tissue. The presence of fibrocartilage was often seen in large macropores (with an average diameter >200 μm). Formation of fibrocartilaginous tissue in almost 100% of the macropores occurred after 33 weeks in the series with a high total pore volume and very well interconnected macropores. The presence of PLLA in the foams appeared to be of no importance for the amount of cell ingrowth into the implants.

In chapter 4 the synthesis of an aliphatic PU was described because the aromatic PU used in chapter 3 will yield the mutagenic, carcinogenic, teratogenic and very toxic 4,4’-diaminodiphenylmethane (MDA) upon degradation. A linear aliphatic PU was synthesized by curing a poly(ε-caprolactone) and 1,4-trans-cyclohexane diisocyanate based prepolymer with cyclohexane dimethanol. Aliphatic diamines are known to be less toxic than aromatic diamines. Porous materials of this polymer were also used for meniscal reconstruction. The compression modulus of these materials is lower (150 kPa) compared to the aromatic PU implants (250 kPa). Due to the low solubility of this polymer, porous materials were prepared by freeze-drying/in-situ polymerization. This resulted in a less interconnected porous structure. These materials showed quicker ingrowth of fibrocartilaginous tissue. 100% fibrocartilage was first observed already after 12 weeks. It is surmized that the ingrowth of fibrocartilaginous tissue into the implants is obtained by transformation of ingrown fibrous tissue rather than by direct ingrowth. For this reason the possibility of using porous meniscus prostheses for the replacement of complete menisci by the formation of a fibrocartilaginous meniscal replica is investigated. Due to the very high shear stresses to which the prosthesis will be exposed, the stress hysteresis phenomenon that linear PU's
are known to exhibit could be of great consequence. The phenomenon may shorten the time to material failure. This problem was solved by chemically cross-linking. Therefore a porous aliphatic PU network, synthesized by crosslinking the poly(?-caprolactone) and 1,4-trans-cyclohexane diisocyanate based prepolymer with glycerol was used as meniscal prosthesis. Tearing out of the sutures was found to be a serious problem. It appeared that crosslinking had a large effect upon the tearing energy of the polymer which decreased from 114 kJ/m$^2$ to 20.8 kJ/m$^2$ for the linear PU and the PU network respectively. In this chapter, tearing out of the sutures has partly been circumvented by using a more complex suture technique. Despite the suturing problems, a meniscal replica was developed after implantation of a total porous PU network prosthesis. After 18 weeks the prostheses contained fibrocartilage only. Degeneration of articular cartilage decreased compared to meniscectomy.

In chapter 5 a high molecular weight 50/50 copolymer of L-lactide and ?-caprolactone is used for meniscal reconstruction. This copolymer appeared to be an elastomer with mechanical properties comparable to segmented polyurethanes but upon degradation it will release non-toxic degradation products only. Two series porous materials with compression moduli of respectively 40 and 100 kPa were implanted in the knees of dogs. Fibrocartilage formation was affected by compression modulus (density) of the implant. These implants showed no fibrocartilage and 50-70 % fibrocartilage respectively. Although the ingrowth of fibrocartilage is very important, it is not necessary for the healing of the lesions. Both copolymer implants induce better healing of the lesions than PU implants and therefore better healing of the lesion, probably due to the high degradation rate of the copolymer. Carboxylic groups formed upon degradation contribute to the adhesion between implant and meniscal tissue. The in-vivo and in-vitro degradation of the copolymer is also investigated. The copolymer degraded through bulk degradation because cracks are easily formed. Although the L-lactide sequences crystallized during degradation, crystalline remnants of the copolymer are not expected to cause problems in the latest stage of degradation.

Chapter 6 describes a method to prepare stiff porous materials of a high molecular weight 50/50 copoly(?-caprolactone/L-lactide). In chapter 5 it was concluded that a compression modulus of 100 kPa was too low to accomplish 100% fibrocartilage. Porous microspheres (50-250 ?m) are agglutinated with solvent in the presence of NaCl crystals (250-300 ?m). By changing the amount of solvent and crystals, the density and thus the compression modulus can be varied over a range of 0.07 gram/cm$^3$ to 0.5 gram/cm$^3$ and 40 kPa to 1100 kPa.
respectively. Three series of copolymer prostheses with compression moduli of 150, 400 and 650 kPa were implanted into knee joints of goats. By comparison a series of porous aliphatic PU network prosthesis, which were successfully implanted in dogs, described in chapter 4, were implanted. The results of the PU prostheses in goats was less successful than they were in dogs. The fact that goats cannot unload the operated leg is probably the reason for the different results. Due to the high degradation rate of the copolymer prosthesis, fibrocartilage formation was not observed. Since the high degradation rate caused excellent adhesive properties, which is essential for the healing of meniscal lesions, porous copolymer described in this paper are probably very appropriate materials for meniscal reconstruction.

In chapter 7 polyurethanes ureas (PUU) with high tear strength are synthesized. In chapter 4 it was shown that a low tear strength of the polyurethane network caused tearing out of the sutures. In this study PUU were synthesized by terminating a 2000 g/mol molecular weight-poly(?-caprolactone) prepolymer with three different diisocyanate: L-lysine-ethylester-diisocyanate (LDI), 1,4-butanediisocyanate (BDI) and 1,6-hexanediisocyanate (HDI). The prepolymer were chain extended with 1,4-butanediamine. These polymers are expected to release non-toxic degradation products. Thermal and mechanical properties are described. Due to phase separation and crystalline hard segments, BDI based PUU exhibit a very high tear strength of 161 kJ/m². Replacing BDI by HDI increases the tensile properties. It lowers the tear strength to 130 kJ/m² and increases the permanent set from 12% to 18.5% as a result of less ordered hard segments. Replacing the diisocyanate by LDI, causes phase mixing and soft segment crystallinity, which had a negative effect upon the mechanical properties. Porous materials with a compression modulus of 750 kPa were made of BDI based PUU. The porous structure is applied using an freeze-drying/salt-leaching technique. These materials seem to be suitable for the use as meniscal prosthesis.

In the appendix two porous 50/50 copoly(L-lactide/e-caprolactone) bottom layers and a high water vapour permeability polyetherurethane top layer are used in a triple-layer artificial skin system as a semi-permanent skin substitute on full thickness wounds in immature pigs. The copolymer was chosen because it showed excellent adhesion to meniscal tissue in chapter 5 and it is known that adherence to the recipient wound is an absolute necessity for an artificial skin to be successful. Two series of materials, with different pore structures, were implanted. In one series, macropores of 90-250 μm are dispersed in a matrix of spherical micropores of < 50 μm. The other material contained channel-like pores with lengths up to 1.5 mm. After 1.2
and 3 weeks the middle layer was removed and replaced by a split thickness skin graft. Attachment of the skin graft to the bottom layer and contraction over a period of two years were verified. The wounds in the untreated control group, which were only covered by a PEU layer, were completely contracted after 6 months. When the wounds were immediately covered with a split skin graft, the wound area increased to 220% after 24 months due to the growth of the pig. No difference in healing was observed when the interface layer was removed after 1, 2, or 3 weeks. After 24 months the wound area increased to 170%. Porous material with channel-like pores showed somewhat better results than porous material with spherical pores.