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# In Vitro Testing Yields Surprises on Crosslinked Bio Meshes

## "Out-of-the-Box" and In Vivo Perormance Appear Unrelated; Expert Warns of Conclusions

by Gabriel Miller

San Francisco—Crosslinking biologic meshes does not improve many of the material properties considered important in hernia repair, at least among meshes tested right out of the box, according to a study presented at the 2011 annual meeting of the American Hernia Society.

"Non-crosslinked porcine dermis products were stronger in every category compared to crosslinked porcine dermis products," said Corey Deeken, PhD, director of the Biomedical Engineering and Biomaterials Laboratory at Washington University in St. Louis, and the study's lead author.

Dr. Deeken said the findings were "surprising, considering that crosslinking is typically done in an effort to improve mechanical properties and resistance to degradation."

Far from clear is how the initial biomechanical properties of a mesh translate in the in vivo setting.

It's important to point out that this is out-of-the-box testing, said Yuri Novitsky, MD, co-director of the Case Comprehensive Hernia Center at Case Western Reserve University in Cleveland. The authors made attempts to draw conclusions about how these meshes would perform during a hernia repair, but it's important to clarify that these data should really be viewed as background to be used to compare [with] what happens to a biologic graft once it's implanted in the body, Dr. Novitsky said.

Crosslinking is an artificial process that makes new chemical bonds in the natural collagen scaffolding of a biologic mesh. Crosslinking agents such as glutaraldehyde or hexamethylene diisocyanate are intended to strengthen and stabilize the extracellular matrix, but the clinical effects of crosslinking are not clear. Several surgeon investigators and industry scientists have argued that crosslinked mesh is more likely to be perceived as a foreign body by the immune system, leading to greater inflammation and less incorporation into the body's natural tissue over time.

Dr. Deeken's study sought to evaluate the effect of crosslinking on the material properties of biologic mesh, including a mesh's ability to resist tearing and stretching and heat, as well as the effects of enzymes.

Twelve biologic meshes were analyzed: eight crosslinked and four non-crosslinked meshes. The materials were derived from both human and porcine sources, and included dermis, pericardium and submucosal tissue types.

The investigators looked at four strength tests that simulated the conditions encountered by a mesh in the repair of a hernia: suture retention, tear resistance, uniaxial tensile strength and burst strength.

Additionally, the meshes underwent thermal testing up to a temperature of 120 C as well as an enzymatic assay to determine the point at which they would degrade.

In the first strength test, pieces of mesh were pulled in relation to a fixed point to determine the maximal load that a mesh could withstand at a single suture point.

Overall, the meshes performed well. Each one surpassed 20 newtons of force, which the investigators "set as the threshold value of acceptable limits for most hernia repair scenarios," Dr. Deeken said. However, there was wide variability, without a clear trend based on crosslinking status alone.

When the meshes were categorized by tissue type, trends did emerge. In particular, the porcine dermis products performed differently based on their crosslinking status.

"Surprisingly, the non-crosslinked porcine dermis products possessed greater suture retention strength than the crosslinked products," Dr. Deeken said.

Bovine pericardium showed no difference in suture retention strength based on crosslinking status.

None of the human dermis products were crosslinked, so they could not be evaluated based on this feature. But there was significant variability in suture retention strength, with AlloDerm having the greatest strength and AlloMax the least.

Generally, these results were similar for other strength tests.

"The tear resistance results were identical in terms of overall trends," said Dr. Deeken. Among porcine dermis products, he noted, "We still see non-crosslinked products having a greater resistance to tearing than the crosslinked products." The trend held for burst strengths, as well.

For all of the strength tests, bovine pericardium showed no differences regardless of crosslinking status.

Measurements of strain—the capability of a mesh to stretch—produced more mixed results. There was no clear trend within porcine dermis; among the bovine pericardium meshes,

crosslinking was associated with less stretch.

Overall, nine of the 12 meshes stretched 10% to 30%, the range found in human cadaver tissue, “meaning that these materials will stretch approximately the same amount as the human abdominal wall,” Dr. Deeken said. Only SurgiMend, Strattice Firm and CollaMend did not stretch as much.

Similar to the strength tests, the enzymatic assay also produced surprising results, particularly for porcine dermis products.

“It doesn’t appear that crosslinking of the porcine dermis products provided any additional resistance to degradation, which again is one of the reasons for performing crosslinking in the first place. However, crosslinking of bovine pericardium did provide additional resistance to degradation,” Dr. Deeken said.

In contrast to the strength and enzymatic degradation tests, the thermal analysis did produce expected results: Crosslinked meshes, with their greater number of chemical bonds, generally withstood higher temperatures before denaturing.

Overall, the study showed that biologic meshes are strong, durable materials, but that crosslinking—specifically among the porcine dermis products—did not produce an appreciable increase in strength.

Therefore, other factors affecting strength must be at work, Dr. Deeken said.

“The results of this study highlight that differences between these scaffolds may be related to tissue type and species type or other variables in processing conditions,” she said. “Coming out of this study, it’s most important to note that crosslinking is not the only factor that we should really be considering when determining the overall properties of these materials in the future.”

A mesh’s “final characteristics” likely result not only from the species and tissue types, but also the manufacturer’s decellularization and sterilization processes, and even variability between tissue donors in age, gender and comorbidities.

Nevertheless, the study presents a baseline from which to move forward.

“This is foundational,” said Michael Hiles, PhD, vice president of Research and Clinical Affairs at Cook Biotech in West Lafayette, Ind., a manufacturer of biologic meshes. “A lot of people, at least engineers, will reference this work.”

Addressing the limits of out-of-the-box testing, Dr. Deeken said her group already had undertaken animal studies comparing five biologic products, both crosslinked and non-crosslinked, and found that de novo strength does not seem to be related to in vivo performance.

“What we see long-term is that the initial strength of the materials, whether that’s due to the

crosslinking status or type of tissue from which the mesh originates, does not impact the strength of the repair site after one year in an animal model," Dr. Deeken said.

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