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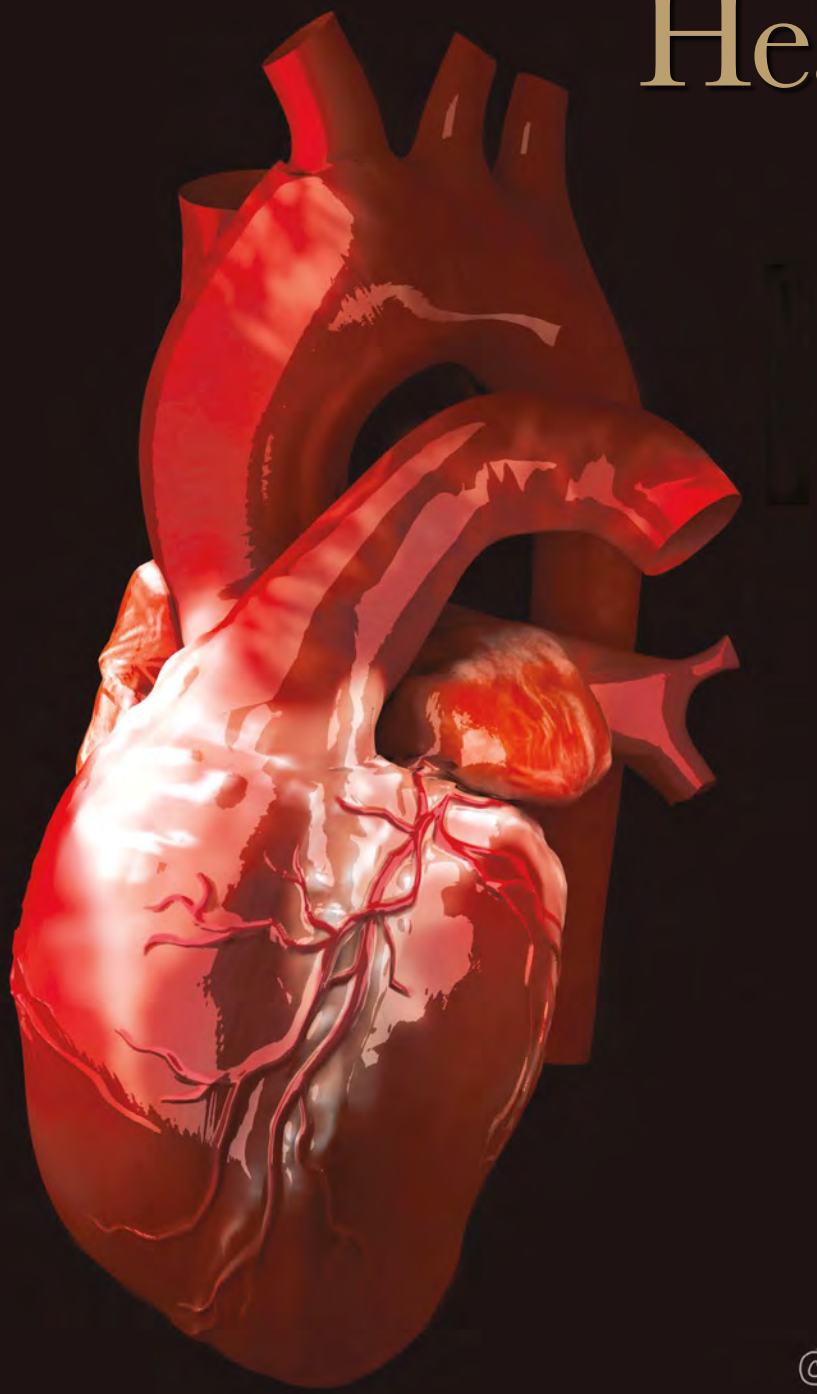

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All articles are externally peer-reviewed with the exception of poetry, short stories and book reviews. All manuscripts are internally reviewed. Informed consent practices and any conflicts of interest are specified in the articles if applicable.

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Preface from the Editors

Dear Reader,

We are pleased to present you with the third issue of the 94th volume of the *UTMJ*. We have consistently sought out unique themes to discuss over the course of this year, but there is perhaps no issue more relevant than that of cardiovascular health, which we highlight in our current issue. Heart disease is the second leading cause of death and affects more than 1.6 million Canadians.[1] However, tremendous progress has been made in the field: the last decade has seen a nearly 40% decrease in cardiovascular disease mortality.[2] Advances have been made in imaging, cellular therapies, regeneration, health policy, and preventative care.

We are thrilled to feature reviews, commentaries, and interviews that encompass a variety of topics pertinent to cardiovascular health. In his review, Dr. Mansoor Husain provides a thorough discussion of the relationship between diabetes and myocardial disease. We are also proud to feature an interview with Dr. Heather Ross, world-renowned cardiologist at the Peter Munk Cardiac Centre, who is on the forefront on cardiovascular research and is spearheading new approaches to treating cardiovascular disease.

This is an exciting time for cardiovascular health, with new disease mechanisms being discovered and new therapies being brought to light. It is with this same sense of duty and optimism that the 2016-2017 *UTMJ* team has endeavoured to compile this issue. We would like to express our appreciation for the dedication and hard work of our team of section reviewers, copy editors, associate editors, the interview team, cover artist, and web developers. We are grateful for ongoing patronage of the journal by our sponsors. Finally, we would like to thank you - the reader; we hope you enjoy reading this issue!

Sincerely,

Ahmad Mousa
Mark Shafarenko

Editors-in-Chief, UTMJ

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1. Health Canada
2. Heart and Stroke Foundation

Increased Risk of Myocardial Disease by Diabetes-Induced Molecular Disturbances

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Abstract

The incidence and prevalence of Type-2 diabetes mellitus (T2DM) is increasing worldwide. Cardiovascular disease (CVD) is the major cause of morbidity and mortality among subjects with T2DM. The relationship linking diabetes and CVD is complex and multifactorial, and a thorough understanding of the pathophysiological mechanisms underlying diabetes-induced cardiac damage is crucial to the development and improvement of treatment strategies for patients with T2DM at high risk of major adverse cardiovascular events (MACE). Heart failure is more frequent and has an especially adverse outcome in subjects with diabetes. Heart muscle disease not explained by either coronary heart disease or hypertension (diabetic cardiomyopathy), is an important contributing factor to the development of heart failure. This review summarizes the molecular mechanisms of certain key contributors to the progression of diabetic cardiomyopathy including insulin resistance, metabolic disturbances, oxidative stress, altered Ca^{2+} handling, and neurohormonal activation.

Introduction

Due to its increased incidence over the past three decades and current status as one of the most prevalent chronic diseases worldwide, T2DM has been firmly established as a major threat to human health.[1] In addition, a close link exists between T2DM and a variety of CVD, namely the enhanced development of atherosclerosis and coronary heart disease, hypertension, and renal disease. These are known to be the leading causes of morbidity and mortality among patients with T2DM.[2-5] Clinical and experimental studies suggest that patients with T2DM are also at increased risk of a particular form of cardiomyopathy known as diabetic cardiomyopathy.[6-11] The following abnormalities are observed in diabetic cardiomyopathy: left ventricular (LV) diastolic and systolic dysfunction, cardiomyocyte hypertrophy, myocardial fibrosis, cardiomyocyte apoptosis, and microvascular abnormalities.[12-16] While it is not well understood to what extent the presumably 'direct' cardiotoxic effect of T2DM has on heart failure, there is a strong epidemiological relationship between T2DM and heart failure (HF).[7,17,18] This review summarizes our current knowledge of the mechanisms and potential therapeutic targets of diabetes-induced impairments in myocardial structure and function, including the contributions of insulin resistance, metabolic disturbances, oxidative stress, altered Ca^{2+} handling, and neurohormonal activation. We also compared the benefits of novel therapeutic agents targeting the condition of heart failure in diabetic patients at high risk of MACE.

Insulin Resistance

Cellular insulin signaling is known to occur through two key pathways. These include insulin receptor substrate-1 (IRS-1)-mediated stimulation of the phosphatidylinositol 3-kinase (PI3K)-AKT signaling, resulting mainly in metabolic responses and the mitogen-activated protein kinase (MAPK) signal transduction pathway involved in the processes of growth and remodeling.[19] As such, insulin-resistant states result in metabolic imbalances and altered growth. A major underlying imbalance in insulin signal transduction is the increased serine phosphorylation of IRS-1 leading to attenuated engagement of PI3K and subsequent AKT stimulation.[20-23] The responsible serine kinases may be activated by altered oxidation-reduction states or nutrition-related factors.[24-27] More specifically, over-nutrition as well as excess activation of the renin-angiotensin-aldosterone system (RAAS) are known to stimulate the mechanistic target of rapamycin (mTOR)-S6 kinase 1 (S6K1) signaling, subsequently attenuating IRS-1, IRS-2, and PI3K-AKT signaling in cardiovascular tissues.[19,28] A recent study has indicated that angiontensin (Ang)-II may activate S6K1 leading to reduced insulin metabolic signaling,

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impaired nitric oxide (NO)-mediated vascular relaxation, altered myocardial glucose utilization, and compromised diastolic relaxation.[29-31] These findings are supported by existing evidence indicating a causal relationship between hyperinsulinemia, hypertension, and coronary artery disease.[32-34] Forkhead box-containing protein, O subfamily (FOXO) activation has also been shown to lead to altered insulin signaling through downregulation of IRS-1 activity.[35,36] A recent study by Qi *et al.* demonstrated that FOXO-mediated impaired cardiac insulin signaling results in stimulation of the β-myosin heavy chain expression, which leads to cardiac dysfunction.[37] Moreover, defective insulin signaling has often been characterized by reduced GLUT4 translocation to the plasma membrane, resulting in metabolic consequences and contributing to diabetic cardiomyopathy (described in more detail below).[38] Thus, both FOXO1 and mTOR signaling may have essential roles in insulin signaling and subsequent substrate metabolism, potentially providing novel therapeutic and/or preventive targets for diabetic cardiomyopathy. Further metabolic imbalances, which may lead to insulin resistance and are known to precede the development of cardiac dysfunction, include mitochondrial dysfunction, inflammation, cytokine upregulation, endoplasmic reticulum stress, and stress kinase signaling.[39]

Metabolic Disturbances

Disturbances in myocardial substrate and energy metabolism have emerged as important contributors to the development of diabetic cardiomyopathy and heart failure.[40,41] Under normal physiological conditions, the heart utilizes both free fatty acids (FFA) and glucose, allowing for metabolic flexibility.[42,43] Additionally, the heart has a limited capacity to store surplus lipids, as fatty acid uptake and oxidation are tightly controlled to ensure sufficient, but not excessive supply, of fatty acids for the heart's energetic requirements.[44] However in T2DM, myocardial fatty acid uptake is increased, leading to increased fatty acid oxidation and lipid accumulation.[44] In insulin-resistant settings, cluster of differentiation 36 (CD36), which normally mediates the uptake of FFA, is localized to the sarcolemma.[45,46] Moreover GLUT4, which is usually translocated to the sarcolemma due to increased plasma levels of insulin, is internalized to its intracellular location.[45,46] This maladaptive positioning of CD36 and GLUT4 results in cardiac metabolic inflexibility and related abnormalities.[46]

Under normal physiological conditions, insulin inhibits lipolysis and accelerates triglyceride (TG) synthesis in adipose tissue.[47] However in settings of insulin resistance, lipolysis and hydrolysis of TGs is increased, elevating circulating levels of FFAs.[47] Enhanced fatty acid oxidation rates lead to an inhibition of glucose oxidation rates, through negative regulation between fatty acid and glucose oxidation (known as the Randle Cycle).[48] In this manner, insulin-resistance leads to reduced glucose uptake and oxidation rates, increased FFA supply and cellular uptake, and an overall substrate shift toward FFA oxidation as the dominating energy source in metabolism.[49,50] This results in increased myocardial oxygen consumption per ATP produced, reduced cardiac efficiency, and excess lipid deposition in the diabetic heart.[47,51,52] Furthermore, the accumulation of FFA in cardiac tissue further impairs insulin signaling, stimulates apoptosis, and reduces cardiac autophagy. This results in the build-up of toxic intermediates leading to lipotoxicity and ultimately to adverse structural remodeling of the myocardium, as well as, impaired cardiac performance.[50,53-56] In later stages of diabetic cardiomyopathy, expression of transcription factors involved in the regulation of glucose oxidation and β-oxidation, such as peroxisome proliferator activator receptor-α (PPAR α) and peroxisome proliferator-activated receptor gamma co-activator 1α (PGC-1 α), are decreased which further reduces myocardial metabolic efficiency.[57,58] Thus, the metabolic switch from glucose metabolism to β-oxidation and the decreased functional efficiency of the myocardium ultimately imposes increased metabolic stress on the failing heart.[57] It is evident that at the cellular level, mitochondrial dysfunction also contributes significantly to the development and progression of diabetic cardiomyopathy.[41] In addition to altered substrate utilization, changes in mitochondrial morphology, uncoupling, fission-fusion dynamics, Ca^{2+} loading, and ATP generation have all been implicated in exerting detrimental effects on the diabetic myocardium.[41,59,60]

Oxidative Stress

In conditions of excess carbohydrate and fat intake along with insulin resistance, an overflow of nutrients into the cell leads to electron transfer to oxygen in the absence of ATP production, favouring a state of increased reactive oxygen species (ROS) production.[61] Additionally, glucose autoxidation, the accumulation of advanced glycation end products (AGEs), angiotensin-II receptor type-1 (AT1R) signaling, and elevated levels of FFA and leptin have been associated with increases in ROS production in diabetic vessels and myocardium.[62-64] Therefore it should come as no surprise that increased ROS formation is also implicated in the pathophysiology of diabetic cardiomyopathy, playing an integral role in LV dysfunction.[65] Indeed, the oxidation of proteins involved in contractility, excitation-contraction coupling, protein folding, antioxidant defence, substrate metabolism, and Ca^{2+} handling play a key role in the development of diabetic myocardial dysfunction.[66-71] Even short (20 minute) exposures of cardiomyocytes to H_2O_2, one of the least damaging reactive species, has been shown to impair cell shortening and can arrest the cell during diastole.[72] Moreover, deleterious effects of ROS on cardiac function have been reproduced in the intact heart *in vivo*, as demonstrated by the beneficial effects of pharmacological agents and transgenic antioxidant expression in pre-clinical models of HF.[73-76] Indeed, there is an imbalance between the production of ROS and antioxidant scavenging of ROS in the diabetic heart compared to other organs, rendering the heart particularly susceptible to oxidative damage.[77,78] Moreover, diabetic settings have been shown to upregulate major sources of high glucose-induced ROS production, including nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and mitochondrial ROS. This results in damaged proteins, DNA, and lipid membrane components leading to ROS-mediated fibrosis and diastolic dysfunction, contributing to the progression of HF.[64,79,80] How-

ever, the heightened activity and expression of NADPH oxidase 4 (NOX4) can be targeted by NOX4 inhibitors for the treatment of a number of cardiovascular derangements.[81,82] In addition, treatment of a rodent model of T1DM with the antioxidant steroid hormone, dehydroepiandrosterone, inhibited the increased expression of several markers of myocardial fibrosis including collagen-I, collagen-IV, and transforming growth factor (TGF)-α, a known activator of fibrosis.[83]

Ca^{2+} Handling

Dysregulation of basal levels of Ca^{2+} in cardiomyocytes as well as irregular Ca^{2+} oscillations during the cardiomyocyte contraction-relaxation cycle are mainly due to deviations in Ca^{2+} transport.[65] More specifically, defects in regulators of intracellular Ca^{2+} concentration have been linked to diabetic cardiomyopathy.[84-89] These include the sarcolemmal L-type Ca^{2+} channel, the sarcoplasmic reticulum (SR) Ca^{2+} release channel, SR Ca^{2+}-ATPase (SERCA2a), the SERCA2a regulator phospholamban, ryanondine receptor 2 (RyR2), and the sarcolemmal Na^{+}/Ca^{2+} exchanger (NCX). Studies of obese diabetic *db/db* mice have reported elevated resting levels of intracellular Ca^{2+}, prolonged intracellular Ca^{2+} decay, slower and smaller Ca^{2+} transients, decreased sensitivity to extracellular Ca^{2+}, reduced SERCA2a activity, impaired Ca^{2+} reuptake, and leakage from the SR.[86,90] Likewise, pre-clinical models of type-1 diabetes have also demonstrated increased basal Ca^{2+} levels, attenuated Ca^{2+} release and reuptake by the SR, delayed recovery Ca^{2+} transients, reduced SERCA2a and NCX expression, as well as aberrant mitochondrial Ca^{2+} handling.[91-96] These impairments said to be a direct result of hyperglycemia, as insulin supplementation can normalize SERCA2a content and activity.[85,94,97] Furthermore, several studies have reported decreased SERCA2a-to-phospholamban ratio, contributing to attenuated cardiac relaxation in diabetic hearts.[98-100] As such, efforts to elevate SERCA2a expression and/or decrease phospholamban expression have been shown to enhance SR function by increasing its capacity to sequester Ca^{2+} during relaxation.[98,101] Transgenic overexpression of SERCA2a in diabetic rodents was able to partially restore diabetes-induced contractile dysfunction by enhancing SR Ca^{2+} uptake.[102] More recent studies have implicated diabetes-induced (glucose-dependent) post translation modifications (PTMs) of Ca^{2+}/calmodulin-dependent protein kinase 2 (CAMK-II), including oxidation and/or O-linked N-acetyl glucosamine addition or removal in the impairment of SERCA2a or ryanodine receptor function in diabetes.[103-105] In addition, SERCA itself is subject to modifications from oxidative stress, ROS and/or AGEs, ultimately leading to the impaired electromechanical coupling and reduced contractility seen in diabetic cardiomyopathy.[72,106,107] The SERCA 674Cys is susceptible to thiol oxidation in the diabetic hyperlipidemic aorta, which has been shown to significantly impair vascular SERCA activity and attenuate SR Ca^{2+} re-uptake.[106] Likewise, exposure to ROS has been shown to reduce cardiomyocyte SR Ca^{2+} content and to inhibit SERCA2a activity resulting in functional defects.[72] Lastly reactive carbonyl species, known to be upregulated in diabetes, induce PTMs to SERCA2a by reacting with its exposed arginine, lysine and histidine residues, impairing its function along with the mechanical function of the entire cardiomyocyte.[71] In addition to therapies designed to increase SR Ca^{2+} uptake, others have aimed to prevent Ca^{2+} leakage. Since unstable or hyperphosphorylated RyR2 channels result in SR calcium leak, one therapeutic strategy is to overexpress its regulatory protein, FKBP12.6.[108,109] Indeed, cardiac-specific overexpression of FKBP12.6 in mice and its adenoviral-mediated delivery in isolated rabbit ventricular cardiomyocytes has resulted in the stabilization of RyR2, greater SR Ca^{2+} content, and improved myocyte shortening.[110,111] Pharmacological intervention inhibiting SR calcium release by altered RyR2 gating or ion translocation has also been investigated. The benzothiazepine, JTV-510 (K201), improved cardiac function by stabilizing the closed state of RyR2, while its derivatives reduced arrhythmic episodes and potentially acting as protective agents against the progression of heart failure. These drugs act as protective agents against heart failure by reducing SR calcium leak through stabilizing the RyR2 to FKBP12.6 interaction.[112-114] An additional therapeutic target for heart failure is S100A1, a calcium-sensing protein that interacts with RyR2 and SERCA2a in the SR.[115] Overexpression of this down-regulated protein in settings of heart failure significantly improved contractile function, calcium handling, and cardiac energetics.[116,117] This may be attributed to its interaction with the F1F0 ATP synthase, thus improving phosphocreatine:ATP and NADH:NAD+ ratios in failing human cardiomyocytes.[118] In summary, some therapeutics such as modulators of SERCA2a expression and activity have shown early signs of success and have progressed to evaluation phases, while others are in relatively earlier stages of development (S100A1). Regulation of SR calcium handling proteins and associated cardiac energetics may represent new treatment options for heart failure.

Neurohormonal Activation

Neurohormonal activation is an important contributing mechanism to the functional and structural abnormalities observed in diabetic cardiomyopathy.[119] Hyperactivation of the RAAS plays a pivotal role in pathological vasoconstriction, and eventual cardiac hypertrophy and fibrosis as a result of increased oxidative stress.[120-122] Indeed, both Ang-II and aldosterone cause oxidative stress-induced calcium overload in cardiomyocytes as well as dampened activity of the sodium-calcium exchanger.[123] Furthermore, this pathway increases myocyte apoptosis and collagen deposition, causing increased cell death, fibrosis, and cardiomyocyte damage.[124,125] Elevated circulating levels of Ang-II and aldosterone have been linked to the pro-fibrotic and hypertrophic outcomes observed in pre-diabetic and diabetic patients with cardiac dysfunction.[126-128] Aldosterone may directly cause or exacerbate cardiac fibrosis by stimulating pro-inflammatory factors leading to the activation of matrix metalloproteinases (MMPs) and increased deposition of collagen and elastin.[125,129] Alternatively, it has been suggested that aldosterone may mediate some of its actions through the cardiomyocyte mineralocorticoid receptor (MR).[130] In the heart, aldosterone is thought to compete with cortisol for MR binding which induces its internalization, where the MR may enhance transcription of pro-inflammatory genes.[131,132] Moreover, aldosterone-MR binding can lead to

activation of ERK1/2 resulting in fibroblast proliferation as well as activation of the JNK MAPK signaling pathway, which has been shown to induce connective tissue growth factor (CTGF), resulting in myofibroblast replacement.[133-135] Aldosterone has also been reported to increase TGF-α and extracellular matrix proteins, as well as the fibrinolysis factor, plasminogen activator inhibitor (PAI-1), which leads to enhanced myocardial remodeling.[133,136] Accordingly, pre-clinical studies report attenuation in increased connective tissue in the hearts of streptozocin (STZ)-induced diabetic mice treated with spironolactone, an aldosterone antagonist.[137-139] On the other hand, Ang-II is reported to further stimulate cardiac fibroblast proliferation through the AT1R-ERK1/2 pathway, while also triggering cardiomyocyte apoptosis by inhibiting the MAPK pathway.[124] Likewise, treatments with angiotensin receptor blockers or angiotensin converting enzyme (ACE) inhibitors have been shown to partially inhibit elevated Ang-II receptor content, superoxide production, and apoptosis in STZ-diabetic hearts.[138,140]

Conclusion

Although numerous pharmacological agents are available to help patients with T2DM improve glycemic control, until recently very few of these have demonstrated any effect on the incidence of CVD.[141-149] Treatment with newly approved drugs, including certain thiazolidinediones (TZD), incretins (ie. glucagon-like peptide-1 receptor agonists [GLP-1RA] and dipeptidyl peptidase-4 inhibitors [DPP4]), and sodium glucose transporter 2 inhibitors (SGLT2i), all of which have anti-hyperglycemic and varying benefits on cardiovascular disease mechanisms, hold promise for the treatment of both the metabolic and cardiovascular challenges of diabetes.[146,147,149-153] More specifically, animal studies of TZDs have demonstrated protective properties such as improved glucose metabolism (by enhancing insulin sensitivity in fat, muscle, and liver cells), inhibition of systemic inflammation, improved endothelial function and blood pressure, inhibition of cardiac hypertrophy and collagen accumulation, and ameliorated LV diastolic function.[154-156] However, major drawbacks associated with the use of TZDs include weight gain, peripheral edema, and the increased risk of HF (due to renal sodium retention and fluid). This renders TZDs (namely rosiglitazone) unsuitable for the treatment of patients at high risk of MACE.[143,157-159] On the other hand, incretin-based agents exert their actions by potentiating signaling via the incretin receptor.[65] The advantage of incretin-based therapies in the treatment of diabetes is the glucose-dependent mechanism underlying insulin-secretion by GLP-1R activation, thereby reducing the risk of hypoglycemia.[65] In addition to maintaining glycemic control, the LEADER study revealed that treatment with liraglutide, a GLP-1RA, resulted in a 21% reduction in cardiovascular death, without a significant effect on hospitalization for HF *vs.* placebo.[146] In a shorter term post-MI study (POST-CON II), treatment with another GLP-1RA, exenatide, was associated with a 23% decrease in infarct size relative to area at risk (AAR) in patients with ST-segment-elevation MI.[160] Most recently, the SUSTAIN-6 study reported a 26% reduction in non-fatal MI and a 41% reduction in non-fatal stroke, with no difference in cardiovascular deaths in patients treated with semaglutide *vs.* placebo.[147] Indeed, *in vitro* and *in vivo* studies have contributed to our understanding of the cardioprotective mechanisms of GLP-1RA, including attenuated hypertrophy and fibrosis of infarcted hearts, and improved recovery of left diastolic ventricular pressure (LDVP).[161] GLP-1RA treatment have also been shown to significantly induce anti-oxidative defence genes, dose-dependently attenuate senescent-positive cells, attenuate thrombus growth, prevent oxidative stress-induced reductions of cellular respiratory capacities, and increase carbohydrate *vs.* fat oxidation in the myocardium.[161-164] Overall, this class of anti-hyperglycemic agents seems to improve cardiac efficiency and functional recovery, proving to be a favorable candidate therapy in the treatment of diabetic patients at high risk of MACE. In comparison, negative findings have been reported for DPP4 saxagliptin, which tended to increase the risk of HF whereas sitagliptin did not appear to increase the risk of MACE, hospitalization for HF, or other adverse events, overall conferring no cardiobenefit.[151,165] Similar to the GLP-1RA, an exciting newer class of anti-hyperglycemic agents, SGLT2i, has recently shown to confer cardioprotective benefit for diabetic patients at risk of HF.[149] The EMPA-REG OUTCOME study demonstrated a remarkable 38% reduction in cardiovascular death and 35% reduction in hospitalizations for HF in patients with T2DM at high cardiovascular risk treated with empagliflozin *vs.* placebo.[149] However, the mechanisms underlying these benefits are not fully understood. It is also not known which of these two seemingly beneficial approaches (the GLP-1RA or the SGLT2i) is best suited to the clinical condition of HF. Nevertheless, preliminary cardiovascular outcome studies such as DURATION-8 have demonstrated that employing combination therapy with both drug classes holds some promise for the management of hyperglycemia and possibly cardioprotection.[166] Conversely, strategies to reduce the production of ROS, or increase its degradation as with antioxidant supplementation, may also be protective against diabetes-induced cardiac dysfunction and remodeling. Additionally, specific inhibitors or gene-targeted therapies of disturbed protein signaling, Ca^{2+} handling (in addition to Ca^{2+} channel blockers), or neurohormonal activation apart from ACE inhibitors, AT1R blockers, and aldosterone agonists represent future options for the treatment of diabetic cardiomyopathy.[167-174] Advances in the elucidation of mechanisms responsible for the development of functional and structural complications in the diabetic heart will certainly aid in the design of more specific therapeutics.

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Conflicts of Interest

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Behavioural Cardiology: The Dual Relationship Between the Heart and the Mind

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Abstract

Behavioural cardiology is an emerging field that examines the behavioural determinants of cardiovascular health, with the aims of improving cardiac health through behavioural interventions. This paper examines the validity of this approach by briefly reviewing the behavioural aspects of cardiology, current research conclusions on the effectiveness of behavioural interventions, and the potential role of behavioural cardiology in clinical practice today. Behavioural cardiology requires further research to validate its effectiveness before implementation in clinical settings.

Introduction

Who are you? Do you have a BMI of 20 kg/m^2, a blood pressure of 120 mmHg/80 mmHg, a resting heart rate of 60 bpm, a blood concentration of 2.2 mmol/L HDL, 5.5 mmol/L LDL, 8.3 mmol/L triglycerides?[1-4] Body mass index, blood pressure, resting heart rate, and blood lipid levels: these are the parameters a cardiologist might examine to assess your risk for cardiovascular health. However, there may be a missing question in this assessment: How are you?

Cardiovascular disease is the leading cause of death worldwide.[5] High blood pressure, abnormal blood lipid levels, and high blood glucose are generally recognized as important contributors to cardiovascular risk.[6-7] Tremendous progress has been made in targeting these risk factors using drugs such as beta-blockers and diuretics, which lower blood pressure, and statins, which regulate blood lipid levels.[8-9] Additional risk factors include diets high in fat or sodium, and physical inactivity.[7,10] Although each of these risk factors may be interrelated, it is important to address the behavioural component of cardiovascular health. In regards to risk management, a balanced diet and regular exercise are the tenets of leading a healthy lifestyle.[6] However, they entail behavioural changes, such as changes in motivation.[18] In addition, certain behavioural parameters, including personality and stress, may act as risk factors for cardiovascular diseases, or influence prognosis once diagnosed.[11-12] Finally, behavioural factors, such as risk perception and self-efficacy, may influence treatment adherence.[13] Evidently, behaviour appears to play an important role in prevention, prognosis, and treatment of cardiovascular diseases. However, behavioural interventions are infrequently used in clinical practice.

This paper will briefly review behavioural cardiology, a field that has been emerging within the last decade, and that outlines the behavioural risk factors of cardiovascular health, the effectiveness of behavioural treatments in improving cardiovascular health, and the integration of behavioural interventions into clinical practice.

The Behavioural Component of Heart Health

Behavioural risk factors associated with the onset and prognosis of cardiovascular diseases include: (1) physical health behaviours (unbalanced diet, sedentary lifestyle, and inadequate sleep); (2) negative mental mindsets (depression, anxiety, anger); (3) chronic stress; (4) social isolation; and (5) lacking a sense of purpose in life.[14-15] For example, depression is estimated to be almost twice as more prevalent in patients suffering from ischemic heart disease compared to the general population.[15] According to the INTERHEART study, psychosocial factors have an odds-ratio comparable to that of more traditional cardiovascular health risk factors, such as smoking and hypertension.[17] Possible biological mechanisms through which these behavioural factors might contribute to cardiovascular disease development further substantiate the influence of behavioural risk factors in the development of cardiovascular disease. These mechanisms broadly include altered activity in the hypothalamic-pituitary-adrenal (HPA) axis, the autonomic nervous system, and the immune system.[16-17]

In addition to acting as risk factors, an individual's behaviour related to risk management and treatment adherence may also influence cardiac outcomes. 60% of cardiac patients are estimated to not follow medical directions, such as drug intake of aspirin or β-blockers.[18] This nonadherent behaviour has been recognized in clinical practice and attempts are be-

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ing made to identify causes of nonadherence and how to solve them. A prominent reason for nonadherence includes lack of motivation.[18] The health belief model, a model developed in the 1950s aimed towards improving healthy behaviours, attempts to address nonadherence by changing an individual's perception of risk of disease and self-efficacy through education, goal-setting, and positive reinforcement.[13-14] As of 2014, 78% of studies that have applied this model appear to show significant improvements in general treatment adherence.[19]

Thus, substantial evidence has accumulated supporting the idea that behavioural factors play a significant role in cardiovascular disease onset, progression, and/or treatment. This correlative evidence has stimulated research into examining the efficacy of behavioural interventions, including cognitive-behavioural therapy, counseling, psychotherapy, relaxation therapy, and education in improving cardiac health outcomes, such as blood pressure, infarction rates, and mortality rates.[19] This type of research, examining behaviour in relation to cardiac outcomes, has been categorized as behavioural cardiology, and is a relatively new field, having emerged within the last two decades.[13-14]

The Effectiveness of Behavioural Treatment on Heart Health

Analyses of behavioural cardiology research conducted thus far reveals that behavioural conditions, such as depression and anxiety, can be improved by treatment, but that this does not appear to impact cardiovascular health.[15,20,22] In contrast, cardiac outcomes such as mortality or non-fatal infarctions do not appear to significantly improve with psychological interventions.[22] A few studies have additionally examined the effects of using pharmacological approaches, such as antidepressants, to treating behavioural conditions in cardiac patients, and there appears to be no effect on cardiac health, in terms of mortality, cardiac events, and QoL.[24] Combined, these studies question the validity of using behavioural treatments in cardiac healthcare. However, several meta-analyses conducted on studies published between the late 1990s and the early 2000s reveal issues regarding many of these original studies, including small sample size, heterogeneous subjects, and poor research design (ex. non-blinded trials).[21-22] Differences in treatment methodology, such as the timing of treatment provision relative to a cardiac event and the type of treatment provided, add further difficulty in assessing the effectiveness of behavioural treatments on cardiac outcome.[23] Finally, traditional cardiology, specifically drug-focused treatments, is continually advancing, and the effectiveness of behavioural treatments in conjunction with newer pharmacological approaches remain to be assessed.[21] These issues illustrate the need for more well-designed research.

Behavioural Cardiology in Clinical Practice

Given that evidence of the effectiveness of behavioural treatments in improving cardiac health is limited, should such treatments still be applied in today's clinical practice? Although the efficacy of behavioural cardiology is inconclusive at the moment, certain interventions, such as stress therapy or education, may yield benefits and are unlikely to produce harm.[15] Moreover, minimally time-consuming and cost-effective methods of screening for behavioural risk factors have already been proposed.[17] These include administering a questionnaire either by a family physician or cardiologist with open-ended questions simultaneously during screenings for background history, in order to identify sources of stress, health habits, and social resources.[16] Following this general initial assessment, they are able to either refer the patient to certain specialists or provide direct interventions, such as education.[17] Therefore, although the effectiveness of behavioural interventions on cardiac health appear limited as discussed previously, behavioural risk assessment, such as questionnaires, and interventions through referrals to professional therapists or education, can still be introduced into traditional clinical practice with relatively minimal efforts.

Conclusion

"The cure of the part should not be attempted without treatment of the whole"-Plato[25]

The importance of behavioural cardiology is that it recognizes behaviour as a critical component to many aspects of cardiology: behaviour may act as a risk factor for cardiovascular disease and behaviour may influence how cardiovascular diseases are managed. Therefore, behavioural interventions would be predicted to improve cardiac health. Currently, there is inconclusive evidence on whether behavioural interventions are truly effective in heart care. Clinical implementation of behavioural interventions, however, appear feasible, making the need for greater research the most significant limiting factor of behavioural cardiology as of today.

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The Role of Plant-Based Nutrition in Preventing Heart Disease

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Abstract

Although there has been a sizeable decrease in death rates from cardiovascular disease over the last 10 years, it remains a leading cause of morbidity and mortality in both developed and undeveloped countries around the world. Results from studies conducted in the last few decades have associated plant-based diets with protection against cardiovascular disease as well as many other chronic disease conditions. Vegetarians have been shown to have decreased risks and prevalence of cardio-metabolic conditions, some cancers, as well as total mortality when compared to those who eat meat. Additionally, vegan diets have been shown to offer further protection against obesity, type 2 diabetes, hypertension, and cardiovascular mortality. To date, this data has primarily come from large prospective cohort studies. Thus, randomized controlled trials are desired to build on and confirm previous findings in order to make better recommendations for nutritional interventions in the prevention, management, and treatment of cardiovascular disease.

Background

Individuals' dietary patterns can fall into several categories depending on the proportion of animal products consumed. Vegetarians are generally considered those who do not consume any animal flesh products including red meat, poultry, and fish, yet consume animal-derived products such as dairy and eggs.[1] Variety in definition exists, however. Some consider themselves vegetarian if they eat fish and animal-derived products, but not red meat or poultry. These individuals are sometimes referred to as semi-vegetarians, or pescetarians. Lacto-ovo-vegetarians are considered to be "full" vegetarians, where the only animal products consumed are eggs and dairy. Lastly, vegans are those who do not consume animal products of any kind, with their sole food sources being plant-derived.

Numbers of vegetarians and vegans in the population remain small. However, the attitudes towards these lifestyles have gained better acceptance, stemming from various reasons relating to moral and ethical considerations of animal cruelty, environmental impacts of meat and dairy industries, as well as the health and quality of life benefits of plant-based diets.[1,2]

Introduction

Despite extensions of lifespan and a 40% decrease in mortality rates related to heart disease over the last decade, it remains the leading cause of morbidity and mortality in both developed and undeveloped countries around the world.[3] Cardiovascular disease (CVD) currently affects more than 1.6 million Canadians, with 1 in 12 individuals aged 20 years or older diagnosed with this chronic condition.[4] For these individuals, mortality rates are 3 times higher than those without CVD. Health Canada estimates that 9 in 10 Canadians over the age of 20 have at least one risk factor for heart disease, and 4 in 10 have three or more risk factors. [4] Key metabolic and physiological factors associated with increased risk of CVD include hypertension, diabetes, dyslipidemias, obesity, poor diet, physical inactivity, smoking, and excessive alcohol use.[5,6] Many of these factors are modifiable and can be addressed by lifestyle changes. As a result of the significant health burden of CVD, larger-scale strategies towards prevention and treatment are needed, and nutritional intervention in the form of plant-based diets has the potential to affect this change.

Research into the health effects of plant-based diets is not a novel topic, with considerable evidence from epidemiological studies beginning in the 1950's associating the consumption of animal products with increased risks of CVD, diabetes, certain cancers, as well as all-cause mortality.[7-9] Thus, it is suggested that substitution of animal products with plant-based ones can lower the risk of developing many chronic diseases and increase longevity.[10,11] Past data sources have consisted of large, longitudinal prospective cohort studies, as well as smaller interventional studies. However, little has been done in recent years, and there has yet to be a randomized controlled

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trial (RCT) focusing solely on dietary lifestyle modifications to confirm or build on findings from these studies.

The aim of this report is to provide a review of studies that have investigated the relationship between plant-versus animal-based diets and cardiovascular disease, with the intention of guiding future research.

Results

Longitudinal Prospective Cohort Studies

One of the first investigations into the health effects of plant-based nutrition began in the 1950's, conducted by Mervyn G. Hardinge as his doctoral dissertation at Harvard University.[12-14] His research was initially met with resistance, but opened the door for subsequent investigation into the health benefits of plant-based diets. In 1999, Key and colleagues presented combined data on five of the largest reported prospective studies testing the hypotheses that vegetarians have lower mortality rates from ischemic heart disease (IHD) as well as certain cancers.[15] After adjusting for body mass index (BMI), alcohol use, education level, and exercise level as potential confounders, pooled data were analyzed to compare death rates from these specific causes between vegetarians and non-vegetarians with similar lifestyles.[16-20]

Data for 76,172 men and women were available, of whom 27,808 were vegetarians. There were 8,330 deaths after a mean follow-up of 10.6 years, with mortality rates for IHD shown to be 45% ($p < 0.01$), 31% ($p < 0.01$), and 8% (not significant) lower in vegetarians at ages < 65, 65-79, and 80-89 years, respectively ($p < 0.05$ for trend). Overall pooled mortality from IHD was 24% lower in vegetarians than non-vegetarians, with the effect further amplified in the younger population. The significantly lower death rate for those aged 65 and under is important, given the chronic nature of CVD where predisposing factors/conditions begin earlier in life. Additionally, the protective factor of plant-based diets was mostly confined to those who had been vegetarian for five years or more, suggesting that simply increasing plant consumption in a non-vegetarian diet would not be beneficial in gaining the protective factors that adopting a fully plant-based diet would.

In 2014, Le and Sabaté analyzed data on three large prospective studies of the North American Adventist populations, comparing non-vegetarian, vegetarian, and vegan diets in disease and mortality outcomes.[1] The rationale for using members of this religious community as participants is due to their population characteristics that provide a natural study group well-suited for the topic in question. Their Church doctrines recommend vegetarian practices, thus many individuals are vegetarian or vegan, yet about half are omnivores similar to the general population.[21] Furthermore, strong emphasis is placed on overall health, valuing abstinence from alcohol and tobacco. Therefore, studying these individuals allows for the control of two major non-dietary confounders known to be contributing factors to CVD.[22]

The first Adventist cohort study took place between 1960 and 1976, the second between 1976 and 1988, and the third ongoing study began in 2002.[22-25] In total, data from 153,138 participants from the United States and Canada were collected. In the most recent cohort, 48% of participants were non-vegetarians, 6% were semi-vegetarians, 10% were pescetarians, 28% were lacto-ovo-vegetarians, and 8% were vegans at baseline. Pooled results from all sub-types of plant eaters showed a 55% decreased risk of developing hypertension, a 25-49% decreased risk of developing type-2 diabetes, a 50% risk reduction for the development of metabolic syndrome, and their BMI values were on average 3-5 points lower when compared to non-vegetarians.[1]

Additional comparisons within subgroups of plant eaters showed vegans to have further risk reduction over lacto-ovo-vegetarians, with chances of developing hypertension and type-2 diabetes 75% and 62.5% lower, respectively, compared to 55% and 49.5% in lacto-ovo-vegetarians. For all cardiometabolic-related outcomes, vegans were at lower risk than lacto-ovo-vegetarians, both of which were at lower risk than non-vegetarians. This effect demonstrates that even though vegetarians consume largely reduced amounts of animal products, the animal-based foods that they do consume may still put them at higher risk than vegans who consume solely plant-based foods.

An important observation in gender differences was also obtained from the Adventist study data. According to Health Canada, men are diagnosed with heart disease an average of 10 years younger than women (55-64 vs 65-74 years of age), and are twice as likely to suffer a heart attack.[4] Given the higher burden of CVD in men, it is relevant that findings showed a 23% and 42% risk reduction in CVD-related mortality in lacto-ovo-vegetarian and vegan males, respectively.[1]

Randomized Controlled Trials

The Lifestyle Heart Trial was the first RCT that investigated the effectiveness and sustainability of comprehensive lifestyle changes, and their effect on the progression of coronary atherosclerosis.[26] Intensive lifestyle modifications included a low-fat vegetarian diet, aerobic exercise, smoking cessation, group psycho-social support, and stress management training. At one year follow-up, subjects in the experimental group maintained lifestyle changes and had a 37.2% reduction in low density lipoprotein (LDL) levels, and a 91% reduction in frequency of angina episodes in comparison to the control group, who were instructed to follow standard care suggested by their primary care physicians. Based on the encouraging findings after one year, the study was extended to allow for a 5-year follow-up to evaluate the feasibility and the effects of long-term lifestyle interventions on CVD risk factors, coronary atherosclerosis, myocardial perfusion, and cardiac events.[27]

In the experimental group, patients lost an average of 23.9 lbs at one year, sustaining an average loss of 12.8 lbs at five years, compared to little baseline change in the control group. LDL levels decreased by 40% and 1.2 % at one year follow-up in the experimental and control groups, respectively. At five years of follow-up, LDL levels decreased by 20% and 19.3% in the experimental and control groups, respectively. The comparable decrease in LDL levels after five years is attributed to 60% of control group patients taking lipid lowering agents beginning after year one of the study, whereas none of the experimental group patients took lipid-lowering agents.

The degree of reduction in LDL levels of experimental group patients is comparable to effects achieved with lipid-lowering agents. This finding gives preliminary evidence to suggest that lifestyle modifications can be superior or non-inferior to standard pharmacological treatment of dyslipidemias.

Coronary angiography was used to analyze all coronary artery lesions that matched at baseline and five-year follow up. In the experimental group, an average decrease of 4.5% and 7.9% from baseline percentages of coronary artery stenosis were found at 1-year and 5-year follow-up respectively. In contrast, the control group averaged an increase of 5.4% and 27.7% stenosis at one-year and five-year follow-up, respectively. Differences in severity of coronary artery lesions were not statistically different between groups at baseline, and the progression of coronary artery stenosis in the control group occurred even though over half of these participants were prescribed lipid lowering agents during the time of the study. Furthermore, the sustained long-term reduction in severity, frequency, and duration of angina episodes in the experimental group after five years is comparable to the degree of symptom reduction achieved post-angioplasty or coronary artery bypass surgery.[28]

Overall, the trial showed more significant regression of coronary atherosclerosis in the experimental group after five years than one year, whereas disease progression continued in the control group and participants experienced double the frequency of cardiac events (cardiac-related hospitalizations, myocardial infarction, coronary angioplasty, coronary artery bypass surgery). Though the intensive lifestyle changes incorporated more than just dietary modifications, this RCT gives valuable insight into the significant role that various lifestyle factors, including diet, have on the progression and reversal of CVD. Results from this study also demonstrate that lifestyle modifications are possible, sustainable, and can be achieved with sufficient compliance when patients receive adequate education and guidance. If patients were more frequently "prescribed" lifestyle modifications by their physicians in the same way that pharmacological treatments are prescribed, similar results to those found in RCTs could potentially be achieved.

Plant-Based Diets in the Prevention of Metabolic Syndrome

It is widely accepted that individual physiological factors such as hypertension, diabetes, and dyslipidemias are associated with a higher risk of CVD.[29] In addition to these individual risk factors, patients diagnosed with metabolic syndrome have a three times greater risk of developing CVD, and a five times greater risk for developing type 2 diabetes (a major risk factor for heart disease) within a 5-10 year period.[30] Patients with ≥3 of abdominal obesity, hyperglycemia, hypertriglyceridemia, hypertension, and low levels of high density lipoproteins (HDL) are said to have metabolic syndrome, of which the global prevalence is approximately 25%.[6] Nutritional intervention is a primary aim of lifestyle modification, where evidence shows that high-protein diets are effective in preventing features of metabolic syndrome by increasing HDL levels and reducing fat mass while maintaining lean body mass.[31,32] Furthermore, protein source, in addition to amount of protein in the diet, is considered a contributing factor to developing metabolic syndrome. In 2017, Chalvon-Demersay et al. published a systematic review of 123 studies, comparing the effect of animal and plant protein sources on markers related to metabolic syndrome.[11] Study participants totaled 516,330 and consisted of individuals possessing one of the metabolic syndrome markers, as well as healthy subjects of all ages for controls.

Amongst studies evaluating dyslipidemias, numerous reports have shown that soy proteins containing isoflavones lead to greater reduction in total and LDL cholesterol in individuals consuming plant rather than animal proteins.[33-35] Additionally, in studies where protein was given as a whole diet rather than supplementation, the degree of differences between plant and animal protein cohorts was amplified.[35-38] This effect is proposed to be a result of factors inherently associated with animal-based diets. Increased consumption of cholesterol and saturated fats, as well as decreased levels of total dietary fibers and polyunsaturated fats, are known to directly cause elevations in plasma cholesterol and triglyceride concentrations.[39] Overall, data presented in this systematic review showed that soy protein with isoflavones, as well as other plant proteins, leads to a greater decrease in both total and LDL cholesterol compared to the ingestion of animal proteins.[11] These results suggest that subjects at high risk of developing CVD could benefit from a plant-based diet.

Furthermore, a 2014 meta-analysis of 7 clinical trials and 32 observational studies showed the consumption of plant-based diets to be associated with lower blood pressure (BP) compared with that of omnivorous diets.[40] Pooled data showed an overall change in systolic BP of -4.8 mmHg and -6.9 mmHg in clinical trials and observational studies, respectively, and diastolic changes of -2.2 mmHg and -4.7 mmHg, respectively. One of the main proposed mechanisms for the changes observed in plant-eaters is said to be related to lower BMI, attributed to less energy-dense foods that are higher in fiber and lower in fat content.[41] However, though weight reduction is an established recommendation towards decreasing BP, in studies controlling for BMI, observed effects of plant-based diets remain.[42] Thus, further mechanisms have been proposed. Meta-analyses of RCTs have shown dietary potassium to contribute to decreases in BP, attributable to its effects on increased vasodilation and glomerular filtration rate, as well as decreasing renin level, renal sodium resorption, reactive oxygen species, and platelet aggregation.[43] Additional contributing factors are various diet and lifestyle characteristics inherent to plant-based diets. Factors known to increase BP (i.e. obesity, sodium intake, alcohol consumption) are lower in plant-eaters, whereas factors that decrease BP (i.e. exercise level, intake of potassium, magnesium, unsaturated fat, protein) are higher.[44-47]

Plant Proteins

Numerous mechanisms have been proposed to explain the lower risks for CVD seen in vegans, including significantly lower BMI and lower total and LDL cholesterol levels, which are well-established risk factors for CVD.[48-51] The increased

amounts of antioxidants, fibers, folate, phytochemicals, and soy protein in vegan diets have been shown to be associated with lower serum cholesterol, trans and saturated fat, as well as decreased incidence of morbidity and mortality from CVD, diabetes, stroke, and certain cancers.[48-51] In 1999, soybeans received a heart health claim from the U.S Food and Drug Administration, stating that soy protein decreased the risk of CVD via its cholesterol-lowering effect, whereas casein protein from milk was thought to be hypercholesterolemic.[54] Primary mechanisms behind the cardioprotective effects of plant protein include its amino acid pattern and protein structure. Animal protein has a comparatively high ratio of leucine to arginine compared with plant protein, which is suggested to be associated with hyper-cholesterolemia and atherosclerosis.[55] Specific to soybeans, the structure of peptide subunits and lack of excess essential amino acids is proposed to result in decreased stimulation of hepatic cholesterol biosynthesis.[56,57] Furthermore, soy protein contains a 7s globulin protein that has been linked to upregulation of hepatic LDL receptors[58] and reduced plasma tryglicerides.[59] Studies have also shown that diets rich in soy protein, nuts, plant sterols, fibers, and low in saturated fatty acids is equivalent to statin treatment in lowering cholesterol and C-reactive protein in hyperlipidemic subjects.[60,61] Therefore, it is suggested that diets containing soy protein may be a valuable treatment option for dyslipidemic patients, especially in those who can't tolerate or are nonresponsive to pharmacological therapy.[62]

Plant-Based Nutrition in Children

Canada, like many nations, is currently in the midst of a health crisis surrounding obesity in both adults and children. Based on current data, 59% of adults and 25% of children in Canada are either overweight or obese, with numbers expected to increase in the coming decades if current trends continue.[63,64] In addition to studies showing the benefits of plant-based proteins on cardiovascular health in adults, similar effects have been demonstrated in children. Studies have shown that the consumption of animal-sourced protein at one year of age is positively associated with increased BMI and body fat by the ages of 6-7 years.[65-67] Excess weight in early life has been linked to insulin resistance, type 2 diabetes, and hypertension, which can predispose children to early onset of CVD.[68] In the absence of interventions, overweight children and adolescents tend to become overweight adults. Therefore, it is important to develop preventative measures that begin in childhood in order to decrease the risk of premature onset of CVD and related health conditions.

Official Dietary Recommendations

According to a 2013 Canadian Diabetes Association publication,[69] a 2015 report from the World Heart Foundation,[70] the 2015-2020 Dietary Guidelines for Americans[71], and the 2016 Canadian Cardiovascular Society guidelines,[72] vegetarian and vegan diets are recommended as dietary patterns that promote health and prevent disease. A 2009 randomized controlled trial showed a vegan diet to be as beneficial as conventional American Diabetes Association dietary guidelines in promoting weight loss, improving fasting blood glucose, total cholesterol, and LDL in adults with type-2 diabetes.[73] Another study showed that participants on a calorie-restricted vegetarian diet had a greater improvement in BMI and LDL levels, and a greater decrease in the need for diabetes medications than those following a conventional diabetes diet (43% and 5%, respectively).[74] Therefore, in counselling patients at risk of developing or being treated for conditions such as diabetes, dyslipidemia, hypertension, and CVD, recommendations for adopting a plant-based diet should be considered.

Discussion

In summary, data from large, longitudinal, prospective studies paints a consistent picture showing significant correlations between diet and health status, emphasizing that vegetarians and vegans live longer and have a greatly lowered risk of developing most chronic diseases.

There have been doubts about the nutritional adequacy of plant-based diets in past decades. However, national dietetic associations have since changed their position statements on dietary recommendations, resulting from increased research on vegetarian and vegan nutrition as well as better understanding of the connections between diet and disease.[80-82] Though numerous assumptions exist in regards to the health of vegans, suggesting that significantly greater challenges exist in meeting nutritional requirements for elements such as vitamin B12, protein, and calcium, vegans can avoid deficiencies with appropriate food choices just as non-vegans can.[83] With vegan diets gaining popularity as an alternative to the "norm" of omnivorous diets, it can be easy to make assumptions based on a lack of knowledge. It could be thought that vegans must be missing key nutritional elements since plant-based diets are not as common, vegan foods are not advertised in the same way that animal products are, and veganism is not the way that humans have traditionally lived. Humans began as omnivores, restricted in their dietary intake, necessitating hunting and fishing for survival. However, we are no longer restricted to the same way of living and thinking about food. In today's society, many of the world's populations now have the resources, the options, and the privilege to have a larger array of food possibilities and to choose what we consume. Just because something has always been done a certain way, doesn't mean that it is the way it always has to remain.

Nonetheless, it can be difficult to convey these ideas and challenge the assumptions and dietary habits of individuals. In order for messages to be heard, it takes time, money, and resources. Large dairy and meat companies have long had the resources to advertise their products, whereas those promoting vegan lifestyles have only recently begun to compete on that level. Just as the truths of animal cruelty in factory farming are not often shared with the public, neither are the significant health benefits of adopting a plant-based diet.[84-86]

An important issue impeding changes in societal dietary patterns is considering the way in which dietary advice is conveyed. Canada's Food Guide serves as the country's nutritional backdrop, underlying policies and programs in areas ranging from publicly- funded school programs to hospitals. Its information is taught to Canadians of all ages, as well as to future health professionals, and is used by food industries

to promote their products. Large cohort studies have presented data reporting that approximately 82% and 91% of the risk for CVD and diabetes, respectively, can be prevented by dietary and lifestyle modifications.[87,88] However, despite efforts to encourage more plant-based nutritional practices, including recommendations by the Canadian Cardiovascular Society, Canadian Diabetes Association, and World Heart Foundation outlined above, changes have been slow.[70] Potential factors contributing to this delayed effect include the well-established popularity and accessibility of Canada's Food Guide, versus the relative lack of availability and easy access to concise resources with alternative recommendations outlined by large health societies.

Another significant challenge hindering the availability of resources on plant-based diets is in the knowledge of those providing information and nutritional recommendations. Physicians are often the first point of contact for those seeking nutritional consultation. However, nutrition and its relation to health and disease is seldom included in medical school curricula in a way that adequately addresses the importance of this concept and its centrality to the processes of disease prevention, management, and treatment. Whether one has a chronic disease or not, health literacy is an important concept to consider, both for health professionals and members of the general public. If appropriate resources are not provided, or are not available and easily accessible, society will continue to be burdened with the epidemics of obesity, type 2 diabetes, and CVD. Therefore, society-wide improvements in knowledge, education, and delivery of information are needed in order to foster meaningful improvements in the health status of populations.

This subject shares similarity to the way in which cigarette smoking was not originally viewed as detrimental to one's health. Lung cancer, now responsible for 1.5 million annual deaths around the world, was considered a rare disease until the 1900's.[89] Cigarette smoking dates back to at least the 18th century, its popularity rising dramatically in the 19th century, and it wasn't until the mid-20th century when evidence began to establish it as the leading cause of lung cancer.[90,91] However, despite results from studies, cigarette manufacturers continued to argue against evidence in efforts to protect sales,[91,92] and even physicians remained unconvinced. In reports as late as 1960, only 1/3 of doctors in America agreed that smoking should be considered a cause of lung cancer, with 48% reporting to be smokers themselves.[93] Therefore, even though the cigarette is considered to be the deadliest artefact in the history of human civilization,[94] efforts to generate and facilitate ignorance long prevented the now well-established awareness of its health dangers. The observation of a similar trend is beginning to emerge in the area of plant-based nutrition, where research results showing its health benefits have existed since the 1950's, although society and physicians remain largely uninformed.

Though there has yet to be a randomized control trial investigating the health benefits of plant-based diets and the health detriments of animal-based ones, the value of prospective cohort studies should not be discounted. Findings that show the benefits of plant-based nutrition can be used to guide shifting views and practices until the time that randomized control trials are realized. Thus, in addition to the current increased environmental impact of animal proteins and the emerging awareness of the cruelty involved in factory farming, plant-based diets are likely to be favored in the future due to their numerous health benefits.

Limitations of Current Evidence

Choice of participants has been a critique of cohort studies that have shown plant-based diets to decrease the risk of CVD. Participants were from populations that place great emphasis on healthy living and comprised a high proportion of vegetarians, thus results may not be generalizable.[10] However, the validity of this concern is questionable, given that investigators deliberately recruited a large proportion of vegetarians, since this is the population desired for study.[16-20] In their report of the 3 Adventist cohorts, Le and Sabaté acknowledged the higher prevalence of vegetarians and vegans as the reason for studying these individuals.[15]

Authors also noted that due to emphasis on personal health, Adventists tend to live longer than their counterparts in the general population. In interpreting their data and its generalizability from the isolated study population, it was found that although both male and female Adventists lived an average of 7.3 and 4.4 years longer, respectively, vegetarian Adventists had a further increase in life expectancy (1.5-2.4 years) over non-vegetarian Adventists.[75] Additionally, the non-vegetarian Adventists used as reference cohorts in the reported comparisons consumed much less meat than the general population. Therefore, it could be hypothesized that the relatively low intake of meat by this reference group would have resulted in smaller observed effects, limiting conclusions that could be made based on the data. However, there were significant observed effects, suggesting that even within a controlled health-focused population, considerable differences existed between the health status of vegans, vegetarians, and meat eaters. This finding indicates a potentially stronger association between plant-based diets and improved health and longevity, rather than an insignificant correlation that may not be generalizable.

The choice and definitions of study populations, as well as the length of the study period are further factors to consider in interpreting contradictory evidence. First, it is difficult to derive meaningful conclusions from self-report data, since individual definitions of vegetarian tend to vary. Some might self-identify as vegetarian if only eating meat on occasion, or if red meat is not consumed but poultry and fish are. Others may describe themselves as lacto-ovo-vegetarian if the only animal products consumed are eggs and dairy. This bias potentially explains conflicting evidence between studies, with some studies showing that vegetarians have no significant differences in disease states and mortality, whereas others have reported considerable health benefits of vegetarian diets. For example, results from cohorts in the EPIC-Oxford study reported no differences in rates of vascular disease, stomach cancer, colorectal cancer, lung cancer, breast cancer, prostate cancer, or all-cause mortality related to diet.[76] Conversely, in addition to the aforementioned data relating to cardiovas-

cular health in the Adventist studies, vegetarian participants experienced an 8% risk reduction from overall cancer, 50% from colon cancer, 23% from cancer of the gastrointestinal tract, 35% from prostate cancer, and 48% from breast cancer compared to non-vegetarians.[1]

Lastly, though there have been some interventional studies examining the health-related outcomes of plant-versus animal-based diets, most involved meal replacements for trial periods ranging from 4-12 weeks, where it was unclear if additional food was consumed, and whether it was of plant or animal origin.[77-79] Furthermore, data from short-term interventional studies is not representative of the potential health benefits of adopting a plant-based diet. The decreased mortality from ischemic heart disease seen among vegetarians in Key and colleagues' analysis was present in those who had followed their current diet for >5 years.[15] It is possible that if populations were followed for more than five years or if study participants consisted of individuals who have been vegetarian or vegan since early life, these results would be further amplified.

Future Perspectives

Given the consistency of results associating vegetarian diets with decreased risks of developing CVD, further randomized interventional trials are warranted. These trials would validate existing findings and further investigate the health effects of these diets in order to make meaningful recommendations and implement guidelines for nutritional planning, assessment, and counseling.

Future studies should focus on comparing meat-eaters to vegans rather than vegetarians. Using vegans as study participants would provide for improved identification and isolation of the relationships between plant-based diets and CVD, since these individuals consume solely products of plant origin. This study population would also eliminate the ambiguity and inherent risk of bias that has existed in studies to date, based on differing definitions of 'vegetarian'. Additionally, studies should focus on those who have followed vegan dietary practices for a significant amount of time, given that the majority of differences between health outcomes in plant-versus meat-eaters were found in individuals who had been vegetarian for more than five years.

Another possible area to explore would be in comparing the current standards for management of CVD and its risk factors with nutritional interventions in the form of vegan diets. Studies could aim to assess the comparative effectiveness of medical therapies such as antihypertensives, cholesterol-lowering agents, and diabetes medications with specific dietary management. If vegan diets are shown to be superior, or equal to standard pharmacological therapy, perhaps they would be the preferred intervention. Though compliance could remain a challenge with dietary interventions as with pharmacological interventions, issues related to drug side effects or adverse reactions would not be of concern. For example, though clinical trials have shown antihypertensive drugs to be effective in preventing cardiovascular death, poor blood pressure control is not infrequent, and drug nonadherence is considered a primary contributing factor.[95-97] Since significant evidence from both observational studies and RCT's exist showing an association between the intake of plant protein and decreased blood pressure,[40] investigations comparing vegan nutritional interventions with antihypertensives could be valuable.

Lastly, though challenges in design and execution would exist, it might be of interest for observational studies to evaluate the prevalence of vegans amongst patients undergoing procedures related to CVD. For example, a comparison between vegans and meat-eaters undergoing angioplasty or coronary artery bypass surgery could provide valuable information in ascertaining how many vegans versus meat-eaters suffer from severe CVD requiring procedural intervention.

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The Potential Use of Big Data in Cardiovascular Research

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Over the last decade, interest in the field of big data has been increasing exponentially in all industries with new technological and methodological capabilities to collect, process, store, analyze and interpret the vast amount of data produced in almost every aspect of people's lives. The data that is generated is frequently used by companies to improve business processes, gain competitive advantages and inform risk management decisions. However, in health care, the use of big data is less developed compared to the commercial and financial industries. Moreover, Canada has yet to fully capitalize on its availability, lagging behind the United States and countries in Europe where big data is being used to improve evidence-based medicine, quality of medical care and health care spending efficiency. Canada has some of the world's most comprehensive population-based health administrative databases and clinical registries from data routinely collected in its universal health care system. Together with the growing use of electronic medical records, the ability to link together different data sources with varying information, using unique encrypted identifiers affords researchers the potential ability to develop very large study cohorts while saving on the costs associated with primary data collection. The wealth of information available on large study populations provides significant advantages for research, such as a greater ability to study sub-populations and rare conditions, as well as subsequent implementation of results.

An early Canadian example of the potential of 'big data' is the CArdiovascular HEalth in Ambulatory care Research Team (CANHEART) initiative, aimed at measuring and improving the cardiovascular health of Canadians and the delivery of quality ambulatory cardiovascular care in Ontario, Canada (URL in Appendix).[1] In this initiative, we have linked 17 population-based health administrative, vital statistic, survey, clinical, laboratory, drug, and electronic medical record databases available at the Institute for Clinical Evaluative Sciences (ICES) using encrypted personal identifiers to create a database of 9.8 million individuals, or almost the entire adult population of Ontario.[1] Information available in the CANHEART database includes socio-demographics, behavioural and traditional cardiac risk factors, health care utilization, comorbidities, drug use and clinical measures and outcomes. The creation of big data cohorts such as CANHEART gives us unique opportunities to enhance clinical research and evidence-based medicine to identify knowledge gaps, better inform clinical decisions, and personalize care.

Using the CANHEART database, we found striking 4-fold variations in the incidence of cardiovascular events among 800,000+ immigrants to Canada born in 201 countries around the world, from eight major ethnic groups. This is partly attributable to differences in the prevalence of traditional cardiac risk factors.[2] More recently, we reported on the cardiovascular risk of 5.5 million adults aged 40-79 years old across Ontario's 14 health service regions. We found a 2-fold difference in cardiovascular risk between the highest and lowest regions. Additionally, 33% of the variation between regions was due to differences in the prevalence of traditional risk factors, 25% was due to socio-demographics including ethnicity, and a further 16% was due to differences in the use of preventive cardiovascular care.[3] Using these findings, our team has developed an interactive online tool which allows users to visually compare data on cardiovascular indicators across these health service regions (URL in Appendix). Examples such as these demonstrate that – despite significant progress in cardiovascular health and health care – disparities in cardiovascular health exist and gaps in knowledge and health care remain. However, they also highlight some of the countless possible uses of big data in the future.

Beyond linkages of only health-related data, combining this data with non-traditional data (e.g., from activity trackers, smartphone applications, genetic studies and environmental data sources) provides further opportunities to improve cardiovascular outcomes. One such opportunity lies in the realm of personalized medicine. By leveraging and linking these information-rich data platforms from large populations, we may be able to develop enhanced cardiovascular risk prediction models that account for emerging risk factors and more accurately stratify patients at risk when compared to current cardiovascular risk prediction algorithms which are based on a limited number of patient characteristics and derived from smaller cohorts. The potential value of machine learning in

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the analysis of large datasets for, amongst other things, outcome prediction has also gained traction recently and is currently being explored.

Big data also has the potential to alter the way we have traditionally conducted randomized controlled trials (RCT). Considered the 'gold standard' of study designs, RCT findings have resulted in many advances in the treatment of cardiovascular disease, including the use of lipid-lowering statin therapy and decisions about percutaneous coronary intervention (PCI) versus bypass surgery.[4,5] However, use of big data in 'randomized registry trials' (RRT) is currently receiving attention as a more efficient and cost-effective method of conducting clinical trials. Rather than recruiting eligible patients (e.g. using recruitment ads), collecting self-reported information and physical and/or biological measures from them at study visits and then following them for a set time period for outcomes, as is often the case in traditional RCTs, patients in a RRT are recruited from existing registries already containing much of the data required for study. By facilitating patient recruitment, measurement of baseline patient characteristics, and uptake of trial interventions by trial participants for whom data is already collected in an administrative database, clinical registry or electronic medical record, use of big data for RRTs could significantly reduce the costs of conducting clinical trials, allow for longer follow-up times and increase the generalizability of the resulting sample.[6,7] One example is the Thrombus Aspiration in ST-Elevation Myocardial Infarction in Scandinavia (TASTE) trial examining whether intracoronary thrombus aspiration improves flow and myocardial perfusion.[8] A diverse and broad cohort of patients in the Swedish angiography and angioplasty registry (SCAAR) platform were randomized to receive either conventional PCI or thrombus aspiration followed by PCI, with outcomes ascertained using SCAAR and other national registries. While already being used in some countries around the world, RRTs remain largely unchartered territory in Canada.

Use of big data in health care comes with enormous opportunities; however, it also presents with many challenges. Valuable personal-level data such as information on vital signs, biological measurements, sleep patterns, family histories and locations visited is being generated and collected at unprecedented rates by everything from fitness trackers to smartphone applications to online health calculators. With the prospect of combining this data with traditional health data sources for the purposes of health research, there is intense debate around who owns this data (i.e., user versus developer), who should be allowed access to it, and what purposes it can be used for. For studies conducted in academic institutions, research protocols are carefully reviewed by Research Ethics Boards, thus helping to ensure patient privacy is protected. However, commercial entities may be able to conduct big data research without similar oversight.

From an application perspective, since these data are not usually collected for health research purposes, how to handle missing data and possible input errors also pose challenges. Addressing these often requires making assumptions about the missing data, developing decision rules and algorithms, and using more advanced techniques (e.g., imputation). Furthermore, capitalizing on the vast amount of data also requires knowledge of innovative methods in data analytics and data science, for which uptake in health care is only beginning.

Although much progress has been made in reducing cardiovascular incidence and mortality in the last few decades, gaps in knowledge and cardiovascular care persist. Innovative methods from leveraging big data and using non-traditional data sources are gaining attention for their potential to contribute to ongoing advancements in cardiovascular health. While big data has generated much interest in the research community, its use is still in its infancy and how it can best be used to improve cardiovascular clinical care and patient outcomes has yet to be determined. Nonetheless, the use of big data in cardiovascular research has the potential to dramatically change how research is conducted in the future.

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Appendix – Links to referenced websites

To learn more about the CArdiovascular HEalth in Ambulatory care Research Team (CANHEART) initiative, see http://www.canheart.ca.

To view data on cardiovascular indicators across Ontario, Canada's health service regions or Local Health Integration Networks, see http://www.canheart.ca/eatlas/.

Diabetic Retinopathy in Canada: Challenges in Screening and Implications for Practice

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Despite being a treatable disease, diabetic retinopathy is the leading cause of new cases of blindness in North America and is the most common microvascular complication of diabetes.[1,2] It a serious vision-threatening condition causing progressive damage to the retinal vasculature, and may affect over one million Ontarians with diabetes.[3] Although treatments are generally well tolerated, targeting prevention and monitoring is ideal when dealing with retinopathy, since treatment is much more successful when detected early. Vision-threatening retinopathy is rare in the first 3-5 years of individuals diagnosed with type I diabetes or before puberty[1] However, almost all patients with type I diabetes and >60% of patients with type II diabetes develop some form of retinopathy during the first two decades of disease1. Glycemic control is most commonly accepted as the most effective protective mechanism against the progression of retinopathy in both type I and type II diabetes.[1] As a significant number of patients with vision-threatening disease may be asymptomatic, ongoing evaluation for retinopathy is of great importance. The Canadian Diabetes Association has published clinical practice guidelines with recommendations on the frequency of screening individuals with diabetes for retinopathy. The current guidelines include initiating screening 5 years after diagnosis for all individuals 15 years of age or older diagnosed with type I diabetes and in all individuals at diagnosis of type II diabetes.[4] Furthermore, individuals with type I diabetes should undergo annual rescreening and those with type II diabetes should undergo rescreening every 1-2 years.[4] However, there exists a significant gap between the published guidelines and the rate of screening among Ontarians.

Although yearly screening for patients with diabetes is covered in most provinces including Ontario, in 2015, only two-thirds of Ontarians aged 20 and older with diabetes were screened for retinopathy within the recommended two-year period.[3] This rate has improved very little over the past three years.[3] Similar numbers have been estimated Canada-wide in 2007.[5] Reasons for this gap need to be explored and targeted. One reason for this discrepancy may be due to confusion regarding the delisting of routine eye exams for healthy adults from the Ontario Health Insurance Plan (OHIP) in 2003/2004.[6] This delisting may have had the unintended consequence of reducing publicly funded retinopathy screening for individuals with diabetes, as the rates of diabetic retinopathy screening among adults aged 20 to 64 years old have dropped most significantly between 2003/2004 to 2005/2006.[6] Many patients with diabetes may be unaware that they are still covered by OHIP for yearly eye examinations as well as any related follow-up assessments that may be required. As of 2015, all provinces and territories in Canada, with the exception of Newfoundland and Labrador, provide diabetics with coverage for yearly eye examinations.[7]

A number of studies have examined barriers to eye care among patients with diabetes, correlating factors such as age, income, education, health insurance, duration of diabetes and financial burdens with changes in compliance.[6,8,10,11] Physicians in one study cite inadequate diabetic patient education as the biggest barrier to screening, whereas patients largely believe that their diabetic education is adequate.[8] Despite knowledge that eye examinations were recommended, patients in this study were found to have limited understanding of the rationale behind screening recommendation and little knowledge regarding retinopathy itself.[8] A recent Canadian study also describes several factors associated with an increased likelihood of patients with type II diabetes obtaining retinopathy screening. These factors include discussing diabetic complications with a health professional, private insurance coverage, duration of diabetes greater than 10 years and higher income levels.[9] One important suggestion from the study is that discussion of the risks of visual problems between physicians and patients is a key approach to improving eye screening utilization.[9] In order to effectively carry out this suggestion, it would be worthwhile to evaluate what and how much diabetic patients understand about their risk of vision loss.

There is a lack of data, however, of patient understanding regarding diabetic retinopathy and its complications in Canada. Most studies on this subject have been conducted in Asian countries, where patient demographics and understanding may be different. Age, level of education, and social economic status are all factors found to affect awareness that diabetes

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may cause impaired vision in one study in India. Across these studies, 80.6% to 88.1% of diabetic patients mention awareness that diabetes could damage their eyes and vision in some way.[10,11,12,13] However, only 41.9% of patients in one study state that annual eye examinations are necessary for diabetes.[12] While none of these studies have been conducted in Canada, patients in Canada may also be unaware of the importance of regular screening suggested by recommended guidelines.

If patients do not understand the risks associated with poor disease control, then their likelihood to adhere to recommended prevention strategies and treatments may be compromised. Physicians play an important role in educating and motivating patients to achieve better metabolic control, which can reduce the progression of retinopathy more than any ocular treatment currently used in ophthalmology practice.[13] Furthermore, patients must be educated regarding the importance of annual eye examinations in detecting early signs of retinopathy, even if they are asymptomatic. It is clear that there remains much work to be done to improve eye screening compliance among diabetic patients in Canada in comparison to other countries such as Iceland, where, according to one study, the compliance rate among non-blind diabetic patients to a biannual screening program was found to be 77%.[14] Another study conducted in Iceland, the first country to initiate a systemic diabetic eye screening program, notes a significantly low prevalence of diabetic blindness following institution of the screening program, which indicates the efficacy in prevention of such a program.[15]

What then can be done to increase the rate of diabetic retinopathy screening in Canada? As a first step, one suggestion is to conduct a study similar to those done previously in other countries: conduct a baseline assessment of patient understanding of ocular complications and the need for regular eye examinations. Several studies conducted in other countries fail to provide a holistic view of patient encounters with their health care providers surrounding diagnosis.[10,11] Thus, in addition to assessing knowledge of retinopathy and recommended guidelines, it suggested that such a study also examines patients' encounters with their healthcare providers regarding diabetic retinopathy education both upon diagnosis and in follow-up encounters. Obtaining this information may help guide future management and education. Better education by healthcare providers with regards to diabetic retinopathy upon diagnosis and over the course of one's illness is an important form of health promotion. Diabetic retinopathy education may vary widely among healthcare providers. In general, it is important that patients understand general information about the condition, concerning symptoms, risk factors (especially modifiable risk factors), ways to prevent or delay progression and recommended screening guidelines, as outlined by a patient education brochure on diabetic retinopathy created by the Canadian National Institute for the Blind (CNIB).[16] Another step is advocating for formal screening programs, as no such program exists in Ontario, in contrast to other medical conditions. For example, Cancer Care Ontario sends invitation letters for those eligible for colon cancer screening, as well as reminder letters explaining the importance of screening when it is time to return for screening.[17] Such a strategy also allows for increased opportunity for patients to initiate a discussion about screening with their healthcare provider, should this discussion not have already been initiated.

In summary, diabetic retinopathy is a serious, yet highly treatable vision-threatening condition. Unfortunately, there exists a significant gap between the published guidelines and the rate of screening among Ontarians, despite provincial coverage for annual screening eye examinations. There is a lack of data on patient understanding regarding diabetic retinopathy and its complications in Canada. Obtaining such information may prove to be useful in guiding conversations and educating patients regarding diabetic retinopathy and ways to reduce risk of its progression. Other strategies include advocating for formal diabetic retinopathy screening programs. With the increasing burden of diabetes on the Canadian population, engaging in these types of health promotion and advocacy can significantly improve the quality of life and health of patients with diabetes.

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CPSO "Effective Referral" Policy Does Not Adequately Respect Physicians' Conscientious Care

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The ruling in *Carter v Canada* and the subsequent passage of Bill C-14 by the Canadian Parliament have had a profound impact on what is deemed healthcare in Canada. With the legalization of euthanasia and assisted suicide, codified under the blanket term "medical assistance in dying" (MAID), participation in the intentional and active hastening of a patient's death has gone from being a punishable act to one enshrined as an essential component of comprehensive healthcare. Many physicians have expressed discomfort with this redefinition of their profession; a poll conducted shortly after the conclusion of the Carter case found that 63% of surveyed physicians would refuse to provide MAID if requested.[1]

The College of Physicians and Surgeons of Ontario (CPSO)'s policy *Professional Obligations and Human Rights* (revised in 2015) sets out the minimum expectations of dissenting physicians with respect to the provision of MAID.[2] Under this policy, physicians who object to a particular procedure or service are required to provide an "effective referral" to a non-objecting physician who can provide the procedure or service in an efficient manner.[2] With respect to MAID, the requirement for effective referral means that Ontario physicians have greater constraints upon their freedom of conscience than those in other jurisdictions where euthanasia or assisted-suicide is legal. For example, the law regulating assisted-suicide in Oregon does not compel physicians to include MAID as part of their therapeutic repertoire either directly or indirectly.[3]

In crafting regulations on MAID, and on conscientious care in general, it is true that the CPSO must take into account its various and sometimes competing responsibilities. Within the *Professional Obligations and Human Rights* policy, the justification for a policy mandating effective referral includes a need to protect equitable access to healthcare for all Ontarians, particularly those from vulnerable populations.[2] This is a perspective shared by stakeholders, such as Minister of Health Dr. Eric Hoskins, who have lauded the CPSO's *Professional Obligations and Human Rights* policy as a balance between patient access to care and physicians' freedom of conscience.[4]

Ensuring access to healthcare is certainly important. However, there are two objections to utilizing a policy of mandatory effective referral to achieve this end. Firstly, it can be questioned whether this balance is the least restrictive means of ensuring access to MAID. Given the reasonable contention that the requirement for an effective referral still compels participation in an act which a rational physician could judge to be unethical[5] (an argument which will be further explored in this article), we would argue that less restrictive means could be pursued if the CPSO and the Government of Ontario demonstrate universal access to MAID to be a compelling public interest. One such proposal, endorsed by major conscience-rights proponents[6] and promised by the Ontario Government,[7] is the implementation of a self-referral system to a care coordination service, whereby patients are able to access a range of palliative care options, including MAID, without the need for a referral from their physician. Such a system removes an extra step for patients seeking these services, while also allowing physicians to decline from participating in MAID.

Secondly, contrary to the CPSO's portrayal of conscientious objection as merely "personal," they are enforcing conformity to a definition of medical care that is neither indisputable nor universal. Declining from participating in MAID need not be about the physicians' "personal beliefs"; it may rather be rooted in their professional judgment on how they are best to fulfill their obligation as physicians, to serve as healers. Hippocrates' Oath enshrines a counter-perspective that limits legitimate medical acts to acts of healing: *"I will neither give a deadly drug to anybody if asked for it, nor will I make a suggestion to this effect… In purity and holiness I will guard my life and my art."*[8] The American Medical Association still "opposes any bill to legalize physician-assisted suicide or euthanasia, as these practices are fundamentally inconsistent with the physician's role as healer" (H-270.965).[9] On this view, acts counter to health are illegitimate, bad medicine. This view is not limited to religious extremists, but is rationally held even by acclaimed experts in end-of-life care such as Balfour Mount, who was awarded the Order of Canada for being the "father of palliative medicine."[10] Physicians who share Mount's conscientious understanding of medicine should not be dismissed as unreasonable. For such physicians, dissociating themselves from MAID is not merely personal but a professional obliga-

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tion. Moreover, they are not suggesting that they will abandon their patients, a concern some have raised.[11] To the contrary, they want to continue undertaking the type of care for which Mount received national recognition.

The CPSO implicitly acknowledges that effective referral is a materially necessary step for a patient to access MAID. Put another way, if referral did not directly facilitate MAID, why would the CPSO take such a strong stand in requiring it? Moreover, the act of referral is not a neutral act; the CPSO describes effective referral as a "positive action," structured in such a way as "to ensure the patient is connected" to a non-objective provider.[12] The referring physician's intention is therefore oriented towards the death of the patient, regardless of whether he or she personally agrees with the patient's decision. Given this close relationship between the referring physician and the act of MAID, there is a negligible ethical distinction between referring for and performing euthanasia. This line of reasoning stands regardless of one's personal view of euthanasia. Indeed, bioethicists opposed to conscientious objection from MAID acknowledge that a mandatory referral policy is ethically indistinguishable from mandating direct participation in the provision of a service, albeit drawing a different conclusion from this analysis.[13]

This argument is well illustrated by Professor Roger Trigg in his recent article, "*Conscientious Objection and 'Effective Referral.*"[14] In it, Professor Trigg uses the analogy of two bank robbers, one of whom orders the other to kill the bank teller during their getaway. Most people would agree that both hold equal responsibility for killing the teller, even though only one fired the lethal shot; Canadian law would consider the referring robber a "party to that offence."[15] The robber giving the instructions acts much in the same way as the referring physician; the instruction helps facilitate the proper timing of the shot and therefore materially contributes to the teller's death, while the act of the instruction indicates support for the teller's death.[14] Note that this analogy does not intend to prove the moral equivalence of homicide and MAID. It is outside the scope of this paper to discuss whether the moral nature of intentionally killing a person is changed when the person requests it. The point here is that a person who directs someone else to do an act shares the same moral responsibility as the person who actually does said act.

The CPSO elsewhere affirms this analysis, acknowledging that physicians who refer for a procedure are complicit in its direct provision. As other authors have noted,[5] the CPSO policy on female genital mutilation (FGM) forbids any physician from performing or referring for FGM, and both the referring physician and the acting physician face professional sanction under the policy.[16] This demonstrates that the CPSO is quite willing to accept the basic ethical analysis that referral for a procedure is not meaningfully different from directly providing the procedure. To conclude otherwise in the case of MAID, and conscientious practice in general, is inconsistent.

If this argument holds, mandating effective referral for MAID is not an authentic protection of physicians' conscientious judgment, and the current CPSO policy is therefore requiring physicians to violate their deeply held moral principles to remain professionals in good standing. A legal analysis of such a requirement vis a vis fundamental Charter freedoms is beyond the scope of this article. Irrespective of the ethical or legal impact of a mandatory referral policy on physicians, this policy stands to have a negative impact on patients, and as such should be rethought by the CPSO.

One of the principal arguments made in favour of limiting physicians' freedom to exercise their conscientious judgment is that it will promote equal access to health services across a jurisdiction.[17] The argument suggests that allowing physicians to refuse to provide or refer for a specific service will prevent some individuals, particularly those in smaller and more remote communities, from accessing certain services in a timely manner.[13] However, physicians who deem MAID to be equivalent to murder would sooner pursue other avenues, such as relocating their practice or leaving medicine altogether, than violate their consciences. This has already begun to occur[18] and would likely accelerate if the CPSO opted to aggressively enforce the new effective referral policy. The net result would be that communities could be deprived of a local physician altogether, and long-standing fiduciary relationships between physicians and communities would be broken. As previously mentioned, if the government of Ontario deems the provision of MAID to be a pressing and substantial concern, it could adopt a less restrictive option to effective referral, as other jurisdictions have done, such as a self-referral system that would give patients more direct access to the services they desire.

One "solution" to this problem which has been proposed by opponents of conscience rights for physicians is to screen out medical school applicants who object to particular practices like MAID.[13] The argument is that even though there is a shortage of physicians in some communities, there is no shortage of qualified, aspiring students. Therefore, by restricting access to medical school to those without conscientious objection, the question of accommodating dissenting physicians will cease to trouble regulatory authorities.[13] Such a practice would pose obvious problems with respect to potential religious or cultural discrimination; in a pluralistic society, the makeup of the healthcare profession should not be a monolith but reflect the diverse cultural experiences and perspectives of the patients it serves. A discriminatory admissions process is further problematic when one considers that the majority opinion regarding medical ethics is constantly changing. All practicing physicians in Ontario entered medical school at a time when euthanasia was illegal, and so a screening policy for conscientious objection would not have eliminated any of them. There may be practices introduced into the medical sphere twenty years from now which trouble the consciences of current medical students and practitioners. In reality, the only way that a screening policy would effectively eliminate future conscientious objectors is by asking, "Are you prepared, upon entering the medical profession, to participate in any practices deemed to be within your scope by your regulatory body, regardless of any objection, ethical or otherwise?" Patients might feel uncomfortable knowing that their physicians have been drawn from the subset of students answering that question in the affirmative. A robust conscience – a commitment to judiciously seek patient wel-

fare with integrity – is not a nuisance to the medical profession; rather, it is critical to maintaining a profession which can continue to merit the trust of its patients.[5] If anything, rather than discouraging conscientious practice in medical students by implementing such a screening policy, medical schools should incorporate education on the importance of conscience as part of their ethics curricula.

Managing the multifarious perspectives on medical ethics, both within and without the healthcare profession, is not straightforward. However, particularly when faced with controversial issues such as MAID, patients deserve to know that they can trust the integrity of their physicians, even if this means that not all services can be obtained from every physician. A recent survey found that 75% of Canadians agree that their physicians should be permitted to avoid participating in MAID, underscoring the strong support held for physician conscience rights in our country.[19] Physicians and patients deserve a policy which respects the diversity of beliefs in Ontario and ensures the vibrancy of conscientious care.

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Cervical Screening: Not Yet Time to Abandon Pap Tests for HPV Testing

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Background

Cervical cancer is a common but extremely preventable cancer, with a survival rate of 93% if detected early.[1] The Papanicolaou test, or "Pap" test, has been the mainstay in cervical cancer screening since inception of cervical cancer screening in the 1960s. Pap tests aim to detect the presence of atypical or pre-cancerous cells, utilizing cytology, in the hopes of preventing progression to cervical cancer. Current Canadian Task Force on Preventative Health Care (CTFPHC) guidelines recommend screening sexually active women between the ages of 25 and 69 every 3 years.[2]

Given that human papilloma virus (HPV) is responsible for 99% of cervical cancers, some clinicians have instead suggested that screening should be done for HPV infection.[3] With the recent introduction of HPV DNA tests, there has been a movement to replace routine Pap tests with regular HPV DNA tests. The idea is to identify HPV carriers before the infection progresses to cervical cancer. Supporting this movement are a few major studies on the benefits of HPV testing. In this paper, the arguments for and against abandoning Pap tests in favour of HPV testing in Canada will be explored.

Benefits of HPV Testing

Recently there have been a number of randomized controlled trials (RCTs) comparing HPV DNA testing to Pap tests and cytology in the detection of cancerous and pre-cancerous cervical lesions. Many studies have shown that HPV testing is more sensitive than Pap tests in detecting abnormalities or cancers.[4-7] HPV testing, in addition to having a higher negative predictive value, has a sensitivity of 76.1%, almost double the sensitivity of Pap tests and cytology, which is 47.8%.[8] Three large RCTs, which examined over 150,000 patients, found that HPV testing had a 60% higher detection rate for grade CIN3 (cervical intraepithelial neoplasia) pre-cancerous cervical lesions than Pap tests.[6-8] The results also showed that HPV testing had a 50-68% higher detection rate for CIN2 lesions.[6,7] When examining only younger women, aged 25-34, one study found that HPV testing had a 127% higher detection rate of CIN2 and CIN3 lesions compared to Pap tests.[6]

In addition, decreased rates of cervical cancer have been shown for up to 6.5 years in patients screened with HPV testing versus Pap tests alone, suggesting earlier detection of pre-cancerous lesions with HPV testing.[4,6] One of these studies, drawing on 4 RCTs done in Europe, found that HPV testing provided 60-70% more prevention of cervical cancer than regular Pap test and cytology screening.[4] This evidence strongly suggests that HPV testing detects pre-cancerous cervical lesions earlier, resulting in fewer cases of progression to cervical cancer.

When examining evidence on Pap tests, there are many limitations that may favour HPV testing. As described, Pap tests have a sensitivity of 47.8%, which confers a higher false negative rate.[8] One study found that Pap tests may miss up to 50% of CIN3 cervical lesions.[8] Pap tests also appear to have a high rate of loss to follow up at 33%, twice the rate compared to that of HPV testing.[9] However, in the study describing discrepancies in loss to follow up, positive Pap tests were only referred after a 6 month follow up , while patients with positive HPV testing were immediately referred to colposcopy.[9] This difference in time between referrals may account for the increased loss of follow-up in Pap tests.

Limitations of HPV Testing

While there are many benefits of HPV testing, such as earlier detection of cervical lesions and possible increased detection rates, this test itself does not come without limitations.

One of the major limitations of all HPV DNA studies described above was the total lack of or very short follow up periods of 3-4 years in most trials, with only one following patients for up to 6.5 years.[4,6-8] Evidence shows that mild, pre-cancerous cervical lesions have a mean progression time to high-grade dysplasia or cancer of over 7 years.[10] Given the slow growth and progression of cervical pre-cancers, more longitudinal studies are required to determine the benefit of this screening method.

In addition, the evidence on the effectiveness of HPV testing for cervical cancer screening is not unanimous. Two large European RCTs found no difference in overall detection rates of high-grade cervical dysplasia when comparing cytology plus HPV testing to cytology alone.[11,12] However, one of these studies found that HPV and cytology resulted in more CIN3 cases being detected earlier, with cases being identified in the first round of screening, as opposed to the second.[11] This suggests that while HPV testing may lead to earlier detection of cervical lesions, it does not appear to lead to increased detection overall. Moreover, none of the mentioned studies

have shown any mortality or survival benefit for HPV screening compared to Pap testing.

Despite evidence suggesting earlier detection, many of the aforementioned trials reveal other limitations of using HPV testing as a screening test for cervical cancer. For the healthcare system, an individual HPV test costs 50% more than a standard Pap test, at $30 per HPV test versus $20 for a Pap test.[9]

It is also important to consider that Pap tests and cytology screen for pre-cancerous changes while HPV testing screens for the causative agent, which does not necessarily lead to cervical changes. As a result, HPV testing results in more false positive screens than Pap tests, leading to a significant increase in colposcopy referrals and follow up tests.[6-8,13,14] In one large RCT mentioned earlier, HPV testing nearly doubled the number of required colposcopies, with a 95% increase in colposcopies performed.[8] This has the potential to drastically increase the cost of cervical cancer screening. An Ontario study found that HPV testing cost an additional $3000 for each additional CIN 2 or 3 lesion it identified.[9] Research modeling total downstream costs per quality adjusted life year (QALY) estimated that biennial HPV plus Pap tests cost $70,000/QALY, in contrast to $30,000/QALY for biennial Pap tests alone.[15] Furthermore, studies have shown that many of the pre-cancerous lesions that HPV testing detects would naturally be cleared by the immune system in younger women without detrimental effects.[6,13] Schlecht and colleagues found that 93% of mild cervical lesions regress within 2 years.[10] One of the studies stated that HPV testing leads to overdiagnosis of self-regressing CIN2 lesions.[6]

In summary, it appears that higher rates of detection for HPV testing may be due to higher detection of early lesions in younger women that often spontaneously regress. This is important to consider for a screening test that is performed on such a large percentage of the population. High rates of false positive tests and increased colposcopies cause unnecessary stress and anxiety for patients, as well as cost to the healthcare system. This is especially important given that many of these lesions would clear on their own and, as mentioned earlier, that HPV testing has not shown any mortality or overall cost reduction benefit for the increased follow-up and up-front costs.

Conclusion

Given all of these factors, there is not yet enough evidence to support switching from Pap tests to HPV testing as the primary modality for cervical cancer screening in Canada. Multiple trials have shown HPV testing to be effective at screening for cervical cancer and its precursor lesions. Evidence strongly suggests that HPV testing is effective at detecting CIN2 and CIN3 cervical lesions earlier than Pap tests before they progress to cancer. However, there is inconsistency in the evidence as to whether or not HPV testing leads to overall increased rates of detection.

Additionally, there is not yet any evidence of mortality or net cost benefit from cervical cancer screening with HPV testing compared to Pap tests and cytology. HPV testing has been shown to increase false positive screening tests, resulting in a large increase in follow up tests – in particular, colposcopies. Strong evidence exists supporting the effectiveness of HPV testing in cervical screening, but more evidence is needed on the net cost and mortality benefits of switching to this this test, which has a higher up-front cost.

Given patient anxiety from a high rate of false positive results, increased up-front costs with no proven long-term benefit, conflicting evidence on overall detection rates for cervical lesions using HPV testing, and the duty to conserve medical resources in a publicly funded healthcare system, it is not yet time to abandon Pap tests in favour of HPV testing as the primary screening method for cervical cancer.

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Interview with Dr. Heather Ross

UTMJ Interview Team (Aidan McParland, Austin Pereira)

Dr. Heather Ross

Heather Ross, MD, MHSc, FRCP(C), FACC is a cardiologist at the Peter Munk Cardiac Centre, Professor of Medicine at the University of Toronto, and Director of the Cardiac Transplant Program at Toronto General Hospital. She is the Ted Rogers and Family Chair in Heart Function. She is also the Head of the Ted Rogers Centre of Excellence in Heart Function. She received her medical degree from the University of British Columbia, her cardiology training at Dalhousie University, and a postdoctoral fellowship in Cardiac Transplantation at Stanford University. She earned her Master's Degree in Bioethics from the University of Toronto.

Dr. Ross served as President of the Canadian Society of Transplantation in 2005, on the executive of the International Society for Heart & Lung Transplantation (ISHLT) from 2002 through 2005, and as Secretary Treasurer from 2007-2010. She is an Associate Editor for the Journal of Heart and Lung Transplantation. She served 5 years on the Canadian Cardiovascular Society Council, 3 years on the Canadian Cardiovascular Society Executive, and on the Board of the Canadian Cardiovascular Society Academy. She served 4 years on the executive of the Heart Failure Society of America. She is currently the Past President of the Canadian Cardiovascular Society. She has published over 250 articles and won numerous teaching awards. In 2015, she was named by Canadian Geographic as one of the top 100 modern day explorers.

UTMJ: Can you tell us a little about yourself?

HR: I was Born in Montreal, and I am a diehard Habs (Montreal Canadiens) fan, sorry! For reasons that remain unclear, at the age of 11, I said I wanted to be a doctor. I had a traditional middle class upbringing. My dad was in sales and my mom was a music teacher. My parents had university degrees, so school was a big priority in the family. We moved to Ontario in 1977, with the changes in English-French relations, even though my father was perfectly bilingual. We lived for a short time in Orangeville and then in Port Credit, but basically I got to university as soon as possible. I went to Queen's University for undergrad and then on a whim, as I didn't expect to get in, I applied to UBC for medical school. I got in! That was awesome. I did a rotating internship at St. Michael's Hospital. Then, I went back out to UBC because the skiing was better, but really for the internal medicine program. I then went to Dalhousie for cardiology, Stanford for transplant studies, and shockingly got a job here. I was expecting to stay here for three years and I've now stayed in Toronto for twenty-one years! I fell in love with the city, which I wasn't expecting, and the program. It has been an awesome experience.

UTMJ: Why did you pick cardiology out of all the internal medicine subspecialties?

HR: When I started medical school, I sort of knew that I wanted to specialize. I liked the idea of knowing an area with a real depth of knowledge. I have the ultimate respect for family doctors because they need a breadth of knowledge. However, I wanted to know everything about one area. The experience that tipped things was when I was an intern, and my grandmother died of a massive infarct. I was the only one there, as my parents were out of town. A few pieces of it made it a moving experience. First, you see things from the patient's perspective, and to see her in the span of a few hours, so vibrant, to having a massive infarct, full pulmonary edema, and then to watch her die was an overwhelming experience; I'm still quite emotional about that.

The second reason came from the doctor who was treating my grandmother and who wanted to intubate her, even though she had a wish to not be resuscitated. It was in the ER setting, and it was chaos in there. The whole idea of understanding goals of care, which is a consistent theme of my research, was very heavy at the time.

Then I did CCU as a resident. I am an adrenaline junky, so the idea of critical care, I loved it. The pace I loved. I flirted with hematology through a Terry Fox scholarship, which I really enjoyed. And when I did my CCU rotation as a resident, there was a heart transplant patient that walked into the CCU. He walked in and was dead by the next morning due to overwhelming rejection. Seeing the impact and immediacy of transplant was quite interesting to me. This interest in cardiology was there from very early on, even before residency, and clearly solidified from these experiences. I had an incredible mentor, Dr. Victor Huckell, a cardiologist in Vancouver. I had a real interest, and then you meet somebody like this, and it makes you go, "Wow!" Those two things happening together made cardiology the field for me.

I then had a running joke that transplant made car-

diology interesting, which isn't fair because cardiology is intrinsically interesting. But transplant is what makes me truly love cardiology. While in Halifax, Dr. Catherine Kells, who went to Stanford, talked a lot about it. The history of heart transplant is vast at Stanford, and that university has played a huge role in the science of transplant. Dr. Sharon Hunt, who was also there, is a real force in heart transplant, vibrant and academically strong. I did my science with Dr. Hannah Valentine there and the mentorship by both of these women was amazing.

How I ended up here was a strange tale too. Imagine a perfect day in Palo Alto, California. Late May or beginning of June, 75 degrees. It was perfectly dry weather, so I biked to work. Every once in a while, I biked the long way home, an approximately 35 kilometer loop. There was a liver transplant doc giving a talk at 5:00 PM about cyclosporine. Again, it was a perfect day, and the Nurse Practitioner, Joan Miller, said that the speaker was from Toronto. She said, "You have to go to support him; he's from Toronto." The speaker was Dr. Gary Levy, a world-renowned immunologist and liver transplant doctor. He's actually an American, but was working in Toronto. I went to listen to his lecture and said, "Hi, I'm a Canadian studying transplant here." I then went on my bike ride. That weekend, I went camping in Yosemite. I found out when I got back that they were looking for someone in Toronto who's done training in both cardiology and transplant. They flew me out for a job interview, and a year later, I was accepted for the job. So the moral of the story was don't miss a perfect day! Don't miss the opportunity for a door opening. If it wasn't for Joan Miller, I wouldn't have gone to meet Dr. Gary Levy at the talk! I came to Toronto not expecting to fall in love with the program or city, but I did!

UTMJ: The cardiac transplant program at the University of Toronto is world-class. Can you talk about your involvement with the development of this program?

HR: For any program to hit the mark, a few things need to happen: you need a research platform, a successful clinical program, and an amazing education platform. For a clinical program, it's about volumes and outcomes. You need to have a critical mass of patients and maintain outcomes of patients. And then an effective administration program behind it to make it happen.

Toronto has a world class multi-organ transplant program. It is the 3rd or 4th largest worldwide, and far and away the largest in Canada. The heart transplant program was small in size for its patient volumes, so we needed to grow the program. For the first five years in Toronto, I did one in one call because that's the way it was at the time. And I don't regret a minute of it. Then, we recruited Dr. Diego Delgado, who trained in Argentina and Chicago.

Funding always was a bit of a challenge, including looking for different ways to get funding. There was no money for a fellowship program, so we started the "Test Your Limits" program, which developed amazing trips to raise awareness about organ donation and to fundraise in order to seed research and establish the fellowship program.

We have also been fortunate to have an incredible foundation, and a culture of philanthropy in Toronto. Specifically, the Rogers family created a center of excellence in heart function, which provided sustainable funding for the fellowship program. We recruited Dr. Michael McDonald, Phyllis Billia, Carolina Alba, Jeremy Kobulnik, and Mitesh Badiwala in the last five years. And the program has grown. Our heart failure program is huge, and it's on an exponential rise. It has been neat to see this growth happen. We had a Heart Links Christmas party in the TGH atrium on the 4th floor and many patients came together for the event. It really does feel crazy seeing the patients and their families. We even had our first thirty-year transplant survivor. What a journey it has been.

Heart failure is a terrible condition; when you have someone in the CCU on inotropes and waiting for a heart, and then they have a successful transplant (which it is in the vast majority of cases), seeing their families is an amazing thing. Every time we do a transplant, I think that is so amazing. Not every day is rosy, but there are more good days than there are bad ones.

I'm being honest when I say I want to come to work every day, because I really do. I feel sorry for people who haven't found that space. I feel very fortunate; when I applied to medical school I didn't have any publications. I hit the GPA you had to hit, and I played in a band and sports, but I had no papers, no first authorships. When I see the people applying now, I say, "Wow." I had one case report. I was passionate, but I feel that the competition level has changed. I personally think that it's unfortunate, because it may make people less rounded.

I still love what I do, more than 20 years in. But I respect the fact that it is very challenging for the new crop of students. I loved the rotating internship after medical school. You didn't worry about anything during that year, except getting experience and learning. There were lots of rotating internships at the time because it was popular. I lived in a house with 5 people interning at 3 different hospitals. You could breathe! There were no exams, no pressure, and you had a year of decompression. The current generation can't decompress. The other challenge is that we also had the opportunity to do electives in different places; it seems now that decisions about electives are more structured, and 'you better do the elective there because you want to go there'. I think it's tough for current students.

And then there's the cost. I did a Terry Fox scholarship, but lots of my friends in medical school took the summer off to go do electives in Africa, do rural practice, especially in UBC in the inner city of Vancouver

with a family physician. For your generation, how can you afford not to work in the summer?

UTMJ: We often discuss the difficulty of getting access to organs and the challenges that this comes with from a transplant perspective. Could you touch on how some of this is addressed here, and perhaps globally?

HR: I think you know that we have an opt in vs. an opt out system in Canada. There has been a lot of discussion over the years about changing this, as there are countries that have presumed consent, or opt out, and they have higher organ donor rates. The GTA (Greater Toronto Area) had one of the lowest organ donor rates per million. A lot of people thought that this was related to the multicultural nature of the city, and that organ donation was perhaps more frowned upon in certain cultures or religions. But virtually every major religious group has come forward and said that organ donation is actually a good thing and have supported it. I think that there has been a lot of work as a transplant community on national guidelines, the organ procurement organizations (OPO's) have put a lot of investment into organ donation, and the numbers are in fact climbing. Currently, one of the tragic reasons we are seeing an increase in organ donors is the crisis in opioid addiction, which is also happening in the US. We are now seeing this as one of the increasing causes of organ donor death, compared to ten years ago. In the past, subarachnoid hemorrhage or intracranial bleed was the most common cause of donor death. In even earlier days, it was MVA accidents/bike accidents, but thankfully the helmet and seatbelt laws and tighter speed limits have lowered this.

It's really a paradox. On one hand, I want to do transplants, but we also recognize that someone has to die for that to be possible. We must do everything we can to enhance the safety of the general population, but we recognize that tragedies do exist. When such a tragedy happens, we want to maximize organ donor potential, while at the same time recognizing that it's an unusual business.

UTMJ: So far, we have talked a lot about how the transplant program has grown and come to be. Can you talk about where you think the future of the field of transplant medicine is going?

HR: For a long time, we have been thinking that stem cells were going to be able to regenerate and replace, that that was going to be the thing. So far, I think that promise has not been as much as we had hoped, though research continues and hope remains.

The field of mechanical circulatory support, or ventricular assist device (VAD), has been a huge growth area. When you look at the volume of VADS implanted, we have seen an incredible uptick. In that field, we have had challenges, such as that of clotting/bleeding. Trying to find the fine line between clotting the device versus the risk of GI bleed. Another example is that a driveline is still required to charge the batteries, even though there has been a lot of work regarding transcutaneous charging of the devices. So there is still a risk of infection and challenges with managing device power. What we need, which almost always happens, is a technology leap.

Real-world life expectancy with a VAD is four years (not in clinical trials). This is a huge advantage to the patient, but transplant life expectancy is eleven years, and it's fourteen years if you survive the first year. So there is still an incremental advantage to transplant, despite the complications and challenges. I think that the hope is that the VAD piece will continue to develop, as there are no concerns about 'shortages', though they are costly.

In truth, the best option is prevention. So the real question is how we deal with a society that is driven by 'thumbs', where people are not exercising. Canada is an obese country, globally we're becoming more obese, and we've urbanized so we are seeing massive upticks in cardiovascular disease in low-middle income countries. Cardiovascular disease is the number one killer on the planet. The WHO (World Health Organization) recognizes that cardiovascular disease and non-communicable disease are the biggest issue we have. We have a global epidemic. We transplant and use VADS in about 5% of the people who could actually benefit. There are so many more patients with advanced heart failure. It has been said that using transplant to treat heart failure is like using the lottery to cure poverty. When you do the math, we know we need to treat people before they develop advanced heart failure. I spend a lot of time talking about how my life is worth one hour a day. But it's really something we must figure out, how to get people outside, doing things, eating better, that's the way forward. I think yes, I am hopeful for VADS and stem cells, but at the end of the day, we need to get at the problem a lot earlier.

UTMJ: There is certainly a role for physicians in providing this type of preventative health information to patients, but in terms of a more global or nationwide strategy, what are some ways that you think governments can be involved with this?

HR: I think that Jane Philpott and the government have made great strides with their plan for improved food labelling. People can't know what they are eating if they don't know what is in their food, and so requiring labelling on everything is critical. I had the opportunity to bear witness at the Senate on the issue of obesity in Canada. That was really an amazing experience to be in front of the Senate subcommittee and talk about this from a cardiovascular perspective and what some of the current issues are. We helped put forward a car-

diovascular health strategy on behalf of the Canadian Cardiovascular Society a number of years ago, and governments changed, but nothing came from it, and that is one of the challenges that we have in the country.

People often do things because they are convenient, easy, and unfortunately, much of the convenient food is not healthy. I am saying this as I have my diet Dr. Pepper, so I am not perfect by a longshot, but we do have to do a better job. I think that my parents' generation did a really good job. They came through the depression and the war and they have always eaten a meal that had protein and vegetables. I am at the tail end of the baby boomers, and I think we have done a poor job because we have been working long hours and have opted for fast. At least when my generation opts for fast, given our reasonable income, our meals look like Whole Foods. The current generation also opts for fast food, but without the same income. As a result, cost issues have made fast options unhealthy, as opposed to fast and healthy. In truth, the Big Mac problem doesn't catch up to you at a young age. However, once you establish that food pattern, the rest of life hits, the exercise doesn't happen, and the food patterns don't change, that's when the obesity happens. So, I think it is critical to support healthy eating at every age. It would be nice to have done a good job at making healthy foods easier; it's almost as if it's somehow inconvenient to eat healthy, and that's a problem.

UTMJ: You are one of the giants in cardiac health and research. What research are you currently pursuing and what are your research passions overall?

HR: The area that I am extremely interested in right now is big data, analytics, predictive modeling, and prevention. I believe that we are at a cusp. Are you are familiar with Moore's Law regarding technology? We are seeing this incredible growth of tech, which is enabling us to monitor things that people have never really appreciated. I think we are at the point where we can do a much better job through big data, and artificial intelligence, in terms of predictive analytics. So, my goal is leveraging tech to monitor patients, while collecting all the data and creating a data ecosystem or data lake, where we can start asking good questions. There is such a volume of data that you can do a better job of predicting when someone is going to get into trouble before something actually happens.

By having massive amounts of data, you can start to make links that people would never have realized before. I think that if you look at computational biomedicine, we are at the cusp in the next five to seven years of taking your genome, all the places that you touch the healthcare system, looking at all of the tech and wearables, all the apps that people use to monitor different things, monitoring food, bloodwork; if you actually put all of that info into one place, you can start asking the right questions. Imagine if I could tell you that, based on what you are doing right now, I know what is going to happen to you. Maybe I could make you change your ways?

UTMJ: As we look at some of the things around your room, you really appear to be quite the globetrotter. We wanted to get your take on how you balance life and medicine.

HR: So, I think the question of balance is an amusing one, because there are a lot of people who don't think I have adequate balance in my life. It's seeing opportunities when they appear, even if you don't actually realize you are in the middle of an opportunity. My version of balance works really well for me. I am divorced and I was not fortunate enough to have kids, and so that changed my life in a different direction and this is where it is. That was a big tragedy for me, but out of my control. When life goes this way, you make the most of where it goes. That is part of the path. You never quite know when it's there sometimes.

It's those moments of serendipity that you often don't realize you are in until after and you go, "Holy cow, that was the most amazing serendipitous moment." A friend of mine from Montreal climbed Mont Blanc with a heart transplant patient and I got really mad at him and said, "I don't understand why you didn't call me!" His next trip was to Bolivia. He's wonderfully French Canadian, and said "Do you want to go to Bolivia with 13 guys on Viagra?". I said, "That sounds really good!" So we went together to climb Mt. Sajama in Bolivia. When I came back from that trip, I met someone outside of medicine who has been an incredibly important mentor in my life. He's in business and he asked what I wanted to do, and I said I think that we can do something much bigger. I think we can take that type of trip, captivate people's imagination, fundraise and promote health, and that is when Test Your Limits was born (www.testyourlimits.ca). This year, we are on our seventh trip and we are going to cycle the roof of the world from Lhasa, Tibet to Everest Base Camp. TYL has allowed me to do the adventure part of my life that I love, while actually promoting what I believe passionately about, which is healthy living. Pure serendipity. We are now on the seventh trip and we have raised more than 2 million dollars from these trips. On the off years, I do trips that I think are fun. I did Machu Pichu, Mt. Blanc, Patagonia, and Annapurna Sanctuary in my off years, because why not?

Interview with Dr. Barry Rubin

UTMJ Interview Team

Dr. Barry Rubin

Dr. Rubin completed an undergraduate degree in physics and physiology, followed by his MD training at McGill University. After a PhD in Experimental Medicine, he finished his General and Vascular Surgery training in Toronto. He is certified by the Royal College of Physicians and Surgeons of Canada in both specialties, and received the Bernard Langer Award as the outstanding graduate of the Surgical Scientist Program at the University of Toronto in 1993. Dr. Rubin joined the surgical faculty at University Health Network (UHN) in 1995, and holds the rank of Professor of Surgery at the University of Toronto.

Dr. Rubin runs a tertiary/quaternary care practice in vascular surgery. Previously Head of the Division of Vascular Surgery at UHN from 2003 to 2010, he is now the Medical Director of the Peter Munk Cardiac Centre at UHN - Canada's largest cardiovascular unit. Core operating principles for the Centre established by Dr. Rubin include: (1) providing patient care in multidisciplinary teams, (2) implementing cutting edge cardiovascular technologies for patient treatment and (3) creating a culture with clearly defined processes that enable innovation.

Dr. Rubin's basic science research laboratory has been continuously funded by the Canadian Institutes of Health Research (CIHR) for 16 years. His basic science work, widely published in high impact journals, focuses on the way the heart responds to injury and the regulation of the immune response to infection. He received the Wylie Scholar Award in 1998 from Vascular Cures, San Francisco (http://vascularcures.org/research/wylie-scholar-program). This career development award is given to one vascular surgeon in North America per year; Dr. Rubin is the only Canadian recipient since the inception of the award.

Dr. Rubin has been Chair and CEO of the Mount Sinai Hospital UHN Academic Medical Organization since 2003, and has been unanimously re-elected to this position 3 times by his peers. This organization supports teaching, research, innovation, recruitment and retention of 1,000 physicians at UHN and Mount Sinai Hospital. Dr. Rubin is also the elected representative of 6,000 academic physicians in Ontario in discussions that relate to the ongoing management of the $250,000,000 per annum Academic Physicians Alternative Funding Plan.

Dr. Rubin is a member of the Health Canada scientific advisory committee on medical devices used in the cardiovascular system. He is past Chair of the Ontario Expert Panel on appropriate utilization of diagnostic and imaging studies, and past co-Chair of the Ontario Multiple Sclerosis expert advisory group, which published guidelines for the follow-up care and treatment for Ontarians with Multiple Sclerosis who have undergone vein dilation therapy. He was also a member of the CIHR – Multiple Sclerosis Society of Canada expert panel on Multiple Sclerosis research.

UTMJ: Can you tell us about yourself, your career trajectory, your interests and what drew you to vascular surgery?

BR: [I'm] Hoping to figure out what I'm going to do professionally very soon, since I am closer to the end of my career than the beginning. What drew me to vascular surgery: The truth is that I was a general surgery resident and I had done a straight internship before that. I didn't think that somebody could be that tired and still be alive, so I thought that maybe I should go into a research lab and take a break. I tried to get into a transplant lab, because I thought transplantation sounded cool although I didn't know anything about it - never did a transplant in my life. The spot had been filled and the next one available was a vascular surgery lab, so I went into the lab. After a year in the lab, my supervisor Paul Walker said - "so you are going to be a vascular surgeon?" and I said "okay". And that is the sum total. I've learnt that there is a lot of serendipity in life. [Vascular surgery] is the specialty that is ideally suited to me. It is highly technical, and very rapidly changing.

I was on call in my senior year of general surgery every second night for a year and during my fellowship year in vascular surgery, I was on call every day for a year (this isn't allowed anymore). I worked every weekend except for the four weeks of vacation that we got. So, I was here 48 weekends in that year and I was routinely up - because we all are when we are residents. In my first 10 years in practice, I did big open operations, great anatomy - you just see everything, I loved that about it. Two foot incisions, thoraco-abdominal stuff like that. After ten years, stent grafts became available. Now the most common operation we do is fixing aortic aneurysms and I rarely make an incision now. It is all percutaneous with the patient awake and they go home the next day. So what you choose to do is going to change at some point because of technology during the course of your career. It doesn't matter what the specialty is. I thought I'd be doing the same operations for 40 years and that would be it, but that's not the way it goes.

UTMJ: Based on your experience with patients you see, what is the spectrum/burden of current cardiovascular

disease? How has this changed overtime? What are some of the reasons for that change?

BR: Cardiovascular disease is the leading cause of death worldwide and the second leading cause of death in Canada. Because of the epidemic of ongoing smoking, abnormal cholesterol metabolism, hypertension, to some extent renal dysfunction and to a very great extent diabetes, there is unfortunately a very significant supply of people with both cardiac and peripheral vascular disease. There are a million people in Canada with heart failure right now, and this number is going to increase by 25% in the next 25 years, so we need to have new approaches and new technologies to be able to deal with that, or else hospitals will be full of people with heart failure. We do have new technologies such as remote monitoring of patients. We are developing a heart monitor for patients that is connected via a Bluetooth connection to your phone, scale, and to your blood pressure cuff. So, if you have someone with heart failure who is retaining water (an early sign of the heart failing), [it can be monitored] - i.e. if you are 70 kg and you step on the scale the next day and you are 71 kg, before you step off the scale there will be an email alert on your phone telling you that you have gained 1 kilo and instructing you to take Lasix and contact your doctor. Another example is monitoring your heart rhythm. If it detects an abnormal rhythm it can alert you to call 911. So, there are lots of cool things that are happening. It is a great field to be in. I am very lucky. There are not a lot of people who love what they do 22 years into their career. I come to work happy about it, excited at the possibilities every day.

UTMJ: The technologies, are they monitored by a live person or work by an algorithm?

BR: Currently there is a mix of both, but we are trying to make it completely automated so it is infinitely scalable. One of my colleagues, Dr. Heather Ross - her and I are actively monitoring patients in Doha, and her team is going to Uganda in the summer to monitor heart failure patients. There are currently 5 billion people on earth that have a cell phone compared to 2 billion that have a tooth brush. So we are trying to deploy this technology in Canada and around the world.

UTMJ: How do you advise patients regarding lifestyle modification to improve their cardiovascular status? Do you have any opinions on how to overcome the challenges to lifestyle modification?

BR: When you start out in practice, you say things to patients like "if you don't stop smoking, you know, you are going to have a heart attack or a stroke or lose your leg" etc. depending on what the cardiovascular disease is. But that is completely, or almost completely useless. Less than 7% of people will stop smoking because you tell them they shouldn't smoke. All patients say they want to stop smoking - if you ask a patient if they smoke and they say no, you can't stop there, you have to ask when they had their last cigarette, because many patients say they had their last cigarette this morning. So they aren't lying [to you], but you know they have a pack of players in their pocket, yellow finger tips, etc.

When it comes to getting people to adhere to stopping smoking, yes you do need to carefully explain the consequences of smoking, but you also need to engage them with support systems such as group therapy, psychological counselling, and suggest pharmacological agents because there are multiple drugs available, none of which on their own are extremely effective, but in combination with advice and therapy they can be effective. If you do these things, perhaps 40-50% of patients will stop smoking long term. In the real world, the risk factors for cardiovascular disease are smoking, smoking, smoking and the rest.

UTMJ: When you see patients who have been very much affected by vascular disease, but are still smoking, how do you counsel these patients when you know there may not be a significant change in their behavior or outcomes?

BR: Try to have some empathy. Smoking can be more addictive than heroine. I remember a while ago - I was on staff maybe 5 years - and I was coming into the hospital in February during a blinding snow storm. There was a patient sitting outside, bilateral above-knee amputations with a 'trache' (tracheostomy tube) and he was smoking through his 'trache'. You have got to be really addicted to be out in the freezing cold and smoking through your 'trache'. So, none of that [weather conditions, tracheostomy tube, etc.] really mattered. I think it is important to recognize how difficult it is for patients to quit smoking.

UTMJ: What is the impact of prevention vs. treatment on cardiovascular disease?

BR: An ounce of prevention is worth a pound of cure. And we are trying very hard to focus much more on prevention. Purely from a health economics point of view, it is much less expensive to our healthcare system if you can get somebody to stop smoking than to treat the consequences of their smoking.

UTMJ: What are some of the recent advancements that have been made in achieving better CV health and treating CV disease?

BR: There are some trials that suggest certain medications are of benefit. Some of them are controversial - should we take an aspirin a day or not? Should you aggressively lower cholesterol or not? There seems to be pretty good evidence for lowering cholesterol, but there are

downsides to it - there are some people who get muscle pains that are difficult to manage. Should you prescribe a coQ10 (coenzyme Q10) inhibitor or supplement at the same time as you are prescribing a statin? How low should your blood pressure be? Should it be 140, 130? Seems like the blood pressure thresholds are getting lower and lower so I think there are a lot of risk factors that you can modify.

UTMJ: What is the greatest barrier to optimal cardiovascular health today?

BR: Probably the combination of lack of exercise, failure to modify risk factors and perhaps our lack of a real understanding of what the genetic predisposition is to cardiovascular disease. So one of the things that's going to happen in the future is it's going to be commonplace for patients to have full exome sequencing and for us to have the big data capabilities to look at cohorts of patients with cardiovascular disease and identify the SNPs and the exomes and the proteomic profiles that are associated with cardiovascular disease. This will be a combination of capability to process that amount of data - so called 'big data' - and to apply artificial intelligence algorithms, which is something we are going to be having a very big investment in at the Peter Munk Cardiac Centre. We will be able to mine this data and look for previously unrecognized associations.

There are many people who develop cardiovascular disease and there are very few that we have a good handle on [in terms of genetic underpinnings]. The real question is: when you identify that gene, what can you do about it? What's going to happen in the future? Will we edit those genes with CRISPR and fix the defects? Will we be able to develop molecular targeted drugs? The pace of knowledge acquisition is very rapid in medicine; it takes only 73 days for the existing knowledge to double!

UTMJ: What is your role in the treatment paradigm of a patient with cardiovascular disease?

BR: It's evolved over time. When I started in practice, I had done a PhD in muscle ischemia and had done ischemia-reperfusion research for many years while I provided clinical care. After about 10 years of that, I began to transition to administration. I was the head of vascular surgery for 9 years and have run the heart centre for the last 6 years. There's nothing like impacting one patient's care in a major way, and the type of specialty that I am in happens to be basically every case is either life or limb: aortic aneurysms, ischemic legs, impaired circulation to your brain. Especially those cases where someone comes in ruptured and ends up leaving the hospital... there's nothing like that. And then if you do health care policy, you can improve how we do research and how the overall system behaves to manage patients with cardiovascular disease. You can impact thousands of patients in Ontario and by extending what we learn around the world, it can affect millions of patients.

It's also fair to say that operating is hard. It's physically demanding. The cases we used to do were 6-8 hours, bent over, and sewing small stuff. I still don't get tired in the operating room, but now it takes me longer to recover. That's just the reality of how it goes and it has also changed since we do most cases under image guidance...you have to wear 10-15 pounds of lead and be careful about radiation exposure. So, it is a dangerous undertaking.

UTMJ: What are your research interests?

BR: I did muscle ischemia-reperfusion injury research for 17-18 years. The first 6 grants that I put into CIHR were rejected - I would answer all the questions and I would get a lower score the next time around than the first time around. There was no rhyme or reason for this and you must be fairly stubborn to continue. The reality is, I was interested in molecular biology and cell signaling. It didn't matter to me so much if it was skeletal muscle or heart muscle and one day, someone said, "There's a lot of money in heart." So, I literally made a copy and replaced the word 'skeletal' with the word 'heart' - proper citations and all. After that I had 17 years in a row of funding from CIHR. The second time I applied, I got rated 1 out of 44. I was so insecure about the whole thing that I called Ottawa and said, "Hey, does this mean I finished first or last?" (laughs). So research is phenomenal. There is something magical about knowing something (when you make a discovery in the lab) that no one knows.

I took a different approach to research. Every fifth week for the first four or five years, I did no call, no operating and saw no patients, I just did research. Of course, during the other four weeks, I had to do five weeks' worth of clinical work because that is how it works. I never published any papers that had the word surgery in the title. People on the grant review panels needed to see basic science papers. I told my guys in the lab that I want one paper every year in a really high impact basic science journal. We published 10-12 papers in really good journals. That turned out to be a really good idea because it is really hard to get funding. It borders on a superhuman effort to compete with people who are doing full-time research at a federal level and, at the same time, do clinical care and throw in a little administration. It's challenging!

Partenariat Santé: Students in Health Care Programs Join Their Efforts to Fight Cardiovascular Disease in a New and Innovative Way in Québec City

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Introduction

Cardiovascular disease (CVD) is a major public health concern, responsible for 30% of all deaths world-wide and is on the rise through all over the world.[1] The term 'CVD' refers to a spectrum of disease, including myocardial infarction and cerebrovascular events, among others. Canada has not been spared from this health problem. According to the Canadian Institute of Health Information and Statistics Canada, 1.3 million Canadians suffer from heart disease (2007), 315 000 have experienced stroke (2009), and over 6 million aged 20 years and older have hypertension (2007-2009).[2]

CVD represents a major financial burden to society. In 2000, CVD was estimated to be the second most costly health-related problem in Canada, with an estimated cost of 22.2 billion dollars/year.[4] Since hypertension is a major risk factor for the development of heart disease, the World Health Organization has insisted on the development of health programs aimed at controlling hypertension (2012).[3] The idea of these programs is that by targeting hypertension, the ever-increasing human and financial cost of CVD could be curbed.

Fortunately, the rise in CVD incidence may be mitigated through early detection, public awareness, and control of preventable risk factors (e.g., adopting a healthier lifestyle). To set-up an efficient community-based program targeting the detection, awareness and control of modifiable CVD risk factors, we considered the methodology and operational-framework of the CHAP study (Cardiovascular Health Awareness Program).[5,6] CHAP is a community based program that "brings together local family physicians, pharmacists, other health professionals, public health representatives, volunteers, and health and social service organizations to work together to promote and actively participate in the prevention and management of heart disease and stroke."[7] Participants of the CHAP study (mean age = 67 years), who were followed for 18 months, showed a reduction in systolic blood pressure (from 142 to 123 mmHg on average) and in diastolic blood pressure (from 78 to 60 mmHg on average). Participants ≥65 years of age also showed a 9% reduction in hospitalization rates for cardiovascular-related causes for one year following the study end. These promising results inspired our team to start a similar community-based program in Québec City, albeit with less financial and technical capacities than CHAP. This program was established in January 2016 and is named '*Partenariat Santé*'.

How *Partenariat Santé* Works

The philosophy behind *Partenariat Santé*

Partenariat Santé offers free services via a volunteer-based model; volunteers are students in various health sciences programs, such as occupational and physical therapy, kinesiology, medicine, nutrition, pharmacy, biomedical sciences, and nursing. *Partenariat Santé's* proposed solution to the detection, awareness and control of modifiable CVD risk factors centres on an interdisciplinary approach. This approach facilitates the sharing of knowledge and skills and the development of targeted solutions.

Multidisciplinary work offers two distinct advantages. First, it provides participants with a more comprehensive service, and second, it allows student volunteers to develop the collaborative skills that they will inevitably need for their professional careers. As such, *Partenariat Santé* benefits both participants and student-volunteers.

Partenariat Santé has four main goals and involves multiple steps:

1. Measuring blood pressure and waist size.
2. Assessing the modifiable risk factors of CVD (as described in Hypertension Canada's guidelines.[8])
3. Establishing a targeted action plan based on the participant's desired lifestyle change(s).
4. Suggesting various locally available community resources that could help in achieving the established goal.

In order to achieve the best outcome for participants, *Partenariat Santé* used motivational interviewing, a process initially developed by Stephen Rollnick to help health care

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professionals encourage change in their patients' behaviours and/or habits.[9]

Target Population

Partenariat Santé offers its services across the greater Québec City area, with community meetings held within businesses, sport complexes, shopping centers, and aboriginal reserves. The inclusion of these diverse locations enabled the targeting of a population of participants who span multiple cultural and socioeconomic classes. We believe this diversity is a key strength of *Partenariat Santé's*.

Volunteer Training

In order to ensure the provision of a high quality standardized service, all volunteers were trained by the administrative council of *Partenariat Santé* and by a professor of the Faculty of Pharmacy at Laval University.

During this training, the philosophy, mission and values of *Partenariat Santé* were presented, along with various tools available to volunteers.

Sequence of Events

The sequence of events is presented in figure 1.

Figure 1. Flowchart presenting the major steps of *Partenariat Santé* meetings

Pre-Meeting Preparation

1) Local community resources (e.g. walking clubs, health clubs, nutritionists, and smoking cessation programs) are identified and contacted; a list of contacts for volunteers is generated.
2) Events are publicized a few days before the meeting is held through various mediums, including the broadcast media (local newspaper, radio and television), Facebook, and on our website.
3) A physician is contacted so that he/she will be present at the meeting.

Proceedings during a Session

1) The location of the event is setup.
2) Participants are welcomed and the goals of the proceedings are explained (in two steps):
3) STEP 1 is performed by a team of 'on-site assistants:'
   - Blood pressure (using an automated Blood Pressure monitor) and waist size are measured.
   - A survey designed to identify relevant lifestyle habits and modifiable risk factors is distributed.
4) STEP 2 is performed by a 'consulting team':
   - Increasing participant awareness: participants are informed of their cardiovascular risk and provided with a pamphlet on the Canadian recommendations regarding cardiovascular health.
   - Controlling Risk Factors ('closing the loop'): participants undergo one-on-one motivational interviewing. Risk factors and willingness to change are discussed and participants are directed towards the appropriate resources.
   - Pamphlets containing information on useful community resources are distributed.
   - Finally, participants are invited to sign an action plan as a way to symbolically 'finalize' their commitment to change. This action plan specifies what habit they wish to change, how they intend to achieve this goal, a timeframe for completion, what their motivations are and what challenges they expect to face.
   - Conclusion of session: participants are thanked for their time and referred to the local resources that can best help them.

Organizing Conferences on CVD Prevention

Partenariat Santé is committed to promoting healthy lifestyle habits within the population by inviting renowned speakers to talk about nutrition/dietetics, physical exercise, biomedical promoters and the lifestyle changes associated with reducing cardiovascular events.

Annual Report and Results

In the span of one year of community engagement, more than 120 student volunteers became involved in *Partenariat Santé*. The program has had more than 500 participants, of which 15% had blood pressure values well over the Canadian standards. This finding is consistent with the statistics reported by the Canadian Institute of Health Information and Statistics Canada,[2] and highlights the ecological validity of our initial sampling.

Future Developments

In order to pursue its mission as a promoter of strong cardiovascular health, *Partenariat Santé* will be expanding along four major axes:

1) Engaging new community partners (e.g., local pharmacies and nursing homes) and promoting *Partenariat Santé* by continuing to contact local social service and medical health providers and by maintaining an informative and up-to-date web page will also be maintained (https://www.partenariat-sante.com).

2) Initiating a comprehensive and longitudinal research program to assess the impact and added clinical value of *Partenariat Santé's* services for the health of Québec city residents. By focusing on the development of a data-driven community program, we will be able to measure the impact of our efforts. Running analyses will also have the added benefit of allowing us to adjust and improve our program. It is our hope that a data-driven program will ultimately lead to concrete benefits for the population of at-risk individuals.
3) Develop an efficient bi-directional referencing-system between *Partenariat Santé* and local health clinics to ensure that patients get quick and optimal health care.
4) Measure additional cardiovascular risk factors (hyperglycemia and hypertriglycemia). This will require the purchase of new automated cholesterol and glycated hemoglobin monitors.

Recognition of Excellence

Partenariat Santé's commitment to the promotion of cardiovascular health in Québec City has been awarded multiple honours and distinctions by various Faculty bodies at Laval University (Faculty of Medecine 2016, RAESSUL 2016 and 2017). In 2016, *Partenariat Santé* won the Faculty of Medicine's 'Dean's Prize,' a prestigious award given in recognition for our contribution to faculty life. The success of the program is also demonstrated by the awarding of the Edward-Assh and Alain-Cloutier scholarships to the founder of *Partenariat Santé*.

The extent of *Partenariat Santé's* influence extends beyond the academic sphere, as can be appreciated by its numerous clinical partnerships. These include, but are not limited to, partnerships with the Fédération des Médecins Omnipraticiens du Québec (FMOQ; union of Québec general practitioners), Fédération of Kinesiologists of Québec, Alliance Santé Québec, l'Association des Diabétiques de Québec, as well as with numerous physicians across Québec City.

Conclusion

The purpose of the *Partenariat Santé* program is to promote cardiovascular health in the Québec City area and to help bridge the gap between individuals, community organizations, and healthcare professionals. CVD is a major cause of morbidity and mortality for Canadians and this evidenced-based community program aims to address this key healthcare issue. Most importantly, *Partenariat Santé* offers a concrete approach to the prevention of CVD.

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Organ Trade between Kidney Donors and Recipients: A Case of Transplant Tourism

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Introduction

Kidney transplantation has gained recognition as an effective therapy for end-stage renal disease.[1-3] Over the past decade, there has been a global increase in the number of patients with end-stage renal disease coupled with a shortage in the supply of indigenous kidneys.[4] These issues have fueled the development of "transplant tourism", where potential recipients travel abroad to obtain organs from donors through commercial transactions.[5] Transplant tourism accounts for approximately 5-10% of the kidney transplant procedures performed annually across the world.[6]

During the 21st century, numerous unfortunate cases of brokers, physicians, and hospitals engaged in illegal organ trades have been featured in the media.[7-8] Postings on websites have offered all-inclusive "transplant packages", where the price of a renal transplant package ranges from US$ 70,000 to 160,000.[5] Transplant tourism highlights the ethical issue of exploiting vulnerable organ donors and potentially causing physical and psychosocial implications for organ recipients.[7]

The purpose of this editorial is to:

1. illustrate a hypothetical case of organ trafficking from the perspectives of the donor ("seller") and the recipient ("buyer");
2. increase public awareness of the medical, psychosocial, and ethical implications of transplant tourism using a cost-benefit analysis; and
3. highlight public health measures that should be implemented by governments, healthcare providers, and policymakers to halt transplant tourism.

The Story of Fiona – A Kidney "Buyer"

Fiona is a 35 year-old woman with deteriorating kidney function. She receives hemodialysis treatments three times each week, with each treatment lasting between three to four hours, at a medical clinic in the United States. Although dialysis relieves symptoms of uremia, she finds it inconvenient and time-consuming to devote such a large amount of time performing this treatment on a continual basis.

Fiona was placed on the waiting list for a kidney transplant for the past 3 years. Unfortunately, her position on the waiting list has not progressed much over this time. In the US, there are over 100,000 patients waiting for a kidney transplant, with an average wait time of five to ten years.[3] Desperate to avoid this lengthy waiting time, Fiona posted an advertisement on an Indian website ("The Organ Trade") to request a kidney donation in exchange for US$ 80,000. She knew that India is one of the most common organ-exporting countries, where organs from local donors are regularly transplanted to foreigners through sale and purchase.[5]

Within one week of posting the advertisement, she received a phone call from an anonymous transplant agency in India informing her that a woman was willing to donate a kidney to her. Fiona was ecstatic to hear that the "gift of life" was awaiting her in India. She immediately made arrangements to travel to India to purchase the kidney from the anonymous donor and undergo the transplant surgery. Two days after her transplant surgery, she quickly returned to her hometown in the United States. Consequently, she suffered numerous post-transplant complications, which subsequently led to graft failure and the need for dialysis again.

It is evident that the transplanted kidney was poorly matched between the donor and the recipient, as neither parties underwent the standard pre-transplant medical evaluation to determine their suitability and compatibility for transplant. This event has reduced Fiona's chances of ever receiving another kidney transplant, as her immune system is now highly sensitized from the previous transplant.

The Story of Arif– A Kidney "Seller"

Arif is a 19-year-old teenager from India who hoped to purchase the latest 64 GB iPad from Apple Inc. However, he was unable to afford this luxury item given his financial constraints. In order to earn extra cash, he called the number in the classified advertisement posted on the Indian website ("The Organ Trade"), which offered a huge monetary com-

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pensation in exchange for a kidney. Although Arif was aware that there may be life-threatening consequences associated with a kidney transplant surgery, he still made the decision to donate his kidney for monetary compensation.

The following week, Arif underwent a surgical nephrectomy. Subsequently, he used the compensation he received to purchase a 64 GB iPad. The joy of possessing something he had always dreamed of seemed to overcome the physical pain caused by the surgery (at least initially). Arif spent several hours every day playing trendy games such as Angry Bird and Fruit Ninja on his new iPad. Within one week, he became a popular person in school – the guy with a shiny iPad and an 'attractive' scar.

Unfortunately, the joyful addiction of 'fame and game' did not last long. Arif was eventually hospitalized due to the intense abdominal pain that radiated through his surgical site. During his nights at the hospital, he suffered other complications including bleeding, fatigue, and nausea. He felt disembodied for selling his kidney and lost his sense of human dignity. Ironically, Arif's economic condition actually deteriorated after the surgery, despite the initial monetary windfall. Not only did he drop out of school, but he also accrued debt from the large medical expenses associated with his post-operative care.

Discussion

This hypothetical case of organ trafficking from the perspectives of the donor and recipient illustrates the dismal side of transplant tourism. Is this organ trade worth it? It may be wise to do a cost-benefit analysis from the perspectives of buying and selling a kidney (Table 1). While transplant tourism may bring short-lived benefits among organ sellers, it often leads to declined quality of life, economic loss, post-operative complications, loss of dignity, and social stigma.[9-12] Using a cross-sectional study of 305 kidney sellers, Goyal and colleagues found that most of the monetary compensation was used to pay off personal debt. However, the average family income declined by one third after nephrectomy ($P<0.001$), and the number of participants living below the poverty line increased.[12]

For organ buyers, transplant tourism is associated with numerous acute complications (e.g. urinary infection, acute kidney injury, graft rejection) and chronic complications (e.g. poor kidney function, graft survival, and overall survival) that can result in graft failure and need for dialysis.[13-18] Compared to domestic transplant recipients, transplant tourists have significantly higher cumulative incidence of acute rejection at 1-year post-transplant ($P=0.02$).[17] Moreover, another study reported that transplant tourists were at higher risk for developing donor-transmitted viral diseases such as hepatitis B and cytomegalovirus infections.[17]

In light of these detrimental effects of transplant tourism, public health measures are currently being developed and implemented by governments, healthcare providers, and policymakers to halt transplant tourism. The federal government has implemented initiatives such as the Organ Donation Breakthrough Collaborative to increase the legal donor pool in developed countries such as the United States, Canada, and Australia.[4] Physicians and health professionals play a key role in raising awareness of organ trafficking and promoting collaborative, evidence-based measures to prohibit transplant tourism. Furthermore, policymakers have suggested changes in the policies of deceased organ donation to that of "presumed consent", which mandates that every deceased individual becomes a potential organ donor unless he or she specifically refuses to consent.[4] It is imperative for developing countries (especially those with a strong history of organ trafficking) to develop a judicial infrastructure to regulate organ procurement and promote ethical considerations within the healthcare system and the public. Further research should be devoted to explore alternatives such as the large-scaled paired donor-recipient exchange program and strategies to promote living donation.

Table 1. Potential Benefits and Costs of Selling and Buying a Kidney

Selling a Kidney		Buying a Kidney	
Benefits	**Costs**	**Benefits**	**Costs**
Monetary compensation	Single kidney	Extra kidney (i.e. "gift of life")	Risk of graft rejection or graft failure
Overseas visa (if transplant occurs overseas)	15-20 inch permanent scar (if open nephrectomy)	Quick way to receive a kidney	Sensitization of the immune system
Purchase of luxury items (e.g. iPad)	Post-surgical complications (e.g. bleeding, infection)	Free from long-term dialysis	Poor post-operative management
	Symptoms from impaired kidney function (e.g. generalized fatigue)		Exploitation of the poor
	Social stigma (e.g. loss of human dignity and integrity)		Poor kidney function, graft survival, and overall survival rate
	Economic issues (e.g. unemployment, school drop-out)		

Conclusion

The altruistic act of organ donation, or bestowing "a gift of life", is being tainted by an increased incidence of organ trafficking. From the case study, it is evident that both the kidney "seller" and "buyer" experienced medical and psychosocial complications after their transplant. Such an illicit act raises the ethical issue of exploiting vulnerable organ donors and potentially causing severe medical and psychosocial implications for organ recipients. Considering its benefits and risks, transplant tourism should not be performed or promoted under any circumstances. Public health measures are currently being developed and implemented to halt transplant tourism, which include establishing a regulated and ethical system of organ procurement, promoting paired donor-recipient exchange programs, and increasing awareness of organ trafficking among healthcare providers and the public.

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Challenges and Priorities Ahead for the WHO's Incoming Director-General

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In May 2017, the 194 member states that make up the World Health Assembly will have met in Geneva, Switzerland to select the World Health Organization (WHO)'s new Director-General. This decision will impact the health of hundreds of millions of people around the world, and particularly those from developing nations. Each Director-General serves a five-year term, earns a salary of about $240,000 USD, and oversees the world public health agency's $4 billion budget.[1] The changing international political landscape and the selection of the next commander-in-chief at the WHO has brought into the spotlight the question of what the WHO's role will look like in the international public health arena moving forward. Margaret Chan, the current Director-General who obtained her medical degree from the University of Western Ontario in Canada, made the health of Africans and women the focus of her first term which began in 2006.[2] After she was elected for a second term in 2011, she pledged to work for universal health coverage, which she deemed "the single most powerful concept that public health has to offer."[3] Fast forward to 2017 and many are questioning whether the WHO holds the same clout as it did once upon a time. Chan's successor will have the job of challenging this perception. He or she needs to bring strong political leadership and priorities to the table to re-establish the WHO as a competent and accountable body.

The most recent test of Chan's leadership was the Ebola epidemic. Chan and the WHO were heavily criticized for their delayed response to the epidemic as it took them six months to declare Ebola as an international emergency.[1,4] The epidemic claimed thousands of lives and mainly affected Guinea, Sierra Leone, and Liberia. But the problem does not lie solely within the WHO. One must only look to the way the WHO is structured to see that the problems run deeper.

For one, as they say, *follow the money*. The WHO is funded through two main methods. The first is from core contributions, where each member state provides the WHO with a certain amount of money to go towards their core operations. This accounts for approximately 20% of their $4 billion budget. The remaining 80% comes from voluntary contributions, where countries provide the WHO with money targeted towards specific initiatives.[1] This money comes with strings attached and depends on the donor country's priorities, which is precisely where the problem lies. Every country has their own priorities, which mainly depends on their politics. This significantly restricts the WHO's ability to practice evidence-based decision-making and respond effectively to spontaneous global health emergencies, as we saw in the case of the Ebola epidemic. An issue that follows as a direct result of their financing structure is that global health interventions tend to be vertical rather than horizontal. That is, they tend to target specific diseases and issues rather than being holistic and targeting health systems. This is not a sustainable solution. There is also the question of accountability. How do we know what's working? Who determines the standards and criteria of a "successful" project? Who does the WHO report to? In most cases, it is the wealthy donor countries. This takes away the power of priority-setting from the poorer recipient countries who better know and understand the needs of their people. Consequently, there is a clear power differential in the global health aid structure that must be addressed. The global health arena is saturated with an ever-increasing number of actors and initiatives. The incoming Director-General will play the role of balancing the interests of this crowded field of stakeholders, from private actors to non-governmental organizations, with the interests of those in need.

There are also many instances, however, where the WHO has been quite successful. Once they declared Ebola to be an epidemic, they were able to significantly expedite the process of developing a vaccine to address the virus.[1] Other notable accomplishments of the WHO include establishing the framework convention on tobacco control in 2003, advancing a successful campaign towards the eradication of polio, decreasing maternal mortality rates, improving access to antiretroviral therapy for HIV/AIDS, and putting mental health on the global agenda.[1,5,6,7] Much of the WHO's successes are due to the agency's unique ability to quickly bring together multiple stakeholders and actors, from scientists to politicians to industry to public health officials. This is arguably the WHO's biggest strength, and is one that the incoming Director-General must capitalize on in order to achieve their priorities.

At the time of the May vote, there were three candidates vying to take on the WHO's top position, one each from Africa, Asia, and Europe: Tedros Adhanom Ghebreyesus of Ethiopia,

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David Nabarro of the UK, and Sania Nishtar of Pakistan.[8] Tedros is a former minister of health and foreign affairs in Ethiopia, and the only candidate who is not a physician. He has the backing of the African Union, who believe it is time for someone from their region to take the helm. This gives him the potential vote of 54 countries, although he will still need the support of many other regions in order to win.[12] Tedros has made universal health coverage the major focus of his platform, while also emphasizing women, children, and adolescent health, health security, and health impacts of climate change.[13] This is important since it is well known that women and children often have unmet health needs due to lack of access. Equitable access to health care is also a key Canadian value which Canada aims to promote around the world. At home, we have seen the benefits of having universal health coverage, which ensures people are able to access health care based on need instead of income. Health Minister Jane Philpott, who voted on behalf of Canada in May, will ideally have considered each candidates' position on this matter when determining who she was going to vote for. It should also be noted that Tedros has been criticized by some in Ethiopia for his political party's involvement in suppressing dissent, although he has not been personally accused of participating.[16] On the other hand, as Minister of Health, he reportedly trained tens of thousands of female health workers, significantly increased the number of medical school graduates, and reduced child mortality by two-thirds, HIV infections by 90%, and malaria and tuberculosis mortality by 75% and 65%, respectively.[13]

David Nabarro has said that as Director-General, he will champion "people-centred" health policies, align the WHO with the Sustainable Development Goals (SDGs), and solidify the WHO's capacity for global disease outbreak prevention.[14] A physician himself, he has managed many of the United Nations agencies' responses to challenges including Ebola, malnutrition, food insecurity, avian flu, and cholera in Haiti.[14,16] He is widely considered as the frontrunner and many see the race as a runoff between him and Tedros. His commitment to delivering results on the SDGs and ensuring strong disease outbreak systems is commendable. However, whether he will be able to change the face of the WHO and create progress on universal health care remains unknown. Interestingly, he only mentions universal health coverage once in his written statement.[14] Nabarro was strongly backed by the British government and seemed to be favoured by Western countries, although none have publically endorsed him.

Sania Nishtar is a cardiologist who briefly served as Health Minister in the 2013 Pakistan caretaker government. In 1998, she founded a successful NGO called Heartfile with the goal of improving health systems, and has championed women, children, and adolescent health issues through her service on various WHO committees. She was the chair of the UN Secretary General's Independent Accountability Panel for the Global Strategy for Women's, Children's and Adolescents' Health and co-chair of the WHO Commission on Ending Childhood Obesity.[15] Nishtar's campaign platform highlights the importance of collaborative leadership and supporting countries to achieve the SDGs.[15] Although she lacks experience comparable to Tedros and Nabarro, who both have significant experience leading and managing national and international health and global disease response systems, it may not necessarily be a bad thing to have someone from outside the status quo at the helm.

Regardless of who is elected, they will all have to advance the principles of the SDGs, enhance the global emergency health response system, address sexual and reproductive health rights, and combat the rising threat of non-communicable diseases.[9] There have been consistent calls from NGOs and civil society that the new Director-General must be willing to stand up to commercial and donor interests and put human rights and public health first.[8] This comes from the striking reality that while scores were suffering from HIV/AIDS, pharmaceutical companies, donor countries, and the World Trade Organization were more concerned about protecting the intellectual property rights of drug manufacturers.[10,11] The persistence of inequalities in global health is also a concern. Women, immigrants, and ethnic and sexual minorities endure a disproportionate amount of discrimination and marginalization which has a direct impact on their ability to access health.[10] The WHO needs to empower both state and non-state actors to minimize these disparities. Lastly, the new Director-General should and must prioritize the task of working with stakeholders, including civil society organizations, to establish rigorous accountability and transparency mechanisms to ensure the right steps are being taken forward.

In an increasingly globalized and interconnected world, the WHO plays an instrumental role in influencing the public health agendas of nation states. It acts as a neutral third party that sets the norms and standards for various health measures and is a coordinating body for research and development. The WHO determines things such as which generic drugs are safe and how diseases are best treated. When the Ebola outbreak occurred, it was up to the WHO to provide guidelines for public health safety measures which most countries adopted. When Zika broke out, it was the WHO that provided guidelines to health care professionals and public health officials on how to advise women who wanted to get pregnant. They also launched the Zika Open platform that allowed critical research on the Zika virus to be accessible to researchers around the world in order to facilitate collaboration and learning.[17,18] In Canada, the WHO has pushed for the recognition of the growing epidemic of non-communicable diseases via the Public Health Agency of Canada's WHO Collaborating Centre on Chronic Non-Communicable Disease Policy.[19] The aim of this partnership is to work with national and international partners to increase knowledge of chronic disease policy, so that it can be translated into practical guidelines for how to advise and treat patients with chronic disease. Clearly, the incoming Director-General will play a vital role in influencing the direction of global health policy for years to come. Indeed, as our world changes, the challenges that physicians face in treatment and prevention will also change, and the WHO election is important as it will set the tone for how such changes should be dealt with.

Health is a political subject, and the WHO is not immune. Each member state has voted for Chan's successor according to their political motivations. What is important is that the

new Director-General learn from the WHO's past and remain committed to strong leadership rooted in human rights, accountability, and public health. The lives of millions of people depend on it.

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The Time is Right for a National Pharmacare Program for Canada

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Abstract

The World Health Organization has declared that all countries should have universal health coverage, ensuring equitable access to treatment and necessary medicines for every patient. Canada is the exception among developed countries with universal health care systems, in that it does not also provide universal coverage for prescription drugs. Out-of-pocket costs for prescription drugs are a significant barrier to treatment for millions of Canadians. In addition, Canada's fractured system of individual provinces and territories negotiating the purchase of their own medicines has diluted Canada's purchasing power and has led to some of the highest drug costs in world. In December 2016, a Citizen's Reference Panel on Pharmacare in Canada recommended the creation of a new national formulary for universal publicly covered medicines, and in April 2017, the Ontario government announced it would cover prescription medications for everyone under the age of 25. A national pharmacare program could provide equal publicly-funded drug coverage to all Canadians regardless of where they live, and through a single national purchasing body and lower administrative overhead, reduce the cost of drugs by consolidating Canada's purchasing power. This program could begin with a list of essential medications, and eventually expand to include a comprehensive list. With strong public support for increasing affordability of and equitable access to medications for all Canadians, clear benefits to health outcomes, and evidence from other countries with single purchaser systems of lower drug costs, the time is right for the provincial, territorial, and federal governments to take action and create a national pharmacare program.

Canada's modern healthcare system was conceived in 1966, when the federal, provincial and territorial governments created the *Medical Care Act*. Founded on the four principles of universality, comprehensiveness, portability, and administration, the act's intention was for all Canadians to have access to medically necessary care, with no point-of-care charges, anywhere in Canada. Over the next 50 years, the services and medications covered by each province drifted apart. Each province has a different formulary of publicly-covered drugs, and individually negotiates their purchase from pharmaceutical companies at different prices and with less bargaining power than a single national purchaser would. A national pharmacare program, with a single national body negotiating the purchase of drugs which would be publicly covered for everyone, would reduce the cost of drugs and ensure equal access for all Canadians, regardless of where they live.

Since Medicare was founded, drugs have become a significantly more expensive part of the cost of healthcare in Canada. While spending on Medicare's core services – hospitals and physicians – has declined relative to other areas of health spending, the cost of drugs has risen to 16.0% of total healthcare costs in 2014, exceeding the cost of physician services (15.3%).[1] Drugs now represent the second largest healthcare budget expenditure after hospitals, totaling $34.6 billion in 2014 ($29.4 billion for prescribed drugs).[1] Hospital stays are now much shorter, and with Medicare only covering doctors' and hospitals' services, this has shifted the cost of prescription drugs onto patients.

While most Canadians have some form of supplemental health insurance, which can help with out-of-hospital drug costs, there are still millions of Canadians who fall through the cracks and are left to pay for their medications out-of-pocket. Out-of-pocket payments account for 22% of prescription drug spending, as approximately 11% of Canadians do not have prescription drug coverage, and a total of 20% of Canadians report being uninsured or underinsured, in that a majority of their prescription drug costs are paid for out-of-pocket.[2] In 2014, the average out-of-pocket annual health expenditure per person reached $868, having grown at an annual rate of 4.5% since records began in 1988.[1]

Paying for medications out-of-pocket can be prohibitively expensive, especially for patients with low incomes. Often, patients may take their medications less frequently than they should so the medications last longer, accumulate debt to pay

for their prescriptions, or forego medications altogether.[2] An estimated 10% of Canadians cannot fill prescriptions because of the expense.[3] Cost-related non-adherence to medications is reported by 26.5% of those without insurance, compared to only 6.8% by those who have insurance.[4]

It is well known that drug coverage, and socioeconomic status more broadly, correlates with health outcomes, morbidity, and mortality.[5] Of Canadians with an income less than $50,000, one in three (31%) reported they or someone in their household did not take their medications as prescribed due to cost.[2] This was roughly double the reported rate (16%) among Canadians with incomes over $100,000 (the reported rate including all incomes was 23%).[2] A 2012 study estimated that as many as 5000 deaths associated with diabetes between 2002 and 2008 of working-age Ontarians could have been prevented by equal publicly-funded prescription drug coverage, similar to that available to people over the age of 65.[6] The current mixed system of private and public insurance coverage as well as out-of-pocket payment for drugs in Canada only serves to reinforce the inequitable impact of socio-economic status on health outcomes.

Most Canadians are covered by supplemental health insurance and many provinces have legislation to cover the poor and elderly. This helps explain the lack of political will for the creation of a national pharmacare program. However, a 2015 survey by Angus Reid found that an overwhelming majority of Canadians (91%) support the concept of a national pharmacare program that would provide universal access to prescription drugs (51% voiced "strong' support).[2] Similar support was found in other surveys published in 2015 and 2016.[7-9]

Two noteworthy events in the past 6 months may be indicative of increasing momentum in public and government support for pharmacare in Canada. On December 6, 2016, the report of the Citizens' Reference Panel on Pharmacare in Canada was presented to the House of Commons' Standing Committee on Health. The panel of 35 members of the public was randomly selected in such a way as to be demographically representative of the Canadian population.[5] The panel heard testimony from twenty experts with diverse viewpoints, including doctors, pharmacists, pharmaceutical and insurance industry representatives, academics, and patient representatives.[5] After examining the options, the Citizen's Reference Panel recommended the creation of a new national formulary for universal publicly covered medicines accommodating the full range of patient needs.[5]

The panel's report stresses that there is a lack of public awareness of the issue of insufficient drug coverage for Canadians without supplemental insurance, and its negative effect on health outcomes, as well as the regional variability in service, access to drugs, and the price of medications.[5] The panel recommended the creation of a universal mandatory public drug insurance system that would provide coverage to all Canadians, including for rare diseases, with private insurance restricted to covering medications not included on the national public formulary.[5] The program could begin with a list of essential medicines that would be covered for all, and expand to cover the complete formulary of medications, approved based on clinical value and cost-effectiveness.

In an article published in February 2017 in the Canadian Medical Association Journal, Morgan *et al.* reported that universal public coverage of 117 essential medicines–accounting for 44% of all prescriptions and 30% of total prescription drug expenditures in Canada – would save $4.27 billion per year, a reduction of 28%.[10] The incremental government cost of the program was estimated to be $1.23 billion per year.[10] While shifting the cost of out-of-hospital medications from private insurance to a tax-funded model would reduce out-of-pocket costs for patients, it would likely require modest increases in tax rates. In March 2017, Adams and Smith published a review that assessed the cost of proposed pharmacare plans.[7] In it, they cited Gagnon's 2014 proposal which estimated the total prescription drug costs in a pharmacare program at $18.8 billion, or $6.8 billion greater than the $12.0 billion level of funding in 2012.[7] However, Gagnon noted there would be additional savings of $2.5 billion through elimination of both administrative overhead from private plans and tax subsidies.[7] The tax exemption for private health and dental plans is projected to cost the federal government $2.9 billion in 2017.[7]

Political will may also be shifting in favor of pharmacare, with the announcement by the Ontario Liberal government in April 2017 that it would be the first province to provide free coverage for anyone under 25 years old starting from January 1, 2018.[11] The 4400 medications included in this plan would be the same as the current Ontario Drug Benefit (ODB), which is limited to those on social assistance or over the age of 65.[11] The extension of pharmacare benefits to under-25s would double the number of people covered for prescription medications in Ontario, from 3.9 to nearly 8 million.[12]

This announcement by the government of Canada's most populous province, which has also called on the federal government to create a national pharmacare program, may signal a change in the willingness of governments to support pharmacare. The Ontario NDP has also made a pharmacare proposal which would cover everyone regardless of age, but would only extend to a list of 125 essential drugs.[11] Both programs have a similar annual cost, estimated at $465 and $475 million for the Liberal and NDP plans, respectively.[11]

At the federal level, the Green Party announced in July 2015 its support for a national pharmacare plan, which is said would save up to $11 billion annually and provide access to prescription drugs for 2 million Canadians who would not otherwise be able to afford them.[13] This plan would adopt the four key recommendations of the Pharmacare2020 report: universal access to necessary medicines; fair distribution of prescription drug costs; safe and appropriate prescribing; and maximum health benefits per dollar spent.[13,14] The Pharmacare2020 report has already been endorsed by 281 professors and university-affiliated leaders in health policy, health economics, pharmacy, and medicine across the country.[15]

A significant proportion of the cost of the national pharmacare program could be offset by the savings that would be achieved through a single national drug purchasing body. Canada's multi-payer drug purchasing system is among the most expensive in the world because of its diminished purchasing power.[16] Prices for generic drugs are 79% higher than the median of prices found in the Organisation for Economic

Co-operation and Development (OECD), and brand-name drugs are 30% more expensive.[16] The current fractured system of 13 individual provinces and territories negotiating drug prices with pharmaceutical companies has less negotiating power than a single national body, which would have more leverage to drive down prices. In Europe, several countries have even joined together to form a supranational coalition to boost their collective bargaining power, negotiating with pharmaceutical companies as a bloc and exchanging data and records, as well as coordinating evaluation methods.[17] What started as a coalition between the Netherlands and Belgium in 2015 has now expanded to include Austria and Luxembourg, with the potential addition of Ireland in the near future.[17]

While the pan-Canadian Pharmaceutical Alliance (pCPA) has negotiated on behalf of the provinces, territories and the federal government in the purchase of some newly-approved brand name and generic pharmaceuticals, a single national purchaser could arguably negotiate from an even stronger position. As of April 2016, the pCPA has had some success in achieving price reductions through joint negotiations on 95 brand name and 18 generic drugs, resulting in savings of $712 million annually.1[8]

Despite the long-standing argument from the pharmaceutical industry that lower drug prices would result in less industry-funded research and development (R&D), this would be an unlikely result of the creation of a national drug purchasing body in Canada since there is limited novel drug R&D performed domestically, and drug development in Canada is in general targeted to an international market. Compared to the major markets of the US and EU, Canadian sales represents a relatively small revenue source for pharmaceutical companies at only 2.0% of the global market.[19] Therefore a decrease in Canadian prices would not be expected to have a significant effect on total profits. More than half of Canadian pharmaceutical production is exported, and more than two-thirds of the Canadian market is supplied by foreign imports.[19] Nevertheless, pushback from the pharmaceutical industry is likely to be a major hurdle in implementing a national pharmacare program.

Similarly, the private health insurance industry would likely oppose a national pharmacare program. The cost of managing a single-payer insurer in each province is estimated to be $1 billion less than the direct cost of managing dozens of public and hundreds of private drug plans, and represents a significant cost-savings opportunity.[16] However, a potential drawback of a national pharmacare program would be the resulting loss of revenue to supplementary health insurers from prescription drug insurance, creating a need to rescale the health insurance business in Canada.[7] Prescription drugs comprised 33% of insured benefit payouts in 2015, and support a large infrastructure that serves as backbone for other supplementary benefits, including dental, paramedic, and vision coverage.[7] An enhanced Medicare program could eventually look to provide publicly-funded coverage for these health benefits as well, which would further extend equal access to basic health services for all Canadians.

Amongst developed countries with universal health coverage, Canada is alone in not also offering universal prescription drug benefits, resulting in insufficient drug coverage for many Canadians and unequal health outcomes.[16] Canada has the highest drug prices in the OECD after the United States, with drugs accounting for 16% of health care costs in Canada. While instituting a national pharmacare program that included a single national drug purchasing body would consolidate Canada's negotiating power and lower drug prices, some have argued that more efforts should be made to lower drug prices first, before considering a pharmacare program. The federal Health Minister, Jane Philpott, has argued that given Canada has the second highest per-capita prescription drug prices, it would be irresponsible to lock in to these prices by adopting a universal pharmacare program at this time.[7,20]

The current Canadian drug coverage system does not provide equitable access to prescription drugs. A national pharmacare program could provide equal publicly-funded drug coverage to all Canadians, regardless of where they live. The cost of this program could be offset by the savings achieved by negotiating drug prices through a single national body, and through a reduction in the tax breaks employers currently receive for providing employee health benefits, as those would be largely replaced by the public program. A national pharmacare program would result in more equal access, affordability, and improved health outcomes for Canadians. By announcing in April 2017 its pharmacare program for under 25s, the Ontario government has opened the door to pharmacare programs in Canada and brought this issue into the spotlight. There is clear public support across the country for pharmacare, and it should be a key priority for provinces, territories and the federal government.

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Preventing Eye Injuries in Youth Baseball Players: A Coach's Perspective

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I remember the first time I saw a baseball player suffer an eye injury. At the time, I was a baseball coach for a competitive youth team. The batter on the opposing team had just hit the baseball, and it smacked the pitcher directly in the orbit. Everyone in the crowd gasped, and he immediately fell to the ground in obvious discomfort. Fortunately, he walked away with a minor periorbital contusion – colloquially known as a "black eye"– and suffered no major injuries to his eye or orbit. After witnessing this injury, I began wondering why the use of eye protection is not widespread in youth baseball. It seems like a simple way to reduce eye injuries, especially given that baseball is becoming increasingly popular in Canada.

According to Baseball Canada, over 120,000 Canadians played baseball in 2016, representing a 14% increase from the previous year.[1] Unfortunately, as illustrated before, participation in baseball comes with the risk of eye injury. In fact, baseball is the leading cause of sport-related eye injury in youth aged 5-14.[2,3] Consequently, it is also one of the leading causes of sport-related eye injury visits to the emergency department.[4,5] Most of these injuries result from blunt trauma of the baseball to the orbit.[6] Blunt trauma can cause many ocular injuries, such as eyelid lacerations, corneal abrasions, hyphema, orbital blowout fracture, and globe rupture. Although many of these injuries will not cause long-term damage, severe eye injuries can lead to visual impairment or blindness.[5] This has the potential to negatively affect quality of life, and to increase rates of depression later in life.5 Thus, there is a need for increased effort to prevent eye injuries in youth baseball players.

Eye protection is a solution to prevent injuries. This includes facial guards attached to players' batting helmets and eye goggles worn by players on the field. It is estimated that up to 90% of ocular injuries are preventable by wearing eye protection.[2] Furthermore, a prospective cohort study by Danis et al. shows a 28% lower incidence in oculofacial injuries after a single baseball season in players wearing facial guards compared to those not wearing protection.[7] Unfortunately, baseball is a sport in which very few players wear any type of eye protection. In the Unites States, only 23.9-27.5% of surveyed T-ball leagues and Little Leagues used face guards in at least one of their divisions.[8] As a former baseball coach, I can anecdotally attest to the low rate of protective eye equipment use. During my eight years of coaching youth baseball, I rarely saw players wearing eye protection.

Several barriers exist to the use of eye protection. A number of these issues are related to design, functionality and appearance. For example, players wearing facial guards on their helmets report discomfort and visual obstruction.[7] Furthermore, players are also concerned about the appearance of this equipment. As a coach, players would frequently tell me that they would never wear eye protection because it "looked funny". Companies should consider engaging youth in designing protective equipment in order to maximize design and function. This may ultimately lead to increased acceptance and use of these devices.

Another barrier is lack of distribution of eye protection. Baseball leagues do not usually provide their teams with facial guards or eye goggles, and parents may not think to purchase their own eye protection, as this equipment is not commonly used. However, baseball leagues supply teams with other equipment, such as batting helmets. Thus, it is not unrealistic to ask them to provide eye protection as well. This would come with increased cost to the league, and solutions would be required to overcome the cost. One option would be to ask parents to pay an increased registration fee. Another option would be to obtain this equipment from charitable organizations that provide protective eyewear to baseball leagues. For instance, the "Play Hard Don't Blink" campaign in Ohio is geared towards promoting the use of eye protection.[9] They provide educational content for children and parents, as well as free protective eyewear.[9] In order to continue providing free eyewear, we must continue to support such charities. Furthermore, organizations in other regions should be encouraged to provide protective equipment.

Educational strategies should also be implemented to increase the use of protective eyewear. These should be targeted at players, parents, coaches, and leagues, and focus on the benefits of using this equipment. Different educational interventions would need to be targeted at each group to optimize success. For leagues, professional and public health organizations should consider reaching out to league representatives to promote eye protection. For coaches, education can be taught at preseason training sessions. In Canada, many coaches must already undergo training to become certified, and

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incorporating a learning component on protective eyewear would be a simple way to increase awareness. Coaches could then be encouraged to educate both parents and players. For parents, leagues should also consider handing out pamphlets, or hanging posters during games, to increase awareness of protective eyewear. Furthermore, leagues could provide resources on their website providing information on protective eyewear. Finally, both parents and coaches should attempt to educate youth players about the benefits of eye protection, and focus on normalizing the use of this equipment.

A definite solution would be to make eye protection mandatory in baseball leagues. In this case, eye protection would become a regular part of the uniform, like a batting helmet. In fact, the American Academy of Ophthalmology supports mandatory eye protection in baseball. This strategy was adopted by amateur hockey, and resulted in a dramatic decrease in eye injuries.[10] Unfortunately, this is not a requirement of most baseball leagues in Canada. Although we should continue to advocate for mandatory eye protection in youth baseball, it does not seem to be on the horizon. In the interim, continuing to educate players, parents and coaches about the benefits of protective eyewear should be the focus.

Eye protection offers a simple solution to preventing eye injuries in youth baseball players. However, strategies are needed to increase the use of this equipment. Baseball leagues should consider providing teams with protective eyewear. Furthermore, companies should focus on improving design and functionality of eyewear. Finally, there should be greater emphasis on education surrounding the benefits of eye protection. Eye injuries can be devastating, and prevention should be the top priority!

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