Celebrating the Impact of Health Research

SUCCESS STORIES IN ARTHRITIS, BONE, MUSCLE, MUSCULOSKELETAL REHABILITATION, ORAL HEALTH, AND SKIN

CIHR Institute of Musculoskeletal Health and Arthritis
Canadian Arthritis Network
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Individual story authors have agreed to their appearance in this publication and approved their individual stories.
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Acknowledgements

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Foreword

The Canadian Arthritis Network (CAN) was established as one of Canada’s Networks of Centres of Excellence (NCE) in 1998. The impact of this NCE has been nothing short of extraordinary in its focus on innovative research that can improve the lives of Canadians who live with one of more than 200 arthritis-related conditions. Whether it be research aimed at new product development, health services improvements, biological advances or increased awareness of the diseases and their impact on people’s lives, CAN has made a difference. These stories bring CAN’s successes to life.

The CIHR Institute of Musculoskeletal Health and Arthritis (CIHR-IMHA) is one of the 13 institutes that make up the Canadian Institutes of Health Research (CIHR), the Government of Canada’s health research investment agency. CIHR-IMHA’s mandate is to support research and knowledge translation activities not only in arthritis but also in skin, oral health, muscle, bone and musculoskeletal (MSK) rehabilitation. This document highlights the impact of research in these focus areas through stories about scientific discovery, patient engagement and improved health outcomes for the Canadian population.

On behalf of both CAN and CIHR-IMHA, we are grateful for the generous contributions of the Impact Stories Advisory Committee. Its members worked tirelessly to develop the call for submissions and to reach out to the research community. They also developed a comprehensive review system, including strict criteria and metrics, to select the top 15 stories for publication in this document. We would like to acknowledge the committee members and in particular the chair, Dr. John O’Keefe, who, along with staff members, committed themselves to its success.

This is a celebration of the impact of research. It is also a call for the continuation of collaborations that will bring academia, patients, consumers, the private sector and funders together to improve products and services and the health care system. We are delighted to share these stories with you.

Phillip Gardiner
Scientific Director (Interim)
CIHR Institute of Musculoskeletal Health & Arthritis

Monique Gignac
Co-Scientific Director
Canadian Arthritis Network

Claire Bombardier
Co-Scientific Director
Canadian Arthritis Network
Introduction

Musculoskeletal health disorders, arthritis, skin diseases and oral health conditions cost the Canadian economy billions each year and exact a physical, mental and emotional toll both on those who suffer from them and on their families. Canada’s research community is reducing these burdens through problem solving, innovation and knowledge sharing.

The purpose of this publication is to increase awareness and understanding of the value and impact of research in these areas; highlight the effectiveness of different research methodologies from different CIHR research themes (biomedical, clinical, health services, population health) in achieving impact; and document and celebrate the legacy of both CAN and CIHR-IMHA as Canadian research funding agencies.

The stories in this publication also demonstrate the value of collaboration between those who conduct research and those who use its results. For instance, the stories illustrate how the voices of community members helped oral health researchers target their research questions to ensure they would meet the needs of communities and care providers; how firefighters co-led a research program that contributed to building an evidence-informed physical demands analysis and screening program that is being used to improve safety and return to work; and the value of peer-to-peer mentoring for people just diagnosed with inflammatory arthritis.

The stories cover a broad range of subjects:

- In the biomedical area, research has focused on transferring knowledge about the genetic basis of muscular dystrophy into interventions that replace the defective gene with one that functions; developing biomarkers to enable early identification of a kind of skin cancer that masquerades as more-benign skin conditions such as psoriasis; elucidating the key role of an enzyme whose absence or mutation results in toxic levels of vitamin D in the body and calcium buildup in the kidneys; developing a bio-engineered blood clot to create a more lasting knee cartilage repair; and understanding the critical role of blood platelets in autoimmune diseases such as rheumatoid arthritis as a first step to a different pathway for treatment.

- Clinical research has led to advances in the treatment of foot wounds in people with diabetes, advances that could put an end to amputation; greater attention to the role of physician bias in gender disparities in hip and knee replacement surgery; the discovery that a commonly used surgical treatment for knee osteoarthritis is of little or no benefit, changing clinical practice in Canada and internationally; and video games that both increase and monitor hand function among people with arthritis of the hand.
• Research is also making health services more effective and efficient, for instance by improving the care path for hip and knee replacement surgery for residents of Alberta, improving outcomes, reducing wait times and saving money in the process.

• Population health research is increasing physical activity and improving eating habits among schoolchildren in BC to reduce obesity and prevent chronic diseases; and focusing on rheumatoid arthritis among First Nations to enable its early detection and treatment.

This collection of stories highlights the significant impacts health research can achieve. Although each is different, as a group, they exemplify the commitment of Canadian researchers to improving the health of Canadians. Research findings that are not widely known or applied, however, remain academic. This publication is a step toward wider knowledge and application of research results in the area of musculoskeletal health and arthritis. By effectively communicating these and future research stories, CIHR-IMHA and CAN are helping to ensure that investments in health research ultimately benefit Canadians and strengthen Canada’s health-care system.
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Treatment on a Silver Platter: The Role of Platelets in Rheumatic Diseases

ERIC BOILARD PhD

Introduction

We have known about platelets for about 150 years — a tiny, plate-shaped (thus the name) component of blood, nearly a trillion of which patrol our blood, on the ready to repair damage to blood vessels by triggering the formation of a blood clot. What we haven’t known, though, is that platelets also play a key immunological function. It is only fairly recently that we have learned about platelets’ vast arsenal of immune activators and mediators.¹ Since this suggested that platelets may have an immune role, we wondered whether platelets could play a role in rheumatoid arthritis (RA), which is an autoimmune disorder.

Uncovering the role of platelets in rheumatoid arthritis

Our first step was to look for platelets in the synovial fluid (a fluid that acts as a lubricant in joints) in people with RA. We didn’t find them — but what we did find, to our surprise, was small microparticles shed from the outside membrane of platelets. These particles were also found in other kinds of arthritis, including psoriatic arthritis, juvenile idiopathic arthritis and gout, but, with few exceptions, were rare in people with osteoarthritis, implying that they play a role in inflammatory arthritis.¹²

THE PROBLEM:
Platelets, which help stop bleeding by encouraging the formation of blood clots, also have an immunological function.

THE SOLUTION:
Learning how platelets, and microparticles shed from their outside, affect the development of rheumatoid arthritis.

THE IMPACT:
The knowledge gained could lead to the development of new treatments for rheumatoid arthritis and other rheumatic disorders and (auto) immune diseases.

Mice depleted of platelets developed much less intense arthritis than mice with normal platelet counts.

¹ Centre de Recherche en Rhumatologie et Immunologie, CHU Research Center, Faculté de Médecine de l’Université Laval
Platelets, in effect, promote amplification of the inflammation that marks rheumatoid arthritis.

When we looked more closely at the microparticles, we found that they were, indeed, pro-inflammatory. When we looked at a mouse model of arthritis, we found that mice depleted of platelets developed much less intense arthritis than mice with normal platelet counts. And when mice lacked a key receptor involved in producing inflammatory platelet microparticles, they had much less intense arthritis. So we knew one thing — that platelets and their microparticles had an important role to play in the cause of rheumatoid and other inflammatory arthritides, or types of arthritis.1,2

The first focus of our research became figuring out how platelets and their microparticles get out of blood vessels, where they normally are found, and accumulate in the synovial fluid, given that neither generally is migratory. It turns out that arthritic joints have microscopic gaps between endothelial cells, just small enough for the microparticles to find their way into the synovial fluid, though not the platelets.1,3 Platelets do play a role though. We found that platelets promote the formation of these gaps in joint cells during periods of chronic inflammation, contributing both to joint edema, or the accumulation of fluid, and to the entry of the pro-inflammatory microparticles. Platelets, in effect, promote amplification of the inflammation that marks rheumatoid arthritis.1,3
Outcomes

This demonstration of an active contribution of platelets in autoimmune inflammatory arthritis brought colossal enthusiasm from the scientific and medical communities. Indeed, the Faculty of 1000 (F1000) considered these findings among the top five discoveries in medicine in 2010. It is obvious that this research will initiate studies on the role of platelets in other rheumatic disorders and (auto)immune diseases.

The Faculty of 1000 considered these findings among the top five discoveries in medicine in 2010.

Research on platelets also provides new targets for arthritis treatment. Treatments currently available target immune cells and, while they can treat inflammatory arthritic diseases such as rheumatoid arthritis, they are, of necessity, also detrimental to the patient’s immunity. By focusing on inhibiting the inflammatory functions of platelets, new treatments can be developed that will have little or no impact on the patient’s immune system. We are currently, with support from the Canadian Arthritis Network, working to identify platelet receptors whose inhibition could impair arthritis without affecting platelets’ ability to stop bleeding by the formation of blood clots.

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References
Seeing the Patient in Front of Them: Addressing Physicians’ Contributions to Gender Disparity in Total Joint Replacement

CORNELIA M. BORKHOFF PhD1 GILLIAN A. HAWKER MD MSc FRCP1 JAMES G. WRIGHT MD MPH FRSC1 DAWN STACEY PhD4 HANS J. KREDER MD MPH FRSC5 GEOFF DERVIN MD MSc FRSC6 PETER TUGWELL MD MSc FRCP1

Introduction

Women are twice as likely as men to suffer from hip and knee osteoarthritis (OA) — yet the “unmet need” for total joint replacement (TJR) (the optimum treatment for relieving pain and restoring joint function when medical treatment fails) is higher in women than men. In fact, women are less likely than men to have discussed TJR with a physician or to be on a TJR waiting list, much less have the actual surgery. Now, new research is focusing on the (unconscious) role of the physician in this gender disparity.

THE PROBLEM:
Physicians are less likely to recommend joint replacement surgery for hip and knee osteoarthritis to women versus men.

THE SOLUTION:
Investigate the role of unconscious gender bias in influencing physicians’ treatment decisions.

THE IMPACT:
Tools that improve patient-physician communication and help physicians overcome biases will ensure that all patients have the same opportunity to benefit from surgery.

1 Department of Health Policy, Management and Evaluation, University of Toronto and Women’s College Research Institute, Women’s College Hospital, Toronto, Ontario
2 Department of Health Policy, Management and Evaluation, University of Toronto and Department of Medicine, Women’s College Hospital, Toronto, Ontario
3 Department of Health Policy, Management and Evaluation, University of Toronto and Department of Surgery, The Hospital for Sick Children, Toronto, Ontario
4 School of Nursing, University of Ottawa and Ottawa Hospital Research Institute, Ottawa Hospital, Ottawa, Ontario
5 Departments of Surgery and Health Policy, Management and Evaluation, University of Toronto and Division of Orthopaedic Surgery, Sunnybrook Health Sciences Centre, Toronto, Ontario
6 Department of Surgery, University of Ottawa and Division of Orthopaedic Surgery, Ottawa Hospital Research Institute, Ottawa Hospital, Ottawa, Ontario
7 Department of Medicine, University of Ottawa and Ottawa Hospital Research Institute, Ottawa, Ontario
The original findings come from a study conducted in the 1990s by Dr. Gillian Hawker and her colleagues. To paraphrase Isaac Newton, “if we can see further, it is by standing on the shoulders of giants”. Theirs was the first research to establish the presence of gender disparity in rates of use of total hip and knee replacements in Canada. The study found that, while there is underuse of TJR in both genders, the degree of underuse among willing and appropriate candidates for surgery is more than three times as great in women as in men. Their paper was published in the *New England Journal of Medicine*, received a Gold Medal from the Royal College of Physicians and Surgeons of Canada and continues to be cited by authors throughout the world.

Subsequent research investigating potential explanations for the observed gender disparity in TJR has focused on the patient. We broke new ground by examining the role of the physician and by doing so in a novel way. Now the results of our study are guiding further research to reduce gender disparities by focusing on the physician rather than solely on the patient.

“Operation Knee”

“Operation Knee” was a methodologically and logistically challenging study that used standardized, or “mystery”, patients to assess whether physicians responded differently to patients identical in every way but gender. The patients — one man and one woman, both with moderate knee OA — were trained to present themselves with identical clinical scenarios.

We found that physicians did, indeed, respond differently. When the patient was a woman, physicians were less likely to recommend total knee replacement (TKR). They also provided the woman with less medical information and less encouragement to participate in the decision to undergo TKR. Physicians also seldom discussed her role in decision making, explored whether she understood the decision, elicited her preferences or discussed post-surgery recovery, which we know to be a specific concern for women.

We broke new ground by examining the role of the physician and by doing so in a novel way. Now the results of our study are guiding further research to reduce gender disparities by focusing on the physician rather than solely on the patient.

Our findings suggest that physicians may be at least partially responsible for the gender disparity in the rates of use of TJR. Our study was the first to demonstrate that patient gender affected physicians’ treatment recommendations and interpersonal behaviour in actual clinical practice and provides some of the most conclusive evidence to date of a significant provider contribution to gender disparity in health care.

The approach we used to investigate gender bias as a possible explanation for the gender disparity in TJR, using standardized patients, was rigorous and original and is an important methodological contribution to the field. Using standardized patients enabled us to design a study that comes closest to controlling for patients’ countless clinical, social and personal characteristics that might influence physicians’ clinical decision making.
It took three years to recruit and extensively train a man and woman with comparable levels of knee OA severity as standardized patients and subsequently arrange 142 physician visits for them. The process was complex, involving everything from recruiting family physicians to provide mock referral letters to the participating orthopaedic surgeons, to involving a radiologist to regularly provide up-to-date bilateral standing knee x-rays with a fictitious hospital file number and the patient’s pseudonym for each standardized patient.

Outcomes and impacts: Extending the research

Our research has led to increased attention to patient-physician communication, both at a primary care and surgeon level, as a source for gender disparities in TJR.

We do not think that physicians are deliberately withholding treatment from women; rather they are just not recognizing the seriousness of women’s symptoms. Attributing women’s symptoms to emotional rather than physical causes or holding inappropriate preconceptions that women don’t receive the same benefit from TJA as men are some possible implicit or unconscious stereotypes based on gender that may be influencing physicians’ treatment decisions.

We are currently examining the extent to which an unconscious gender bias explains physicians’ treatment decisions, using a customized implicit association test (IAT). We are evaluating whether this test could also be used to measure the effectiveness of a skills course that focuses on increasing physicians’ awareness of the unconscious biases that may be influencing their decision making and provides them with the capacity to overcome such biases.
We are also evaluating whether a knee OA patient decision aid (PtDA) with a one-page “patient preference report” (considered the first published knowledge translation tool to communicate a patient’s clinical severity and individual concerns in clinical practice) developed by our group is a viable clinic-based intervention to overcome these biases. There is good evidence that PtDAs improve patients’ decision quality, knowledge and expectations, but few studies have evaluated their effect on patient-physician interaction. As well, no studies have examined the impact of PtDAs in reducing disparities in the utilization of any medical or surgical procedure. And whether the use of PtDAs improves shared decision making between physician and patient overall and as effectively with female patients has been virtually unexplored. Nonetheless, PtDAs do prepare patients for participating in an informed discussion about treatment options with their physician and help physicians to be more aware of patients’ individual concerns and preferences. We therefore believe that their use will result in physicians recognizing the seriousness of women’s symptoms, and seeing the patient in front of them, thus “neutralizing” any unconscious stereotypes physicians might hold.

Our achievement advances the field of health services research, with an explicit focus on reducing inequities in access to musculoskeletal care for disadvantaged populations. Our further research will provide effective tools to overcome these inequities.

**ACKNOWLEDGEMENTS**

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**References**

It’s All Relative: Early Detection of Rheumatoid Arthritis in First Nations

HANI EL-GABALAWY MD FRCPC

Introduction

Aboriginal people in Canada, particularly the Cree/Ojibway First Nations (FN), bear a disproportionate burden from rheumatoid arthritis (RA). This chronic progressive autoimmune inflammatory disease affects just 1% of Canadians in general, but 2% or more of First Nations People. If not detected and treated at an early stage, this painful disease can cause catastrophic functional loss and progressive lifelong disability, leading to substantial loss of earning power, social stature and quality of life. It also results in enormous costs to society, both in direct health-care costs and indirect costs from lost productivity.

Not only is RA highly prevalent and severe in Cree/Ojibway FN, the disease also exhibits a strong tendency towards familial clustering in this population. We are taking advantage of this tendency to learn how to detect — and possibly prevent — RA at its earliest stages, by studying the first-degree relatives of FN people with RA, including parents, children and siblings, who may be at highest risk for future development of the disease.

THE PROBLEM:
First Nations people are more susceptible to rheumatoid arthritis (RA) than the general population.

THE SOLUTION:
Study First Nations people with RA and their first-degree relatives to learn how to detect the disease earlier.

THE IMPACT:
Reduce the catastrophic impact of RA through early detection — and, one day, possibly prevent the disease altogether.

Working with communities to uncover clues to RA

In Manitoba, the study has recruited RA patients and their first-degree relatives from the Winnipeg area, and we have worked closely with members of two remote Manitoba FN communities, Norway House and St Theresa Point, to identify and recruit RA patients and their relatives in these communities. Drs. Janet Markland and Elizabeth Ferucci have recruited RA patients and their first-degree relatives into
the study from urban and rural settings in Saskatchewan and Alaska, respectively. In total, we recruited 300 people with RA and more than 500 of their first-degree relatives, as well as 300 geographically matched people with no family history of RA as a comparison group. We have followed the first-degree relatives for several years to understand more about who will develop the disease. Our work with these cohorts has allowed us to assemble a clearer picture of the risk factors for disease development.

Rheumatoid arthritis affects just 1% of Canadians in general, but 2% or more of First Nations People.

Specifically, we defined genes associated with RA and with RA-associated autoantibodies in the FN population. Since the major genetic risk for RA, called the “shared epitope”, is very common in the FN population, present in 60–70% of healthy individuals, only a small proportion of whom will develop RA, we have found several other genes that further affect this risk of disease development. We have also found that about one-third of first-degree relatives of people with RA have the RA-associated autoantibodies, compared to about 1–3% in people with no family history, suggesting that many first-degree relatives, despite having no signs of RA, are more predisposed to developing it.

We also explored the association between having these autoantibodies and smoking and periodontitis (gum disease), to learn more about the link between genetic susceptibility and environmental risk factors. We found a strong association between bacteria that cause gum disease and the presence of RA autoantibodies. This suggests an important link between gum disease and RA, and implies that reducing gum disease may affect the future risk of RA development. Our studies in the two FN communities indicate that gum disease is common, which may increase RA in these communities. Smoking, another well-known risk factor for RA, is also very common in the FN population, thus further increasing risk.

We also monitored the evolution of autoantibodies and serum cytokines (which regulate immune-system functioning) in people who had autoantibodies but had not yet started to manifest symptoms of RA. We found that high levels of cytokines in first-degree relatives may be another risk factor for future RA development.

Finally, in following the high-risk relatives over several years, we have seen the RA autoantibody profile in individuals developing the first symptoms of RA become expanded and amplified in the period immediately preceding disease onset, thus giving us valuable biomarkers for predicting imminent RA. We have now, as a result, been able to generate a clinically meaningful model, incorporating both symptoms and biomarker signatures, to help predict the onset of RA in a high-risk FN population. Early detection means treatment can begin early, thus minimizing or slowing its progression.

Even more exciting, we are now designing clinical trials aimed at preventing RA before it even starts.

Outcomes

The most obvious impact of our research is a way to detect RA and begin treatment early — and work toward a way to prevent it altogether.

Our research has also had important impacts for the participating communities. We have trained local community members to undertake clinical research, thereby increasing capacity for research in these communities. The people we
have trained now serve as research assistants, as well as advocates for early RA detection and treatment. We were also able, through a partnership with the Centre for Aboriginal Health Research at the University of Manitoba, to provide an indigenous student an opportunity to take on one aspect of the project. She presented her work at a meeting, and has since started medical school in another country.

We have been able to generate a clinically meaningful model, incorporating both symptoms and biomarker signatures, to help predict the onset of RA in a high-risk FN population.

Through the use of radio “call in” programs regularly held in the communities during the study visits, we have substantially increased knowledge about RA, its early symptoms, and the value of early detection and treatment among the communities at large. We have also enhanced local access to rheumatology services through regular outreach clinics held during study visits.

We have held focus groups in the community with RA patients and their first-degree relatives that explored individual perceptions of RA risk and the willingness of individuals to undertake prevention strategies, both pharmacologic and non-pharmacologic. These will be helpful in planning future prevention studies.

Finally, we have held two major international symposia in Winnipeg, in 2009 and 2012, the first funded by the Canadian Arthritis Network (CAN) and the Canadian Institutes of Health Research (CIHR) and the second funded by CIHR, to advance the research agenda for RA and rheumatic diseases in FN. These symposia have brought together Canadian researchers who are undertaking various RA projects in First Nations communities and helped to integrate our RA research project with international initiatives designed to develop risk models and prevention strategies for RA.

We are now exploring the possibility of developing appropriate surveillance mechanisms for detecting imminent RA in remote FN communities. This will allow us to undertake unprecedented RA prevention studies in conjunction with the international community.

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Funding: Canadian Institutes of Health Research (CIHR), Canadian Arthritis Network (CAN)
A Better Way to Restore Knee Cartilage

CAROLINE D. HOEMANN PhD1 GEORGES-ETIENNE RIVARD MD2 HANI EL-GABALAWY MD3 MARK HURTIG DVM4 MICHAEL BUSCHMANN PhD1

Introduction

We subject our knees to a lot of abuse over the years — and all that stands between a healthy knee joint and an arthritic one is a thin and smooth layer of elastic tissue called cartilage, which covers the ends of bones that form the knee joint. In fact, the most serious and irreversible damage to the knee involves the loss of cartilage.

This cartilage, also known as articular cartilage, has a poor capacity to heal by itself; small lesions, if left untreated, can progress to generalized knee degeneration, which generates considerable pain during simple daily activities. Surgical methods developed in the 1950s, and still used today, help “resurface” exposed bone and restore knee function, using marrow stimulation therapy. In these procedures, called microfracture surgery, the surgeon creates small wounds in the bone below the cartilage lesion to induce bleeding, which in turn stimulates cells from the underlying bone marrow to migrate into the lesion and rebuild new tissue. This approach can alleviate symptoms in most patients, but the effects frequently don’t last. Repaired tissue often lacks the resilient qualities of cartilage and breaks down with use, often within two-to-three years after the surgery.

THE PROBLEM:
Repairs to knee cartilage are effective in the short term, but in many patients, do not last more than two-to-three years.

THE SOLUTION:
Develop a bio-engineered blood clot to create a more lasting cartilage repair.

THE IMPACT:
The BST-CarGel® implant has been approved for use in Europe; approval in Canada is pending.

Our work has built the science behind an entirely new way to repair articular cartilage, allowing patients to return to daily activities with less pain and better quality of life.

1 Department of Chemical Engineering and Institute of Biomedical Engineering, École Polytechnique
2 Division of Hematology and Oncology, Hôpital Sainte-Justine, Montreal
3 Rheumatic Diseases Research Laboratory, University of Manitoba
4 Department of Clinical Studies, University of Guelph
Developing new, affordable therapies that create a durable cartilage repair tissue is a major challenge. Our work has built the science behind an entirely new way to repair articular cartilage, allowing patients to return to daily activities with less pain and better quality of life.

**Engineering a solution**

Around 12 years ago, we came up with a completely new idea of how to repair damaged articular cartilage, by amplifying the natural response to marrow stimulation using a bio-engineered blood clot.

The novel blood clot was formed by incorporating a biomaterial called chitosan into whole blood. The resulting bio-engineered blood clot is more adhesive and more voluminous than normal blood clots. The liquid implant can coagulate just like whole blood in a cartilage lesion with microfracture holes, and was found to improve cartilage-repair tissue quality in several preclinical models.

We set out to understand how chitosan-stabilized blood clots guide inflammatory cells to recruit more stem cells from the bone marrow to the cartilage defect. Our research revealed that that biodegradable chitosan has a number of unique abilities and features that make it ideal for repairing cartilage.

First, chitosan has a unique ability, not shared by other polymers, to attract more neutrophils, alternatively activated macrophages and blood vessels to healing bone defects. In addition, chitosan has a “calming” effect on inflammatory cells, stimulating these cells to release molecules that delay fibrosis and remodel the bone lesions, which allows more blood flow and helps rebuild and integrate new bone tissue. Chitosan also stimulates macrophages, a specialized type of white blood cell that helps heal all wounds, to release specific stem cell chemotactic factors. In addition to these findings, we also discovered that coagulation factors currently used in the clinic to stop bleeding can be used to help hybrid clot implants solidify in the surgical defect, and to promote new blood vessels to grow into the bone channels created by marrow stimulation.

Our research revealed that biodegradable chitosan has a number of unique abilities and features that make it ideal for repairing cartilage.

To translate our findings to other scientists, we carried out traditional knowledge translation activities, including publishing our findings in scientific journals and presenting them at a variety of international and national conferences. We also used more non-traditional avenues, such as interviews for newsletters and on-line blogs, to make our research accessible to the public.

Most importantly, the therapy we developed was successfully translated to the clinic thanks to a partnership with BioSyntech Inc., now Piramal Healthcare Canada. Following encouraging results from the treatment of 33 patients with the chitosan implant, through a Canadian humanitarian-based special access program, a randomized controlled clinical trial was carried out in Canada and Europe with 80 patients recruited. A superior outcome was obtained for patients who received the BST-CarGel® treatment compared to those who received only microfracture surgery.
Outcomes

The clinical trial has led to product approval of the BST-CarGel® for clinical use in Europe. Approval for clinical use in Canada is currently pending. Thus, our research has led to a new treatment for patients with degenerating knee cartilage; we continue to make important advances in understanding how to heal cartilage lesions from bone marrow responses.

Our research program, by allowing us to build the science behind an entirely new and affordable therapy for articular cartilage repair, has also paved the way for further advances in scaffold-guided bone and cartilage repair. Results from this program, initiated in 2005, demonstrated, in preclinical models, that a more hyaline and integrated cartilage repair tissue can be obtained when marrow stimulation defects are treated with a chitosan-blood implant, compared to marrow stimulation surgery alone.

Our data also show, however, that in patients with chronic cartilage lesions, there are important alterations in the subchondral bone that could create a more challenging repair environment. One of the persisting challenges is the heterogeneity of the repair tissues, which is most probably related to the pre-existing subchondral bone environment. Future research will focus on advancing our knowledge of the subchondral reactions to biomaterial implants and how white blood cells and the surgical environment can be fine-tuned to stimulate a reproducible and optimal stem cell influx. Continuing research will allow us to further improve this therapeutic approach in middle-aged patients and patients with chronic lesions, who represent a large share of those needing treatment. The next steps will also involve creating new implants that can be delivered by arthroscopy, a minimally-invasive procedure for orthopaedic repair therapies.

ACKNOWLEDGEMENTS


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A Randomized Trial of Arthroscopic Surgery for Osteoarthritis of the Knee

ALEXANDRA KIRKLEY MD1,2 TREVOR B. BIRMINGHAM PhD1,3 ROBERT B. LITCHFIELD MD1,2 J. ROBERT GIFFIN MD1,2 KEVIN R. WILLITS MD1,2 CINDY J. WONG MSc4 BRIAN G. FEAGAN MD4,5,6 ALLAN DONNER PhD4,6 SHARON H. GRIFFIN CSS1 LINDA M. D’ASCANIO BScN1 JANET E. POPE MD5,7 PETER J. FOWLER MD1,2

Introduction

In a perfect world, all surgical or medical treatments would have strong evidence supporting their effectiveness. As our research demonstrated, however, sometimes the strong evidence actually refutes accepted practice.

Our focus was osteoarthritis of the knee. Extremely common, this degenerative disease represents a major source of pain and disability for Canadians, and a huge cost to the Canadian economy. There are several treatments for osteoarthritis of the knee, including physical therapy, medication, and surgery. One of the most common surgical techniques for osteoarthritis is arthroscopic debridement, in which a device is inserted into the knee joint, allowing the surgeon to see the structures in the knee, remove unwanted tissue, and smooth the cartilage surface. The theory is that the surgical intervention will allow for smoother mechanical operation of the knee and a better outcome for patients. In practice, though, despite its widespread use, there has been surprisingly little high-level evidence to support its use. Due to this lack of evidence, our research team (led by Dr. Alexandra Kirkley) carried out a clinical trial between January 1999 and August 2007, to compare the outcome for patients who received surgical versus non-surgical therapy — and we were surprised at just how ineffective this common surgery proved to be.
Gathering needed evidence

Our study, a single-centre, randomized controlled trial, randomly assigned 192 patients with moderate-to-severe osteoarthritis of the knee to one of two study groups. One group received arthroscopic debridement surgery together with optimized physical and medical therapy, while the other received solely optimized physical and medical therapy, without surgery. All patients were followed for two years, and their outcome was measured using a number of generic and disease-specific health status questionnaires (such as the Western Ontario and McMaster Universities Osteoarthritis Index) to evaluate pain, stiffness, physical functioning and other factors important to patients. Scores were obtained at baseline (i.e., before treatment) and at 3, 6, 12, 18, and 24 months after treatment.

A surgical treatment that was part of the normal process of care for osteoarthritis of the knee failed to show any benefit for patients.

The findings were clear — there were no significant differences between the surgical and control treatment groups at any point after three months. “Patients assigned to arthroscopic surgery were no more likely to report improvement with respect to physical function, pain, or health-related quality of life than were those assigned to the control group.”

“Patients assigned to arthroscopic surgery were no more likely to report improvement with respect to physical function, pain, or health-related quality of life than were those assigned to the control group.”

When they were published in the "New England Journal of Medicine" in September, 2008, our study results immediately generated considerable interest and discussion. In an editorial published in the same issue, Marx concluded by stating “Surgeons must practice evidence-based care and use sound clinical judgment to make the best decisions for individual patients.” The study was also featured in a 2009 article in the "Journal of the American Medical Association", describing evidence-based advice for treating osteoarthritis of the knee. Media coverage related to this study was extensive, with feature stories in the "New York Times" and "Globe and Mail". "Time Magazine" featured the study in its annual review of medicine in 2008.

Outcomes

This CIHR-funded study has had a significant impact, with 90 citations in the past four years. This study, together with the results of Moseley et al., is changing clinical practice around the world. In 2009, Mounsey and Ewigman concluded — based on the results of these two high-quality randomized controlled trials — that surgeons should “not recommend arthroscopic surgery to adults with osteoarthritis of the knee”, but should “treat knee pain with medical and physical therapy instead.” In 2012, Felson referred to the Kirkley study in an article in "Best Practice & Research Clinical Rheumatology".
stating that “large randomized trials have suggested that arthroscopy has a limited role as a treatment of osteoarthritis.”

The total reduction in this surgery translates into national savings (in the US) of between $82 million and $138 million annually.

The clearest impact of this type of study is in the area of knowledge translation; specifically, the impact of research on health services and clinical practice. Although there is still room for improvement, faced with objective evidence of the limited efficacy of arthroscopy for knee osteoarthritis, surgeons across North America have significantly reduced the rates for this procedure. In 2012, Howard et al. published the results of a study entitled “Evidence of no benefit from knee surgery for osteoarthritis led to coverage changes and is linked to decline in procedures.” They set out to determine if the results of clinical trials were associated with changes in practice patterns, and concluded that arthroscopic knee surgery declined in Florida by 47 percent between 2001 and 2010, and specifically found that “rates also declined following publication of the results of Kirkley and colleagues’ trial in 2008.” They estimate that the total reduction in this surgery translates into national savings (in the US) of between $82 million and $138 million annually, indicating clearly that “clinical trials of widely used therapies can lead to cost-saving changes in practice patterns.”

ACKNOWLEDGEMENTS

Individuals, communities/cities/regions and organizations involved:
Dr. Alexandra (Sandy) Kirkley was a founding member of the Canadian Arthritis Network (CAN) and an active participant until her tragic death in an airplane accident in September, 2002.

Funding: Supported over the period 1998–2007 entirely by operating grants from the Canadian Institutes of Health Research (CIHR), entitled “Arthroscopic surgery versus non-surgical treatment of osteoarthritis of the knee.”

References
Peer to Peer Mentoring in Early Inflammatory Arthritis

DAWN RICHARDS PhD¹ JENNIFER BOYLE PhD² PAULA VEINOT³ DR. MARY BELL³,⁴

Introduction

Receiving a diagnosis of inflammatory arthritis (IA) — arthritis caused by the body’s own immune system — can be difficult. The medical resources to treat such arthritis are greatly improved today, with relatively new drugs able to treat and slow the progress of the disease. Other non-medical support is often lacking, or dependant on the patient being resourceful enough to find it on his or her own.

Our research focuses on the potential benefit of peer support on the health and quality of life of individuals with early inflammatory arthritis (EIA), using both qualitative and quantitative evaluation methods. Peer-support models have been successfully used for persons with various chronic conditions, including HIV/AIDS,¹ cancer² and diabetes.³ Our research is a feasibility study exploring the value of expanding such models into the field of arthritis. In this context, peer support consists of the provision of emotional, appraisal and informational assistance⁴ by a peer — a person who shares common characteristics and who is able to relate to and empathize with the person being supported on a level that would not be possible for a non-peer.⁵

THE PROBLEM:
People newly diagnosed with inflammatory arthritis need support.

THE SOLUTION:
Train people living with inflammatory arthritis to act as peer mentors.

THE IMPACT:
Evidence of the effectiveness of peer mentors is providing a new dimension in rheumatology care.

“It’s different, I guess, in a clinical setting with a therapist versus having other people that you can talk to from life experience... please don’t stop.”

¹ Canadian Arthritis Network Consumer Advisory Council
² The Arthritis Society — Ontario Division
³ Sunnybrook Health Sciences Centre, Rheumatology
⁴ University of Toronto, Medicine
Our multidisciplinary research team importantly includes two individuals who live with IA (i.e., consumers), one of whom feels very strongly, based on personal experience, that this type of resource is sorely lacking as a patient supplementary healthcare resource. These consumers are integrated into every aspect of this research and provide an important patient perspective to our project.

**The importance of someone to talk to**

The intervention we developed is based on the work we did in the first phase of the project, a needs assessment. This assessment phase featured one-on-one interviews with IA patients, family/friends and health care providers to explore their needs and perspectives on peer support and was augmented by a literature review (i.e., a meta-ethnography) to explore the perceived impact and experience of participating in peer-support interventions. We held working groups and research team meetings to discuss various aspects of intervention development (i.e., peer-mentor training, peer-mentoring program, evaluation).

The feasibility study itself (see Figure 1) consisted of a peer-mentor training model with thorough accompanying support resource material. Experts external to the project, including four consumers, reviewed all training materials, which we modified based on their feedback. We trained nine peer mentors, using both didactic and interactive sessions to ensure they were knowledgeable and comfortable with their proposed role of mentoring a newly diagnosed IA patient. We
also recruited nine individuals with EIA (mentees) and paired them with a peer mentor to receive one-on-one support (face-to-face or telephone) approximately once a week for 12 weeks.

When we collected and analyzed evaluation data, we found the peer-mentor training process, peer-support program and outcome measures were feasible with modifications. For instance, we found that peer mentors’ self efficacy significantly increased after training, followed by a decline immediately post-program and subsequent recovery after three months. Mentees experienced improvement in terms of overall arthritis impact on health-related quality of life, coping, and social support.

We also conducted qualitative interviews with nine peer mentors and eight mentees. The peer-mentor training was positively received: “It will help me problem-solve in my own life and has given me additional resources,” said one mentor. Mentors reported that training increased their knowledge, inspired ideas for new self-management techniques and coping strategies, and made them realize how far they had come in their disease experience.

Most importantly, mentees appreciated the emotional, informational, appraisal and instrumental support they received. As one of them said, “It’s different I guess in a clinical setting with a therapist versus having other people that you can talk to from life experience. I’ve been saying that all the way through the program, as soon as I heard what they were doing, that this is 100% needed for the arthritis community... I just know when I was given the binder and this kind of information, it’s like if somebody had handed me this on the day of diagnosis, that would have been critical for me, because this is as important as medication, because this is all your information and resources...please don’t stop.”

Peer mentors similarly reported benefits and learned from mentees’ fortitude and self-management skills. Both mentors’ and mentees’ experience of peer support was informed by the unique relationship with their peer partner. A “connection” was facilitated by similarities in personality, age, gender, interests, life stage, positions of responsibility at work, diagnosis, disease severity and limbs affected. Participants were unequivocal about the need for peer support for individuals with IA.
Outcomes

Our study has clearly demonstrated that early peer support may augment current care in rheumatology. We thought these findings would be important, so adopted an integrated knowledge translation approach from the start, as evidenced by our multidisciplinary team, consisting of consumers, researchers and partners from The Arthritis Society.

We delivered many interim presentations, including at international venues. Manuscripts on the needs assessment and the evaluation phases of the pilot feasibility study have been submitted for publication.6,7

We have now expanded this research to a small pilot randomized controlled trial, partially funded by the Canadian Initiative for Outcomes in Rheumatology Care. We hope to demonstrate the effectiveness of peer support in EIA management, which we believe will positively and measurably affect health outcomes. The research team feels strongly that the development of a peer-support intervention, in which program materials have been well thought out and peer mentors have been well-prepared to work with their newly diagnosed mentees, is a much-needed patient resource. Ultimately this program will better prepare EIA patients to deal with their intimidating diagnosis and the new daily challenges they face living with arthritis for the rest of their lives.

References
Exercise is Fun? 
You’re Kidding — Right?

DR. TONY SZTURM¹ DR. BARBARA SHAY¹ DR. JAMES F. PETERS² CYNTHIA SWARNALATHA SRIKESAVAN PhD GRADUATE STUDENT³

Introduction

It’s no sleight of hand — a computer based rehabilitation platform we developed at the University of Manitoba is helping to monitor and improve hand function among people with arthritis that affects their hands.

Difficulties performing everyday activities when patients have arthritis of the hand is accepted as part of the disease, leading to more disability and restricted participation in the activities of daily living, including social life. Our platform meets the urgent need for home programs (HP) supplemented with informed client support and regular monitoring, to improve hand function and, in doing so, relieve disability and restore some of the satisfactions of daily life.

Developing the platform

Our disciplines don’t often cross paths, but beginning in 2006, we began a collaborative effort, as researchers of the School of Medical Rehabilitation and Department of Electrical/Computer Engineering. Our purpose was to design and validate a portable “interface device” that can effectively replace a standard computer mouse when doing exercises to rehabilitate hand function (specifically manipulating objects with the fingers). This smart device converts signals from miniature motion sensors to signals equivalent to that of a computer mouse. In this way nearly any object or utensil — or even body part — can be changed to function exactly as a computer mouse simply by attaching the motion sensor. Multiple objects with varied sizes, shapes, weights and functional demands for precision can be used for exercise and to practice a

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¹ Associate Professor, Department of Physical Therapy, University of Manitoba
² Professor, Computational Intelligence Laboratory, Department of Electrical and Computer Engineering, University of Manitoba
³ Applied Health Sciences, University of Manitoba
variety of gross or fine motor skills and, importantly, while playing fun computer games. Not only do the object and task have specific therapeutic value, but so does the choice of computer game. Different commercial video games require different levels of movement amplitude, speeds, accuracy and repetition as well appeal to individual preferences. We have tested and categorized a hundred easily accessible, inexpensive commercial computer games. Thus a broad range of objects and computer game combinations are available to exercise two, three, or four fingers or the whole hand/arm.

In a parallel phase of the research we developed a game-based rehabilitation telemonitoring application. This addressed the challenge of quantitative and objective outcomes measurement and gave us a means to obtain electronic records for Telerehabilitation. The game software automatically logs clients’ performance and computes their movement quality, efficiency and accuracy during the manipulation task. The software also prompts the clients to self-report pain and stiffness levels related to each manipulation task or training session. The resulting mobility data, pain and stiffness levels can then be used to track change as a function of intensity, volume of practice, and tolerance.

From 2008 to 2011, we conducted a series of studies of both healthy young adults and individuals with arthritis in order to establish and validate the game-based exercise system and embedded monitoring. We wanted our intervention to focus not only on physical impairments, but to include goals and outcomes related both to activity (carrying out tasks) and participation (involvement in life situations). We evaluated finger and hand function while handling a wide variety of objects/utensils involved in common daily activities described by the International Classification of Functioning, Disability and Health (ICF). Standardized game tasks were performed, for example, by manipulating a small knob or key, salad tongs, long stem wine glass, water jug and liquid detergent bottle. Based on the experimental data, direct observations and self-reports, a framework was developed to match objects with their specific therapeutic values. Depending on physical and ergonomic properties of common objects, many different object-task combinations are possible. Knowledge of the therapeutic value can allow the therapist to prescribe graded exercises to target specific goals, for example, mobility, strength, speed, accuracy or endurance. This innovative approach provides a highly flexible and personalized treatment tool.

We have now begun a pilot randomized controlled trial to test the effectiveness of our computer game-based hand exercise program in the home of individuals with arthritis. The control group performs conventional hand exercises, while participants in the experimental group receive therapeutic objects to use with the Telerehabilitation hand-exercise platform. We worked with knowledge users to shape the research questions and develop the training program based on several key principles:

- **Client-centred care:** A personalized training program based on individual abilities and treatment needs.
- **Motivation:** Maximizing participation is an important goal of long-term interventions. An emerging treatment approach is to combine effective activities with computer games, thus making exercise and rehabilitation interactive, engaging and enjoyable.
- **Cost-effectiveness:** Having an affordable computer-based platform that integrates both treatment and assessment is
efficient and time saving; can document compliance by monitoring volume of practice and intensity; provides timely feedback and support to client and health-care provider; and provides electronic records.

- Trend analysis: The platform and applications enable training of multiple functions. It includes data analysis methods that identify performance of each training session. This can be used to track the trajectory of change, and determine dose-response relationships.

“Simple exercise programs are so monotonous. This is interesting and challenging because it’s exactly like playing a video game... It’s fabulous. It’s going to help people a lot.”

Preliminary findings of the pilot project indicate that individuals with arthritis were actively engaged with each therapy session, felt that exercises done with gaming were fun, and had less pain and stiffness after task training. One participant, who has had rheumatoid arthritis for 22 years, said the complex therapy program has helped her deal with her pain.

“The program they’ve developed is very detailed because the hand has so many fine motor functions and (the objects used in the games) allow you to use all functions of the hand,” she said. “Plus, simple exercise programs are so monotonous. This is interesting and challenging because it’s exactly like playing a video game....It’s fabulous. It’s going to help people a lot.”

Outcomes

We now know that the system we’ve developed — both the platform and the application — has the potential to deliver high-quality and personalized hand rehabilitation programs with assessment in a home setting. In addition to helping people with arthritis, our system could streamline rehabilitation services, leverage therapist time and permit extended, regular practice at times that are most convenient for the people using it.

The system also has potential to be expanded. It could, for instance, be adapted to provide quality prevention and rehabilitation programs for people in rural and remote communities, something that is currently in short supply. It also has potential beyond simply arthritis. In recent work, we have adapted it to assist the declines in balance, mobility, vision, and cognition that can come with aging. This approach enables individuals to be monitored and supported in various community settings by their health team and through a client-centered e-health application.

ACKNOWLEDGEMENTS

Individuals, communities/cities/regions and organizations involved:
Corrie Billedeau, Emeritus Member of Consumer Advisory Council, Canadian Arthritis Network; Patient Partners, Health Sciences Centre, Winnipeg

Funding: Canadian Institutes of Health Research (CIHR), Canadian Arthritis Network (CAN), Manitoba Centre of Excellence Fund (MCEF)
When Too Much is Definitely Too Much: Genetic Mutation Prevents Vitamin D Breakdown

GLENVILLE JONES1

Introduction

In post-WWII Britain, there was an “epidemic” of a disease called idiopathic infantile hypercalcemia (IIH), which causes the build-up of calcium in the kidneys. The rising incidence of the condition was blamed upon excessive vitamin D fortification and caused the government at the time to abruptly stop vitamin D fortification practices. The incidence of IIH fell marginally after the end of such fortification, but the disease continues to be reported all over the world, including Canada.

Recently, two German pediatric nephrologists, Martin Konrad and Karl-Peter Schlingmann, and I showed that one of the main causes of IIH is loss-of-function genetic mutations of CYP24A1, the enzyme responsible for the breakdown of vitamin D. Loss of CYP24A1 function results in too much vitamin D and, since vitamin D is one of the main players in maintaining blood calcium levels, excessive blood calcium. This, in turn, causes damage to the kidney, kidney stones and soft tissue calcification.

THE PROBLEM:
Idiopathic infantile hypercalcemia causes build-up of calcium in the kidneys for no apparent reason.

THE SOLUTION:
A genetic mutation that prevents the breakdown of vitamin D has been shown to cause the disease in children and may play a role in adults with kidney stones as well.

THE IMPACT:
Increased ability to diagnose, manage and treat hypercalcemia in patients throughout the world.

This is one of those clear examples of bench to the bedside — and back to bench — research.

1 Department of Biomedical and Molecular Sciences, Queen’s University
Basic science the foundation for clinical application

I have been studying CYP24A1 for the past two decades, with my work showing its exact role in a breakdown pathway for the major forms of vitamin D. In 1996, with the help of Parteq, the patient and commercialization office at Queen’s University, and in partnership with Dr. Martin Petkovich, I co-founded a start-up biotechnology company, Cytochroma Inc. which went on to develop CYP24A1-inhibitors. These drugs are now in Phase 2 clinical trials. In addition, working with Dr. Rene St-Arnaud of the Shriner’s Hospital in Montreal, and using a “knockout” mouse, bred to have the loss-of-function mutation of CYP24A1, we have shown that the enzyme seems to be the only route for vitamin D excretion; thus, the genetic defect leaves the animal susceptible to vitamin D toxicity.

We started out not knowing the full importance of CYP24A1 — but this discovery fully justified the many years we have spent studying its basic science aspects.

Our focus was on basic science to gain a better understanding of CYP24A1. But our German colleagues contacted us because they’d found genetic changes to the enzyme in patients with IIH. They wanted to know — and so did we! — whether these were simply genetic variants, known as polymorphisms, or were they loss-of-function mutations.
ACKNOWLEDGEMENTS

Collaborators: Karl-Peter Schlingmann and Martin Konrad, Children’s Hospital Muenster/University of Muenster; Rene St-Arnaud, Shriner’s Hospital/ McGill University; Celia Rodd, Montreal Children’s Hospital/McGill University; Dr. Charles Bishop, CEO, Cytochroma Inc, Markham ON

Funding: Canadian Institutes of Health Research (CIHR) multiple operating and university-industry grants; Cytochroma Inc, Markham ON

Thanks to our previous work and our development of a computer model for human CYP24A1, we were able to discern fairly quickly that the changes in CYP24A1 in babies with IIH were probably loss-of-function mutations. Nonetheless, we recreated most of the genetic changes found in the patients in the cultured cell model and showed that, in all cases, the mutation wiped out enzyme activity. It was indisputable evidence — CYP24A1 mutations cause IIH.

Without these CIHR-supported basic science tools, the task of proving the role of CYP24A1 would have been much tougher. In other words, our basic science groundwork and engineered tools set the stage for the clinical breakthrough. We started out not knowing the full importance of CYP24A1 — but this discovery fully justified the many years we have spent studying its basic science aspects.

Outcomes

Our work was published as a landmark study in the New England Journal of Medicine in August 2011 and has already resulted in several reports, particularly in American journals, confirming that mutations of CYP24A1 cause hypercalcemia not just in children but in adults too. Indeed, patients identified as adults frequently have kidney stones and thus our work has spawned studies of the frequency of CYP24A1 mutations in patients with such stones. In fact, from recent estimates of the frequency of CYP24A1 polymorphisms and mutations in the population (one in 120), this may turn out to be a significant cause of kidney stones.

Our work has also led to streamlined methods for the diagnosis of CYP24A1-related disease, with improved mass spectrometry-based methods to detect the 24-hydroxylated metabolites of vitamin D that are absent in IIH patients. Armed with these new tools, Celia Rodd (McGill and Montreal Children’s Hospital) and I have initiated a program to test all the estimated 600 Canadian IIH patients identified in pediatric centres across Canada. This is one of those clear examples of bench to the bedside — and back to bench — research. We believe that our research will eventually help in diagnosing, managing and treating all hypercalcemic patients throughout the world.

References


Introduction

There is a crisis in children's health. Current statistics indicate that only 7% of Canadian children and youth achieve recommended levels of daily physical activity.\(^1\) In addition, Canadian children and youth spend close to 9 hours/day in sedentary pursuits\(^1\) and more than 75% of youth aged 2–17 years do not consume the recommended 5 or more servings of fruits and vegetables.\(^2\) These poor activity and eating habits are leading to declines in cardiovascular fitness and high rates of overweight, obesity and type 2 diabetes among Canadian children and youth.\(^3,4\) This crisis is a major public health concern that threatens to substantially increase the burden of chronic disease in Canada. There is a need for effective and sustainable solutions to promote healthy living among children and youth. As children spend the majority of their waking hours in school and schools reach a diverse population, schools are often the venue of choice to implement health promotion

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THE PROBLEM:
Physical inactivity and poor eating habits are leading to high rates of overweight and obesity among Canadian children and youth, with an impact on rates of chronic diseases such as type 2 diabetes.

THE SOLUTION:
A school-based physical activity and healthy eating program that has been rigorously evaluated and has spread across the province, the country and even internationally.

THE IMPACT:
Gains in bone mass and strength, improvements in cardiac fitness and blood pressure and increased awareness of dietary requirements among participating children.

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1 Department of Orthopaedics, University of British Columbia
2 Department of Family Practice, University of British Columbia
3 Centre for Hip Health and Mobility, Vancouver Coastal Health Research Institute
4 Child & Family Research Institute, Vancouver, BC
5 JW Sparta, Richmond, BC
6 School of Exercise Science, Physical and Health Education, University of Victoria
programs. However, few school-based programs have proven effective or sustainable.

There is a crisis in children’s health. High levels of physical inactivity and poor eating habits are leading to high rates of overweight, obesity and type 2 diabetes among Canadian children and youth.

The Action Schools! BC (AS! BC) is an exception to that rule. AS! BC, developed in 2002, is a best practices model designed to help elementary schools create individualized action plans to promote healthy living while achieving academic outcomes. AS! BC promotes the creation of inclusive and diverse daily physical activity and healthy eating opportunities and supports schools in making healthy choices the easy choices for students, teachers, administrators and other members of the school community. Our vision is that healthy living will be integrated into the fabric of BC schools and maintained through partnerships with families and communities.

Evaluation supports expansion

In 2003, shortly after the program began operation, we set out to evaluate the efficacy of AS! BC for increasing physical activity and improving a variety of health outcomes in elementary school children and to do so in a rigorous manner. First, the AS! BC Support Team developed practical and relevant professional-development, curriculum-linked resources (teaching resources and support materials) that supported a Comprehensive School Health approach and contributed to specific health and academic outcomes. Many of these resources were included in the AS! BC Classroom Action Bin, which we provided to teachers in participating schools. Second, our Evaluation Team conducted a randomized controlled trial that involved 10 elementary schools in Vancouver and Richmond, BC (seven intervention and three usual practice). From these 10 schools, more than 500 grade 4-6 students volunteered to participate in our comprehensive, evidence-based health outcome evaluation that spanned one-and-a-half school years.

We found that, through promotion of physical activity across six Action Zones, AS! BC had a significant positive influence on the number of minutes of physical activity provided to students. This included an additional 15 minutes/day of physical activity delivered within the Classroom Action Zone and incorporated a simple high-impact jumping program, Bounce at the Bell. Due to the

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Individuals, communities/cities/regions and organizations involved:
University of British Columbia, University of Victoria, JW Sporta, Province of British Columbia (Ministry of Health, Ministry of Education), 2010 Legacies Now, Directorate of Agencies for School Health (DASH BC)

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increase in physical activity, children in the intervention schools had significantly greater gains in bone mass and strength\textsuperscript{7–9} and improvements in cardiovascular fitness and blood pressure.\textsuperscript{10} They also showed increased awareness of dietary requirements compared with children in usual-practice schools. Further, despite the 15-minute reduction in time devoted to the regular curriculum, children in intervention schools maintained a level of academic performance similar to that of children in usual-practice schools.\textsuperscript{11} Results of focus groups showed teachers, parents and students were highly satisfied with the AS! BC model and its resources.\textsuperscript{12}

Children in the intervention schools had significantly greater gains in bone mass and strength, improvements in cardiovascular fitness and blood pressure, and showed increased awareness of dietary requirements.

These positive findings had a significant impact on school health in BC by providing a foundation for the scale-up of AS! BC and the development of additional modules and school health policies. Specifically, in 2004, we received financial support from the BC Ministry of Health to roll out AS! BC across the province and, in 2005, we developed K-to-3 and middle-school components. This was followed by a student leadership component in 2006 and a province-wide healthy-eating component in 2007. AS! BC contributed to the implementation of Daily Physical Activity for children in kindergarten through Grade 7 and Guidelines for Food and Beverage Sales in BC schools.

Over 2005–07, we evaluated AS! BC as disseminated more broadly to schools across four BC provincial health authorities. Although teachers in this trial had substantially less interaction with the AS! BC Support Team than in our efficacy trial, we noted a 38–42% increase in cardiovascular fitness (adjusted percent change) over year one in children attending intervention schools.

The 2011–12 school year marked Year 8 of the provincial roll-out for AS! BC; as of June 30, 2012, 1,455 (92%) of BC schools were registered with the program. Participation in AS! BC workshops delivered by the Support Team has far exceeded expectations, with 86% of BC schools, representing more than 62,000 teachers, administrators and other key stakeholders, having participated in one or more workshops since 2004. The significant uptake confirms the value and relevance of the AS! BC framework for action, and the support services and resources available. Further, the scale up of AS! BC has provided the foundation for leading-edge research on implementation of school health frameworks. Continued efforts are needed to continue to engage schools across the province, and support implementation and sustained action to contribute to the health of BC children.

Outcomes

Partnerships were integral to the success of AS! BC to date, and continue to pave the way forward. National and international partnerships enhance AS! BC by providing connections with broader social movements promoting healthy living, enabling collection of new best practices and interventions, and connecting the Support Team with other organizations committed to promoting healthy schools.
Across Canada, informal agreements or collaborations are in place with Yukon and Nova Scotia; information and resources are shared informally with Alberta, Saskatchewan, Manitoba, New Brunswick, Newfoundland and Labrador, and Nunavut. Alberta’s Ever Active Schools Program adopted the AS! BC Classroom Action bin model, and integration of AS! BC teaching resources and support materials into the Alberta Project Promoting Active Living and Healthy Eating (APPLE Schools) is being discussed. In Saskatchewan, the in motion program sent delegates for training, purchased Classroom Action bins, and created a school program with elements adapted from AS! BC. In addition, with support from Health Canada’s Aboriginal Diabetes Initiative, AS! BC training, support materials and teaching resources were provided to target Saskatchewan schools in collaboration with the Yorkton Tribal Council and the Prince Albert Grand Council. 

Internationally, the AS! BC Evaluation and Support Teams communicated with researchers and practitioners in South Africa who have incorporated the whole school framework and technical support services based on the consultation. AS! BC also received recognition from the Irish parliament, organizers of the 2014 Commonwealth Games and from the President of the Norwegian Physical Activity and Nutrition Council.

Moving forward, the AS! BC Support Team will continue to support new and existing Action Schools, and build on established partnerships with other organizations committed to improving the health of Canadian youth. These efforts will ensure that AS! BC continues to provide more opportunities for more children to make healthy living choices more often.

References
Treating a Devastating Disease: The Case of Duchenne Muscular Dystrophy

DR. JACQUES P. TREMBLAY PhD

Introduction

Duchenne Muscular Dystrophy (DMD) is caused by a mutation in the dystrophin gene. This devastating disease puts sufferers — who are always male — into a wheelchair by age 10 and on a respirator by 17, by which time many are dying. Few males with DMD reach the age of 30.

In 1987, dystrophin was identified as the culprit gene in the disease. Since that time, my lab has focused on finding a treatment for this untreatable disease. Our research has shown promising results.

About DMD

DMD is caused by a mutation in the dystrophin gene that prevents the formation of dystrophin protein. In all people, intense muscle activity damages muscle fibers. In healthy people, though, these damaged fibers are repaired by the fusion of cells called myoblasts. In people with DMD, the absence of dystrophin leads to increased fragility of the muscle fibers and to their frequent damage, even following just normal activity. The increased frequency of damage, and therefore repairs, leads to a progressive inability of myoblasts to carry out their repair function, resulting in a reduction in the size and number of muscle fibers, which are gradually replaced by fat and connective tissues. This generally starts around four-to-five years of age, at which time affected boys will start to have trouble walking, running or climbing stairs — the first signs of a devastating disease that causes much suffering, both for the patients and their families, and ends in premature death.

THE PROBLEM:
Duchenne Muscular Dystrophy causes ever-weakening muscles and, usually, death by age 30. There is currently no treatment.

THE SOLUTION:
Transplanting myoblasts with a normal dystrophin gene can result in normal muscle cells.

THE IMPACT:
A way to treat this devastating disease and alleviate the suffering of patients and their families.

1 Department of Molecular Medicine, Laval University
Replacing dystrophin

In our efforts to find a treatment for DMD, we have focused on transplanting myoblasts with the normal dystrophin gene. These myoblasts can fuse with the host’s damaged muscle fibers and not only repair the damage but also introduce in these fibers nuclei containing the normal dystrophin gene. Thus the transplantation of these normal myoblasts results in the expression of dystrophin in the patient’s muscle fibers.

Around four-to-five years of age, affected boys will start to have trouble walking, running or climbing stairs — the first signs of a devastating disease that causes much suffering, both for the patients and their families, and ends in premature death.

We first worked in vitro, showing that fusing one normal myoblast with several myoblasts containing a mutated dystrophin gene unable to produce dystrophin, led to the expression of dystrophin over whole small muscle fibers (myotubes) formed in culture (Huard, Labrecque et al. 1991). These results led to an initial clinical trial in 1990. The results were initially promising. Muscle fibers expressing dystrophin were observed in three of the four DMD patients who were transplanted (without immunosuppression) with myoblasts obtained from healthy, histocompatible brothers or sisters. One of these patients had 36% dystrophin-positive fibers (Huard, Bouchard et al. 1991; Huard, Bouchard et al. 1992; Tremblay, Malouin et al. 1993). We observed increases in strength in the patient who had the highest percentage of dystrophin-positive fibers and even more increases after a second transplantation from the same donor. However, subsequent transplantation did not lead to more improvements and the patient progressively lost the initial gains in strength.

When we looked more deeply into why the benefits did not last, we found that, while no antibodies were detected against the donor myoblasts themselves, antibodies were detected against the myotubes formed by the fusion of these myoblasts (Roy, Tremblay et al. 1993). To our surprise, we found that one of the proteins leading to this immune response was dystrophin itself! Because the patients had not previously produced dystrophin, the transplantation of normal myoblasts led to an immune reaction to this new protein.

We turned our attention to identifying the best immunosuppressive drug to prevent this immune response. We were conscious that four other research groups in Canada and the United States that had conducted similar clinical trials of myoblast transplantation, but not using histocompatible donors and using immunosuppression, had all obtained negative results. We later found out why that might have been — the drug that had been used by at least one of the research groups actually killed the myoblasts that were proliferating in the muscles after transplantation (Vilquin, Kinoshita et al. 1995).

Experiments to identify the best immunosuppressive drug for myoblast transplantation were made in a mouse model missing dystrophin, mimicking the DMD patients. After trying several drugs, we identified a new drug called FK506 (now commercialized under the names Tacrolimus or Prograf) that permitted successful transplantation of normal myoblasts in a mouse model of DMD, called mdx.
Following myoblast transplantation using this drug, up to 90% of the muscle fibers expressed dystrophin in the mdx mice (Kinoshita, Vilquin et al. 1994; Kinoshita, Vilquin et al. 1994). We were unsure about progressing straight to using the drug in humans, thus we first tried the drug in dogs also bred to be unable to express dystrophin. Unfortunately, the dogs did not respond well to FK506 immunosuppression and, even in combination with other immunosuppressive drugs, the results were modest (Ito, Vilquin et al. 1998). However, FK506 showed more promise in monkeys, (Kinoshita, Vilquin et al. 1995; Kinoshita, Roy et al. 1996), indicating that it might also work well in humans.

The monkey experiments also identified a second problem that had limited the success of the early trials of myoblast transplantation: limited migration of the transplanted myoblasts into muscle fibers. (Skuk, Goulet et al. 2000; Skuk and Tremblay 2001; Skuk and Tremblay 2001; Skuk, Goulet et al. 2002). Finally, the monkey experiments also allowed us to determine that we had not injected enough myoblasts in the original clinical trial and that the ideal number of myoblasts to inject is 30 million myoblasts per cubic centimetre of muscle (Skuk, Caron et al. 2003; Skuk, Paradis et al. 2007).

With our knowledge advanced in this way, we received permission from Health Canada for a new phase I clinical trial, which successfully demonstrated that, with adequate immunosuppression, successful myoblast transplantation was possible. The trial, which began in 2002, involved nine DMD patients aged between five and 15 years old. We transplanted 30 million myoblasts in only one cubic centimetre, this time using donations from participants’ father or mother, since using minor brothers or sisters as donors was no longer allowed by the Research Ethics Board. We used FK506 (Prograf), which had become the drug of choice for organ transplantation in children, to suppress their immune systems.

A muscle biopsy done one month later confirmed that the normal dystrophin gene was present and expressed at both the messenger RNA and protein level. Indeed up to 26% dystrophin-positive fibers were detected (Skuk, Goulet et al. 2006; Skuk, Goulet et al. 2007).

We have now received approval from Health Canada for a phase I/II clinical trial to verify whether the transplantation of myoblasts throughout a complete muscle not only restores the expression of dystrophin but also increases strength of that muscle.

Outcomes: Extending the research

Having shown that myoblast transplantation offers potential for treating DMD, we are now focusing on ways to improve the treatment, including the possibility of genetically correcting the patient’s own myoblasts, thus removing the need for life-long immunosuppression therapy. We have already shown that such correction is possible using a lentivirus (a virus used to deliver DNA into a host cell) coding for micro-dystrophin (Moisset, Skuk et al. 1998). We are also working, with Dr. Mitsuo Oshimura of Japan on using a human artificial chromosome to introduce the full-length dystrophin gene. One problem is that the patient’s own myoblasts may be difficult to grow because they are senescent after five years. We have, however, shown that it

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is possible to produce induced pluripotent stem cells (iPSCs) from the patient’s own fibroblasts, which we were then able to differentiate into myoblasts. These myoblasts were then genetically corrected with a lentivirus coding for micro-dystrophin and were successfully transplanted in the muscles of immunodeficient mice, where they fused and led to muscle fibers expressing micro-dystrophin. This ex vivo gene therapy approach, if it is shown to be effective in humans, could be a means for avoiding the long-term immunosuppression currently required when using donor myoblasts.

Myoblast transplantation is an exciting development, not only for DMD, but also for other types of muscular dystrophies, in part because it can provide additional myogenic cells and restore strength to already-damaged muscles. We anticipate, following the completion of our new phase I/II clinical trial, further progress towards the development of a cellular therapy for DMD and other muscular dystrophies.

References


The Evolution of FIRE-WELL: Improving Firefighters’ Health through Research and Partnership

KATHRYN SINDEN PhD CANDIDATE1 JOY MacDERMID PT PhD2

Introduction

Firefighters provide an essential service within our communities; they respond to emergency situations and ensure our neighborhoods are safe. The intersecting and cumulative effects of the cardiovascular, physical and emotional demands of firefighting, have been linked to high rates of injury,1 with musculoskeletal disorders (MSD) accounting for one-third of all injuries.2 Although female firefighters represent only 3% of all firefighters,3 the number of female firefighters is increasing and they experience elevated risks of injury compared to their male counterparts.4 Firefighters and their municipal employers are challenged to support optimum health given the complex physical and psychological challenges associated with firefighting.

The Knowledge-to-Action (KTA) process model5 is a theoretical framework based on synthesis of multiple planned action theories and has guided our program of research with the firefighters. One of the guiding tenets of the KTA is that evidence about effective

THE PROBLEM:
High rates of injury among firefighters.

THE SOLUTION:
Working with firefighters to develop ways to prevent injury.

THE IMPACT:
A standardized, evidence-based screening program being used by firefighters to assess injury risk.

Evidence about effective musculoskeletal injury prevention needs to be contextualized to this unique occupational context to ensure that the outcomes are relevant.

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1 School of Rehabilitation Sciences, McMaster University
2 Professor, Assistant Dean of Rehabilitation Science, CIHR Chair — Gender in Measurement and Rehabilitation of Musculoskeletal Work Disability, School of Rehabilitation Sciences, McMaster University and Hand and Upper Limb Centre, Clinical Research Laboratory, St. Joseph’s Health Centre
musculoskeletal injury prevention needs to be contextualized to this unique occupational context to ensure that the outcomes are relevant. To date, there has been little translational work directed towards injury management programs for firefighters. For example, it is not known what musculoskeletal tests or screening processes might detect MSD in firefighters. The following story tells of the evolving participatory research and knowledge translation (KT) partnership between researchers and firefighters focused on development of FIRE-WELL, an evidence-based injury management program. This case emphasizes the barriers and facilitators to KT within this complex occupational context (see Figure 1).
Building partnerships to build success

Developing effective partnerships between occupational stakeholders and researchers can be difficult, but is critical when identifying effective KT strategies. Active engagement of occupational groups during the initial phases of research is known to ensure the identified methods and outcomes are contextually relevant. The development and implementation of the FIRE-WELL project was led by firefighter research partners as full co-principal investigators which is essential to effective KT.

For instance, one of the early projects undertaken during the evolution of FIRE-WELL was the development of a firefighter physical demands analysis (PDA). The PDA involved cataloguing and weighing all firefighting equipment and describing the physical demands associated with firefighting tasks. This was selected by firefighters as a critical task and supported implementation of work restrictions and return to work plans and use of current evidence-based guidelines. Regular stakeholders meetings were conducted during the development of the PDA to ensure that the PDA could be used across multiple applications within the fire service. For example, the firefighters’ return-to-work (RTW) specialist needed general information about firefighting tasks that could be modified to facilitate RTW. The occupational health and safety team, on the other hand, required detailed information to identify specific injury risks. The researchers and fire service were able to work together to review local information on job tasks/equipment/roles, PDAs from other municipalities, existing PDA development guidelines and how information was used in various injury management decisions. The firefighters made key decisions about the format and content of the PDA, while researchers used best evidence.
guidelines on PDAs to ensure quality. The fire service, insurers and employees now use this PDA to facilitate RTW, while occupational health and safety professionals use the PDA to identify tasks that predispose firefighters to injury. Building trust during our growing partnership was key to success in the making and implementation of the PDA as well to the development of FIRE-WELL.

The challenges of partnerships across “cultures”

Although engaging all stakeholders through regular meetings ensured all perspectives were considered in developing FIRE-WELL, the project was also met with challenges. The groups had different, sometimes conflicting, priorities and obligations. There were periods where research decisions were on hold for contract negotiations or leadership decision and periods where firefighters decisions were on hold waiting for funder decisions. One of the biggest challenges in this regard lay in the nature of the research process. Researchers know that research grants are not adjudicated immediately and are often unsuccessful on the first attempt. Stakeholders, though, experience frustration during the prolonged period of inactivity while waiting for grant funding and can lose the enthusiasm generated during the grant application process. Maintaining relationships and confidence in the partnership during these “hurry up and wait” cycles is a challenge.

We solved this challenge by maintaining engagement through ongoing meetings, reassuring our firefighter partners about the nature of the granting process and accomplishing small projects using internal resources and graduate students. For example, the work of graduate students enabled us to complete a qualitative study of the unique challenges faced by female firefighters. This study resulted in a publication, providing a much-needed success. Furthermore, as attention to gender differences grew in different fire services, our proactivity on this issue increased confidence around the usefulness of research.

Firefighters are goal-oriented; this culture and focus, with regular communication, were critical to expediting FIRE-WELL.

Once we were successful in receiving the Partnership in Health System Improvement (PHSI) grant for the FIRE-WELL project, the firefighters and their stakeholders were immediately engaged in initiating the work. Firefighters are goal-oriented; this culture and focus, with regular communication, were critical to expediting FIRE-WELL. One of the challenges in developing the screening component of the project was adapting protocols to be both valid and feasible. Researchers reviewed with firefighters the stages involved in the study and how the tasks were evolving to replicate the physiological and physical demands associated with firefighting. Once the research plan, space and protocols were established, the firefighters provided critical organization, allowing us to screen 150 firefighters in a six-month period. Their willing participation in this activity was seen as an indication of the level of commitment and partnership established between the researchers and fire service during the preliminary phases of this research program.
Outcomes

Our partnership with firefighters during the evolution and implementation of FIRE-WELL has resulted in mutual benefits. As researchers, we have improved our understanding of the unique challenges of implementing KT in a complex occupational context; firefighters have gained insights into the nuances of developing and implementing a research program.

As a result of our partnership, a standardized evidence-based screening program has been developed and is being used by firefighters in injury risk identification. Our research findings are also supporting next phases, including the development of ergonomic modules that will be used to teach injury prevention strategies during high-risk firefighting tasks.

The outcomes from this research program will improve our ability to identify risk of injury among firefighters, improving their health and ultimately, that of the communities within which they serve.

ACKNOWLEDGEMENTS

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Making the Care Path Consistent: Alberta Protocols Paying Off for Patients

STEPHEN WEISS PhD

Introduction

Alberta has taken the battle to reduce stubbornly high variability in its provincial care path for hip and knee replacements to the front lines of health care, and the move is paying off.

In 2005–2006, Alberta developed and evaluated a fully integrated care path in a multi-disciplinary setting for patients needing hip and knee surgery. The evaluation showed it produced superior results compared with conventional care. Patients had significantly greater improvement in general health, less pain and greater ability to perform daily activities after their hip or knee surgery than those who received conventional care. An added bonus — their wait from decision to have surgery to date of surgery was one-eighth that of conventional care patients.

Based on these findings, Alberta adopted the care path as the standard of care in 2007. Spreading it across the province, however, proved slow and the extent of adherence to its protocols and procedures varied from site to site. At the same time, patient waits in Alberta and most other jurisdictions in Canada remained well above the national benchmark of 26 weeks.

THE PROBLEM:
Standardized care path for hip and knee replacements was being applied inconsistently in Alberta.

THE SOLUTION:
Non-monetary incentives encouraging frontline health-care teams to adhere to the care path’s practices and protocols.

THE IMPACT:
Patients home sooner. 32,000 hospital bed-days saved. More surgery capacity. Reduced waits for surgery.

Alberta Health Services (AHS) decided to test the effectiveness of non-monetary incentives for increasing adherence to the care path and accelerating its spread across the province. It turned to the people on the front lines of health care, forming a multidisciplinary team at Calgary’s Rockyview General Hospital to conduct the test in 2009.

1 Chief Operating Officer, Alberta Bone and Joint Health Institute
The Rockyview team set performance targets in key areas of the care path and created a scorecard to track its progress toward the targets. Non-monetary incentives included increased autonomy over orthopaedic bed management in the hospital, educational opportunities and team recognition. Adhering to the care path, the team reduced wait time, had patients up and moving earlier after surgery, and had them out of acute care sooner without any adverse effects.

**Expanded 12-month research project**

Positive results at Rockyview were followed by an expanded 12-month research project in 2010 to test the impact of incentives at all of the 12 hip and knee replacement surgery sites in Alberta. The project was sponsored by AHS’s Bone and Joint Strategic Clinical Network (BJSCN). Alberta Bone and Joint Health Institute (ABJHI), which designed the care path and managed the trial in 2005–2006, was enlisted to coordinate the work.

A secondary aim of the expanded research was to determine the extent to which adhering to the care path’s benchmark four-day stay in acute care while also reducing the stay in sub-acute care would have an impact on provincial wait times. Freeing up beds would open up capacity for more surgeries, reducing wait times. This became significantly more urgent in 2010 as AHS set aside the 26-week national benchmark in favour of even more ambitious targets — progressively shorter annual waits culminating in a maximum wait of 14 weeks for nine of 10 patients by 2015.
A multidisciplinary team was formed at each of the hospitals performing hip and knee replacements in Alberta. Using the Rockyview model, team members came from across the care continuum — acute care units, rehabilitation, operating rooms and hip and knee central intake clinics. They included surgeons, nurses, therapists and managers.

Each team selected at least one key performance indicator (KPI) in each of six dimensions of health-care quality: accessibility, appropriateness, acceptability, effectiveness, efficiency and safety. Shorter acute care stay (efficiency) and reduced wait for surgery (accessibility) were mandatory, but KPIs selected in the other dimensions were discretionary. Each team developed an improvement plan, tracked its performance on a standardized scorecard, and met monthly to review progress. Results were shared within hospital units to encourage broader interest and among teams to create an undercurrent of competition.

Length of stay in acute and sub-acute care declined an average of 1.3 days — a large gain in view of the 10,000 hip and knee replacements performed in Alberta annually. The acute and sub-acute bed-days saved set the stage for increasing surgery volumes and reducing wait times in the subsequent year.

The incentive was a commitment from AHS to return a portion of any resource savings to hip and knee replacement services in areas where the teams could see the impact of their success first-hand.

The study design — involving frontline clinicians and managers — encouraged each team member to address the question: “What do I do in my area of the care path that affects others on my team?” This, in turn, led to the next logical step, which was to address the issue at the heart of the research: “How do all of us work together as a team to improve results?” These questions were critical because they reflect the nature of care delivery along the integrated care path, which involves a multidisciplinary partnership rather than a provider-to-provider handoff.

Associated improvements in wait times

The implementation of an integrated care path is having its intended impact on wait times. Beyond that, though, and in parallel with this work, ABJHI has been developing a system that will make Alberta’s wait times data on hip and knee replacements more reliable, supporting further reductions.
Up until now, data have been flawed because definitions of key events during the wait and practices used to measure data have differed markedly across the province. These inconsistencies have made the wait times reported from different locations unreliable, which in turn has made reducing waits much more difficult. Hip and knee wait times reporting in Alberta, as in most jurisdictions, has also focused exclusively on just two major timeframes — from referral to consultation with a specialist and from the decision to have surgery to the date of surgery. The wait between important steps within these timeframes has been largely ignored, leading to missed opportunity to identify and address causes of delays.

Further, data have not distinguished between voluntary delays caused by patients and the involuntary delays caused by deficiencies in the health-care system. Voluntary delays — for example, a patient’s decision to travel or refusal to take time off work — are factored into provincial wait times even though they are unrelated to system performance.

In response, AHS set out to develop Wait Time Rules and enlisted ABJHI to lead the work. These rules would provide standardized definitions of wait times between key events from referral to surgery and the metrics used for measuring performance. Wait times between seven key events were selected to be tracked:

- date of referral;
- date the referral is received;
- date of consultation with a musculoskeletal physician;
- date of consultation with an orthopaedic surgeon;
- date of decision to have surgery;
- date patient is ready for surgery; and
- date of surgery.

Each team developed an improvement plan, tracked its performance on a standardized scorecard, and met monthly to review progress. Results were shared within hospital units to encourage broader interest and among teams to create an undercurrent of competition.
Data on the date patients are ready for surgery is unique and makes Alberta the first jurisdiction in Canada able to identify and measure voluntary delays. This enables service planners to focus wait-time reduction efforts solely on the operational areas over which they have influence, such as operating room time, hospital bed space and referral processing.

Alberta’s Wait Times Rules also capture data on patient characteristics and demographics. This information gives the province an accurate snapshot of who is waiting, where they are waiting and how long they have been waiting on a real-time basis. As a bonus, the rules have laid the foundation for developing a provincial online referral system that will show primary care physicians the availability of specialists across the province. The Wait Times Rules are now being phased in.

**Outcomes: Incentives and measurement effective for spreading the care path**

The outcomes of the 2010 research project demonstrated that incentives and performance measurement form an effective mechanism for spreading the care path. All teams followed its protocols and procedures. Furthermore, length of stay in acute and sub-acute care declined an average of 1.3 days — a large gain in view of the 10,000 hip and knee replacements performed in Alberta annually. The acute and sub-acute bed-days saved set the stage for increasing surgery volumes and reducing wait times in the subsequent year.

Translation of this research, beginning with the Rockyview incentives project, resulted in a permanent provincial program to build on the teams’ improvements. Outcomes have been impressive. Since the start in 2010:

- adherence to the protocols and procedures in the care path has solidified;
- length of stay in acute care has declined to a provincial average of 4.1 days, closing in on the four-day benchmark with no detrimental impact on patient safety or satisfaction;
- a projected 32,300 bed-days — 22,400 in acute care and 9,900 in sub-acute care — will be saved by March 31, 2013, the end of the current fiscal year, with a value of more than $22 million;
- used solely for hip and knee replacement patients, the savings would have opened up bed capacity for additional 8,625 surgeries without having to add a single new bed; and
- key performance indicators have improved across all the dimensions of quality.

In addition, Alberta is now on a trajectory to meet, or even better, its ultimate wait time target of 14 weeks by 2015.

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The Inconvenient Tooth: Making Room for Influential Voices to Inform Research

MARY McNALLY¹,² DEBORA MATTHEWS¹,² JOANNE CLOVIS¹ MARK FILIAGGI¹ SANDRA CROWELL² MARTHA BRILLANT¹ KAREN McNEIL²

Introduction

Bringing knowledge users together with knowledge creators helps inform research priorities and direction and ensures that research findings can be applied in practice. Making such connections, through a knowledge translation (KT)/knowledge exchange (KE) approach, has resulted in important developments in our research that are helping to ensure that, as people age, their oral health can be maintained.

Responding effectively to changing oral health needs

Canadians are both living longer and maintaining more of their natural teeth. These are welcome trends but are resulting in new patterns of oral disease and significant challenges for oral health care. A decade ago, we began to examine these trends in Nova Scotia. Like the rest of Canada, oral health care services in Nova Scotia typically fall outside of mainstream healthcare, isolating oral health in terms of research, clinical care and health services and policy. Good oral health is a key feature of optimal general health and quality of life. Eating, speaking and socially interacting with comfort and confidence are important goals for oral health at any age. But with no oral health database, little understanding of care needs and few standards or policies to guide care and promote oral health at later stages of life, we recognized that we had to find ways to identify and bridge these gaps.

THE PROBLEM:
Changing, and largely unknown oral health needs as older adults keep their natural teeth longer.

THE SOLUTION:
Involving research users in identifying research priorities and developing solutions.

THE IMPACT:
An oral care education program for college educators and personal care providers and increased emphasis on oral health among partners in health, continuing care and education.
That horse is already out of the barn. You need to look at those who will be seniors, so we can make plans for them.

Knowledge users, including seniors, clinicians, policy makers, personal and professional care providers, administrators, educators, health promoters and health-service funders, profoundly influenced our research and helped to create a shared awareness of its importance. The following three vignettes illustrate the surprising directions research can take when we listen to the voices of those who are most affected by the research.

**That horse is out of the barn**

It turned out that our own conception of the target audience for our work was too limited — something we wouldn’t have known without the participation of community members. At that time, nearly 10 years ago, we knew that half a century of modern dentistry was resulting in more seniors retaining their teeth into old age. At the same time, we knew very little about the oral health status and treatment needs accompanying this trend and even less about how goals focused on optimizing oral health would inform the arrangement, delivery and support of oral health education and services. So one of our first research priorities was to address the lack of epidemiological information about the oral health of older adults in Canada.

We held interdisciplinary workshops that included engagement with seniors and seniors’ organizations to begin to build capacity for carrying out this research, with a view to informing health services and policy. We were clearly focused on seniors over the age of 65 until given pause by a voice from the community: “That horse is already out of the barn. You need to look at those who will be seniors, so we can make plans for them.”

**Outcome:** We re-framed our research question to include adults aged 45 and older, in addition to those at the latter end of the age spectrum. This has led to knowledge that informs both present and future health service needs of older Nova Scotians. Given that Nova Scotia currently has the oldest population in Canada, the trends we are seeing now are informative to a national audience and key to identifying research priorities.

...at this point I think I want an advanced directive to ensure all my teeth come out before I enter a nursing home. At least I know dentures may be easier to get out of my mouth to be cleaned.

**I want all my teeth out**

Sometimes we got a message that stopped us in our tracks. In tandem with the epidemiological research described above, we undertook a province-wide environmental scan that included a health-services evaluation (from the perspectives of seniors and multiple levels of care providers) as well as best practices and policy scans (involving government, education and continuing care sectors) to inform oral health service action planning. As we were identifying research priorities, we were taken aback by the poignant message of a nurse manager from the continuing care sector: “…at this
point I think I want an advanced directive to ensure all my teeth come out before I enter a nursing home. At least I know dentures may be easier to get out of my mouth to be cleaned.”

Given the advances in dental health over the last half century, this was a disturbing commentary from someone who was intimately aware of the system. It is not entirely clear whether the nurse manager quoted was primarily concerned with the difficulty associated with receiving care or the consequences of dental disease. Either way, she identified a troubling problem that became a key focus of our research.

**Outcome:** We entered into a collaborative partnership with three long-term care facilities to create “Brushing up on Mouth Care”, a comprehensive, hands-on education and resource program focused on daily mouth care for dependent older adults. End-users and administrators were directly involved in the processes that led to the creation of this open access web-based resource, which includes oral health toolkits, education resources and videos and assessment and care-planning guidelines.

**Mouth care is off the radar**

While all this work was ongoing, one perplexing question kept coming up: why personal care providers seemed well-equipped to undertake many difficult and even unpleasant tasks associated with personal care, yet mouth care was apparently “off the radar”.

Educators in personal-care provider programs provided an answer: the lack of adequate resources available for training students. Unlike other domains of personal care, there were no laboratory models or hands-on resources to provide an opportunity for students to practice. The same educators also told us that new graduates are an exceptional means of creating heightened awareness about updated standards of practice among older practitioners in the field.

**Outcome:** We developed a unique university-college partnership that has led to the introduction of *Brushing up on Mouth Care* resources to more than half the personal care providers and all of the practical nurses trained in Nova Scotia each year. Eleven community colleges have also introduced mannequins in their personal care laboratories to enable students to practice techniques.

These vignettes offer striking examples of how stakeholder voices can pave the way forward in research and knowledge exchange and provide concrete examples of far reaching impact. They truly only scratch the surface in demonstrating the value of these voices and demonstrate how a field that has traditionally been at the margins of mainstream healthcare can be informed by both beneficiaries and end users of research.

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**Key collaborating stakeholders:**
Nova Scotia’s Capital District Health Authority, Eastern Shore Tri-Facilities Long-term Care Centres; Nova Scotia Community College, School of Health and Human Services; Northwoodcare Incorporated; Health Association of Nova Scotia; Nova Scotia Department of Health and Wellness, Continuing Care Branch; Nova Scotia Department of Seniors; Nova Scotia Group of IX Seniors’ Organizations; Nova Scotia Dental Association

**Funding:** Nova Scotia Health Research Foundation, Canadian Institutes of Health Research (CIHR)
Engineering a Natural Solution for Chronic Diabetic Wounds

PAUL GRATZER PhD PEng

Introduction: Alarming statistics
An estimated 366 million people worldwide are affected by diabetes. Of those, 15-20% experience non-healing (chronic) foot ulcers and of those, 85% will ultimately require amputation. In starker terms, someone in the world is losing a limb to diabetes every 20 seconds. As the number of people afflicted by diabetes is increasing significantly every year, expected to reach 439 million by 2030, equivalent to 7.8% of the world adult population, this problem can only be expected to grow. In Canada, nine million people are affected with diabetes today; by 2020, $16.9 billion dollars will be spent directly on diabetes. Our lab has developed a new way to heal diabetic foot wounds that could potentially eliminate the need for amputation; we are working to make it available to patients.

Someone in the world is losing a limb to diabetes every 20 seconds.

THE PROBLEM:
No effective, low-cost way to treat foot wounds in people with diabetes, leading to amputation.

THE SOLUTION:
Developing and commercializing a scaffold that encourages the growth of new tissue.

THE IMPACT:
A potential end to amputation within two-to-three years.

An unmet need
The options for treating foot ulcers in people with diabetes are often insufficient. Currently in Canada, the standard of care involves removing dead or infected tissue within the wound site, wrapping the wound with saline-soaked sterile gauze and providing a method to keep the patient from walking on the affected area during healing. The patient will be seen weekly and the standard of care

1 Associate Professor, School of Biomedical Engineering, Department of Process Engineering and Applied Science, and Department of Surgery, Dalhousie University
treatment will be repeated until healing is successful, a process that can take up to six months. Often, however, healing does not occur. The risk of the patient experiencing an infection increases dramatically if significant healing (>50%) does not occur within four weeks. Infected wounds can receive another level of treatment involving the application of anti-microbial dressings and topical anti-septic agents. If these measures fail, the infection will persist and spread, until surgical removal of the affected portions of the foot is the only option. There is a third line of treatment prior to amputation, which involves the use of biologic agents or engineered tissues. This is used in the United States but, due to the very high cost of these treatments, it is used very infrequently and usually as a last-ditch effort to save the affected limb from surgical amputation. Currently, these types of products are not available in Canada for the treatment of diabetic chronic wounds.

Patient, heal thyself

Our Matrix Engineering Lab at Dalhousie University is using a technology known as “decellularization”. In a process somewhat analogous to removing the yolk and the white from an egg without damaging the shell, we extract immune-reaction inducing cellular materials from animal or human tissues. This leaves behind an intact, native, non-living protein matrix scaffold that acts as a foundation for the repair and regeneration of tissues. The scaffold is both safe and sterile, because decellularization has removed any bacteria or viruses from tissues. Our research has shown that, after decellularization and with the processing methods we have developed, the remaining scaffolds retain the essential properties of their tissue of origin. Further, these scaffolds encourage cells to migrate back into them and begin forming new living tissue. This has been shown for a variety of tissues obtained from animals and, most recently, humans. These results indicate that once the decellularized scaffolds are implanted into a patient’s body, they can combine with the patient’s own cells to repair and ultimately regenerate new living tissue.

Translating this new treatment to the patient

There are a number of areas where decellularization of human tissues would have a great impact on patient treatment and outcomes. One growing and unmet need identified early on was the treatment of chronic diabetic wounds. The use of decellularization technology could potentially eliminate the need for amputation. To be successful, however, the decellularization technology would not only have to be effective at healing the wounds, but also easy to use and cost effective.
With commercial development funding from CIHR and Nova Scotia funding agencies (Springboard, InNOVAcorp, ACOA) and support provided by the Capital District Health Authority (CDHA) in Halifax, we have developed a sterile decellularized human skin-derived scaffold capable of facilitating healing in chronic diabetic wounds. In addition, to ensure that this new treatment would be affordable and, therefore, available, we developed in parallel an innovative automated manufacturing system to provide large numbers of these scaffolds at a very low cost. As a result, the new technology can be used as a front-line treatment and create a new standard of care for treating chronic diabetic wounds.

We anticipate that our product can eliminate amputation as a necessary option in the treatment of chronic wounds in diabetic patients within two-to-three years.

We have secured patent protection for our discoveries and we have established a company, DeCell Technologies Inc., which will be bringing decellularized tissue-based products to the Canadian market and, in turn, to Canadian patients. Currently, DeCell Technologies Inc., is completing pre-clinical studies on its first decellularized human tissue derived product, called DermGEN. This product is specifically targeted at treating chronic diabetic foot ulcers and will be undergoing clinical testing with diabetic patients in the fall of 2013. We anticipate that our product can potentially eliminate amputation as a necessary option in the treatment of chronic wounds in diabetic patients within two-to-three years.

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References
See TCL: Research Providing Solutions to Hard-to-Diagnose Skin Cancers

YUANSHEN HUANG¹ YOUWEN ZHOU¹²

Introduction

After 17 years of suffering from an itchy, scaly and red rash on his back and legs and after 17 years of being told he had eczema and being prescribed ineffective steroid creams, a new doctor finally told Michael¹ he had cutaneous T cell lymphoma, a type of skin cancer that has no cure.

Cutaneous T cell lymphoma (CTCL), a group of skin lymphoma, is a notorious chameleon, mimicking a wide range of benign skin disorders, such as psoriasis and chronic dermatitis. But this group of skin cancers, which arises from abnormal accumulation of cancerous T lymphocytes, affects more than 30,000 people in North America, many of whom are diagnosed only at a late stage of the disease.

Part of the difficulty in telling CTCL from psoriasis and chronic dermatitis is the lack of an accurate diagnostic test. So it is not uncommon for many individuals with skin lymphoma to go through what Michael went through, being treated for benign skin inflammation only to later on be diagnosed with skin lymphoma. And although patients diagnosed with CTCL early have a normal life expectancy, survival is poor once the disease progresses to the advanced stage, for which there is no cure. We have developed the world’s first diagnostic test for cutaneous T cell lymphoma and the potential for new therapies to treat the disease.

THE PROBLEM:
No way to diagnose a virulent skin cancer that presented like much more benign skin disorders.

THE SOLUTION:
Identification of molecular “markers” to help diagnose the disease.

THE IMPACT:
The world’s first diagnostic test for cutaneous T cell lymphoma and the potential for new therapies to treat the disease.
The “See TCL” story

The “See TCL” project has two objectives: First, to identify unique markers for skin lymphomas and evaluate whether they can be used to diagnose or predict the course of the diseases; and second, to learn whether these markers are actually the reason that cancerous cells multiply uncontrollably in skin lymphomas. If we can confirm that these markers are, indeed, the “on switch” for the disease, we can then look for ways to switch them off and eliminate the tumour cells.

We have accomplished our first task. Over the past three years, we have identified a set of specific molecular markers (disease-signature changes) in skin lymphomas. We can now “see” the malignant T cells in skin lymphomas, and tell them apart from other benign inflammatory skin diseases such as psoriasis and chronic dermatitis. As a result, we now have the world’s first and only diagnostic test for CTCL, the SeeTCL™ technology, and have started a British Columbia-registered biotechnology company to commercialize the technology.

It is not uncommon for many individuals with skin lymphoma to go through what Michael went through, being treated for benign skin inflammation only to later on be diagnosed with skin lymphoma.

The road to this achievement had many steps. We undertook traditional knowledge translation activities, including publication in scholarly journals and presentations at multiple national and international conferences. Our work was showcased in the Crossroad for BioTransfer 2012 meeting, where Canadian research centres, universities and technology transfer offices show their best life sciences technologies for commercialization. In addition, part of this project has received...
CIHR commercialization support in the form of a Proof-of-Principle grant.

Outcomes

Through a collaborative effort with dedicated researchers in the skin lymphoma research community, website developer, business consultants, university and industrial liaison office of University of British Columbia, and Technology Development Office of British Columbia Cancer Agency, our research findings have been translated into measurable changes.

We have developed and are commercializing the world’s first specific and sensitive diagnostic test for skin lymphomas.

We now have the world’s first and only diagnostic test for CTCL, the SeeTCL™ technology, and have started a British Columbia-registered biotechnology company to commercialize the technology.

We are also making progress on our second objective, which was to gain a better understanding of the cause of skin lymphomas. We now know that, in addition to resistance to programmed cell death, skin lymphoma cells also grow by producing higher-than-normal amounts of a growth-promoting protein, TOX. If we could eliminate this cancer growth factor, the cancerous cells can potentially be wiped out.

We are now working to turn this potential into a clinical weapon to fight skin lymphomas. We have found a gene-based method to specifically turn off the production of the TOX cancer promoter and are currently testing this method. At the same time, we are developing the world’s first skin lymphoma experimental model to facilitate development of skin lymphoma therapies. We believe that our goal, of not only being able to diagnose CTCL, but also treat it, is within reach, enabling people like Michael to lead long and healthy lives.

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Notes & References

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