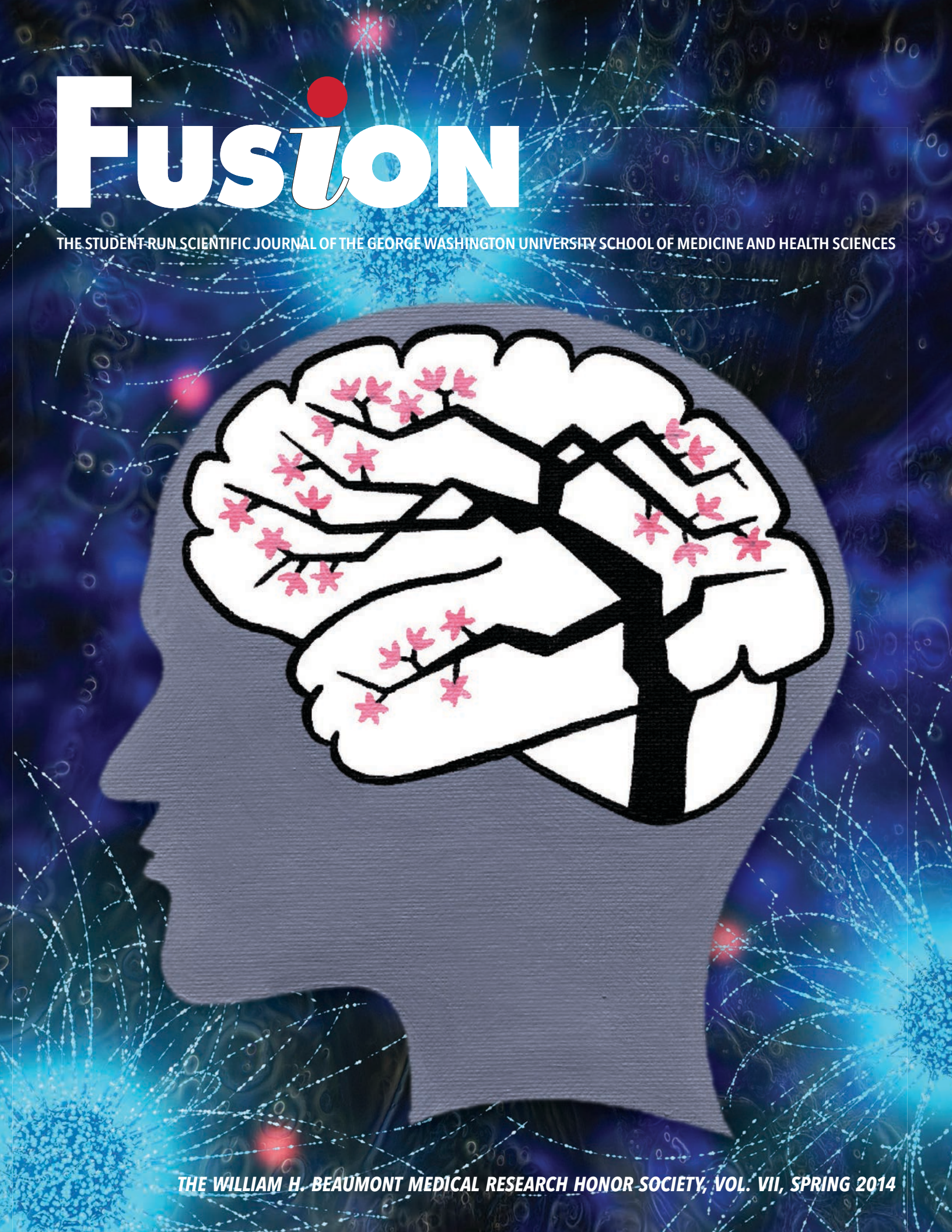
FUSION

THE STUDENT-RUN SCIENTIFIC JOURNAL OF THE GEORGE WASHINGTON UNIVERSITY SCHOOL OF MEDICINE AND HEALTH SCIENCES



THE WILLIAM H. BEAUMONT MEDICAL RESEARCH HONOR SOCIETY, VOL. VII, SPRING 2014

Welcome to Fusion

Dear GW Community and fellow research enthusiasts,

As part of our commitment to fostering student interest in research, the William Beaumont Medical Research Honors Society at The George Washington University School of Medicine and Health Sciences is proud to introduce the 2014 edition of *Fusion* — a student-run research journal that serves as a forum for students to share their research experiences with the GW medical community.

This year's edition focuses on the theme of putting basic science research into clinical practice. Medicine is an incredibly dynamic and rapidly evolving field. At the same time, basic science is identifying new molecular pathways, genetic polymorphisms in disease, and targeted pharmaceutical therapies at an impressive rate. While these developments are aimed at advancing the medical field, the integration of these innovations into clinical practice also poses a unique challenge for today's healthcare professionals.

Never before has the collaboration and coordination of researchers and health care providers been more important. As future health care professionals it is imperative that we seek to continue to integrate these dynamic aspects into our own practice. However, learning these skills most often requires us to immerse ourselves in enriching experiences outside the classroom, and it is these endeavors that *Fusion* highlights. This publication features a "fusion" of clinical, basic science and public health research, reflecting the experiences of a number of enthusiastic and dedicated members of the GW SMHS student body. We hope that as you enjoy reading the following articles you are inspired to seek opportunities that will help strengthen your own skills as future healthcare professionals.

Lastly, we would like to thank all of our authors and artists who help to make *Fusion* a great success each year. We also extend our many thanks to the Office of the Deans for their generous support, and to the staff at SMHS Communications and Marketing for helping to make *Fusion* a reality.

Sincerely,
Your editors:

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The brain is the most complicated organ in the human body. Anatomical and physiological circuits provide us with the ability to communicate, experience emotion, learn, create memories, and much more.

The cover image was created by second-year medical student Cate Haring, while she was conducting neuroscience research at Children's National Health System in Washington, D.C. Over the course of her research Haring was struck by the beauty, complexity, and mystery of neural circuits involved in both health and disease. Novel imaging techniques and molecular diagnostic studies are beginning to shed light on the pathogenesis of neurological conditions, however there remains much to be discovered. Haring used cherry blossoms in the cover image to represent the beauty she found in neural circuits and the current neuroscience research being conducted in Washington, D.C. Behind the acrylic painting is a representation of neurons firing.

Fusion
is a publication of the William H. Beaumont Medical Research Honor Society. The journal is published by SMHS students in collaboration with the SMHS Office of the Dean and the Office of Communications and Marketing.

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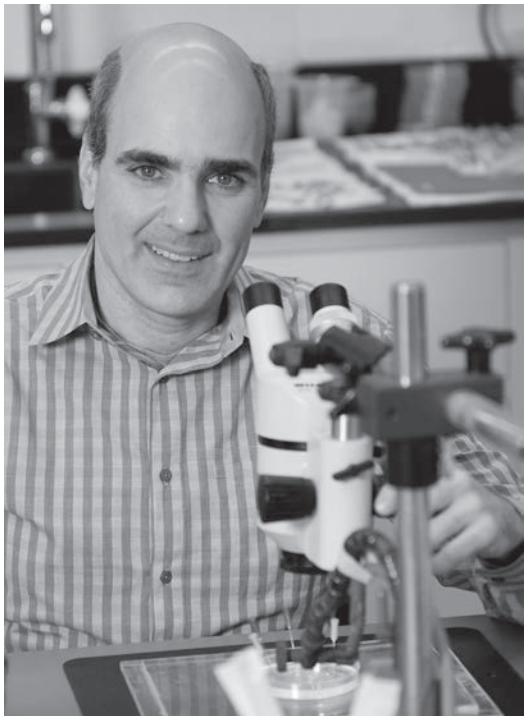
Serendipity and the Path to Discovery



Anthony-Samuel LaMantia, Ph.D.

In the 1960s and 1970s, equipped with of "first generation" tools of molecular biology — as well as classical biochemistry and the emerging discipline of "cell biology" — a whole generation of physicians and scientists worked side-by-side to fight a "war" on cancer. The partnership was inspiring, and facilitated by medical education at the time. First- and second-year medical students were taught by the faculty members who were actually doing the research, and lectures often included the newest data from their own or other laboratories. This "hot off the bench" approach primed a whole generation of physicians to be ready to apply insights of basic molecular biology not only to new diagnostic and therapeutic approaches to cancer, but also to new infectious diseases that arose 20 years later (HIV, SARS, Ebola virus), and the newer "genetic medicine" that crystalized following completion of the first-draft human genome sequence in the late 1990s. This progress produced declines in mortality and morbidity due to cancers: now diagnosis, though serious, is not a shameful death sentence. New treatments provide multiple opportunities for intervention, and in some cases partial or even complete (as one can tell) cures. Neuroscientists view this nearly 60-year odyssey with admiration and a little bit of envy — if only we could report the same level of advance.

The achievements of neuroscience seem slower, and clinical benefits have not yet been fully realized. When I was a student-scientist in the mid 1980s, there was a sense that a "first draft" of the rules of neuron structure, physiological function, and behavioral output by which nervous systems operated was nearly complete. The foundational work of the people who taught me about the nervous system — including Pasko Rakic, M.D., Ph.D.; Patricia Goldman Rakic, Ph.D.; and Gordon Shepherd, M.D., D.Phil, at Yale University; Eric Kandel, M.D., and Dale Purves, M.D., at Cold Spring Harbor Laboratory; and many others — inspired me. The work we read by then leaders in the field such as Viktor Hamburger, Ph.D., and Nobel Prize winners Paul Greengard, Ph.D.; David Hubel, M.D.; Rita Levi Montalcini, M.D.; Erwin Neher, Ph.D.; Bert Sakmann, M.D.; Thomas Sudhof, M.D.; and Torstein Wiesel, M.D., gave me a sense that the inpenetrable gray lump that most biologists dismissively considered the brain to be, could actually be studied using the same approaches as every other organ system. A second wave of revolutionary developments in molecular biology and genetics in the 1990s made it possible to consider the foundational "first draft" of how brains might work as a starting point to define molecular and cellular mechanisms that lead to devastating and intractable brain diseases.

At that moment I was fortunate enough to begin my scientific career as an independent investigator — first at Duke University, then at The University of North Carolina at Chapel Hill (UNC), and now at GW. I acquired a new tool kit of molecular biological approaches, with the help of my collaborator and friend Elwood Linney and several gifted students and post-docs. We focused on studying novel cell signaling mechanisms. We wished to understand how neural stem cells in the very early embryonic brain receive instructions that gave them identity. Surprisingly, the molecular mechanisms we identified were the same ones used for similar — though not identical — tasks that faces, hearts, and limbs together during early embryonic development. At this point, a truly fortunate event occurred: an academic psychiatrist, Jeffrey Lieberman, M.D. (who is, by the way, a GW Medical School alumnus) made me aware of a recently defined genetic disease — DiGeorge or 22q11 Deletion Syndrome, with an incidence rate of 1/3000 live births caused craniofacial, limb, and heart malformations recognized at birth (and, in the case of heart malformations, repaired shortly after birth to insure survival), followed by a

Newer "genetic medicine" that crystallized following completion of the first-draft human genome sequence in the late 1990s helped produce significant declines in mortality and morbidity due to cancer. Using those tools of molecular biology, today's scientists could unlock similarly transformational discoveries in the world of neuroscience.

remarkable increase in early onset schizophrenia in many patients, autism and mood disorders in most others. Jeff Lieberman and I recognized that the basic biology I had done and the clinical characteristics of this disorder likely had something to do with one another. With Jeff Lieberman's instruction in the details of clinical brain disorders such as schizophrenia and autism, and using the tools of molecular biology — especially the ability to model human genetic disorders in the mouse — we defined how the genetic lesion that "causes" 22q11 Deletion Syndrome disrupts the shared mechanisms for heart, face, limb, and brain development. We also found, to our surprise, that this genetic disruption goes on to compromise development of neural circuits in the cerebral cortex that are essential for specific cognitive behaviors.

The happy accident of meeting Lieberman occurred by chance during a scientific meeting (in Hawaii ... doubly lucky for me!), and resulted in my migration from Duke to UNC where Lieberman was at the time. Jeff is now the chair of psychiatry at Columbia University, and Director of the New York State Psychiatric Institute. His work on the efficacy of antipsychotic drugs defines clinical practice, and his ongoing work on the biology of schizophrenia and other affective disorders is a model for translational research — he's an inspiring GW alumnus. My goal, as I took on the role of founding director of the GW Institute for Neuroscience, was to facilitate many more similar "happy accidents" for GW clinicians, scientists, and students here in Foggy Bottom (sorry, no Hawaii trips). Together, we can define a new translational research enterprise in the neuroscience of brain diseases. Our efforts over the past four years are only now beginning to produce exciting results, but we are well positioned to drive full speed ahead— with fellow neuroscientists throughout the country and world — toward the seemingly bleak horizon of brain disease, and improve the outlook with new discoveries. Perhaps 60 years from now, another GW faculty member, writing another faculty letter for the Beaumont Society's journal *Fusion*, will look back on our collective efforts at GW, and throughout the scientific community, in the same way that we now look back upon the beginning of the "war on cancer": — an intrepid collaboration between physicians and scientists — those already trained, and those in training — that defined a path to better outcomes for generations of patients yet to come.

– Anthony-Samuel LaMantia, Ph.D.
professor of pharmacology & physiology, and founding director of the GW Institute for Neuroscience

Moderate Weight Loss is Sufficient to Affect Thyroid Hormone Homeostasis and Inhibit Its Peripheral Conversion

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TABLE 1: Study Participants' Characteristics and Laboratory Data[$]

	Non-Overweight Group	Intervention Group	
Parameter		Baseline	12 Months
Weight (kg)	65.7±2.1***	101.2±2.5	94.9±2.7###
BMI (kg/m2)	22.2±0.4***	33.9±0.7	31.5±0.7###
Blood pressure (mm Hg)			
Systolic	114.1±1.7	118.6±1.7	117.3±1.7
Diastolic	68.7±1.2	69.0±1.1	68.5±1.2
Fat Mass (kg)	15.1±1.07***	41.7±1.5	36.6±1.6###
TSH (ng/dL)	1.8±0.16	2.2± 0.2	1.9±0.2
Free T4 (ng/dL)	1.24±0.50**	1.12±0.02	1.09±0.03
Total T3 (ng/dL)	100.6±3.1**	112.7±3.1	101.8±2.6###
Reverse T3 (ng/mL)	0.33±0.03*	0.26±0.01	0.26±0.01
Leptin (ng/dL)	9.3±2.2***	39.1±3.6	34.5±3.4
REE (kcal/24h)	1307.5±46.9***	1634.5±47.8	1612.9±43.1
Body Composition Adjusted REE	-	-	1575.9±60.3

Comparison Control and Intervention Group at Baseline: *p<0.05, **p<0.01, ***p<0.001
Comparison Between Baseline and 12 Months: #p≤0.05, ##p<0.01, ###p<0.001
[$]*Data Expressed as Mean±SEM*

Obesity is a source of considerable morbidity and early mortality in the United States and is the result of a sustained imbalance between energy intake and energy expenditure (EE)[1]. Thyroid hormone (TH) and particularly tri-iodothyronine (T3) play a critical role in the modulation of Resting Energy Expenditure (REE) and substrate metabolism[2]. While dietary restriction has been shown to inhibit the Hypothalamus-Pituitary-Thyroid axis by a fall in leptin, whether nutrient deficits impact on peripheral TH metabolism is less known. A better understanding of the interaction between moderate calorie restriction, weight loss, and TH homeostasis could produce valuable information on the adaptive (or maladaptive) response to dietary intervention.

The action of TH in the target tissues is the result of a multi-level control system. This allows the precise time- and tissue-specific delivery of the hormonal signal via the interaction of T3, the active form of TH, with its nuclear receptor isoforms[3]. The pool of T3 is the net result of its secretion from the thyroid gland, the peripheral conversion of the prohormone T4 into T3, and its degradation. Peripheral conversion of T4 into T3, achieved by the combined actions of the deiodinases type-1 and type-2 (D1 and D2) is responsible in humans for a substantial component of the circulating and tissue pool of TH[4].

Forty-seven subjects BMI≥25≤45 Kg/m2 and 30 non-overweight controls were enrolled into the study. Overweight subjects underwent a one-year individualized calorie-restricted diet (-600 Kcal/day deficit) and were encouraged to increase physical activity, achieving 5-10% weight loss. Various metabolic measurements were performed at 0, 1.5, 3, 6, 9, and 12 months.

The intervention resulted in 6.3±0.9 kg (6.5±1.0%) weight loss (Table 1). At baseline, TSH and T3 levels correlated significantly with fat mass. After weight loss, T3 decreased significantly (from 112.7±3.1 to 101.8±2.6 ng/dL p<0.001) in the absence of significant changes

in TSH or free T4 (fT4). The decrease in serum T3 correlated with the decrease in weight. T3: fT4 ratio (used as an index of peripheral conversion of TH) decreased significantly in individuals who lost >5% body weight. After correcting T3 for changes in fat mass, the decrease from baseline remained statistically significant. Longitudinally, while TSH levels had a non-significant reduction, and fT4 levels showed a small but significant reduction (Figure 1 D, E), the decrease in T3 was more robust (p=0.001) (Figure 1C). The decrease in serum T3 correlated with the decrease in weight (R=0.294, p<0.001). No statistically significant changes in reverse T3 levels were observed over the course of the study (Figure 1F).

A relative inhibition of peripheral 5'-deiodination of the pro-hormone T4 into T3 is likely responsible for some of the observed changes in the thyroid homeostasis, as indicated by the significant decrease in the T3:fT4 ratio, a sensitive index of conversion of TH in the individuals who had a greater degree of weight loss[5]. Our results indicate that T3 levels closely correlate with individual nutritional status, and moderate weight loss results in a significant decrease in T3 with minimal changes in other thyroid hormone homeostasis parameters. The data suggest a decrease in peripheral conversion of the pro-hormone T4 into its hormonally active metabolite T3 is at least in part responsible for the changes in thyroid hormone level.

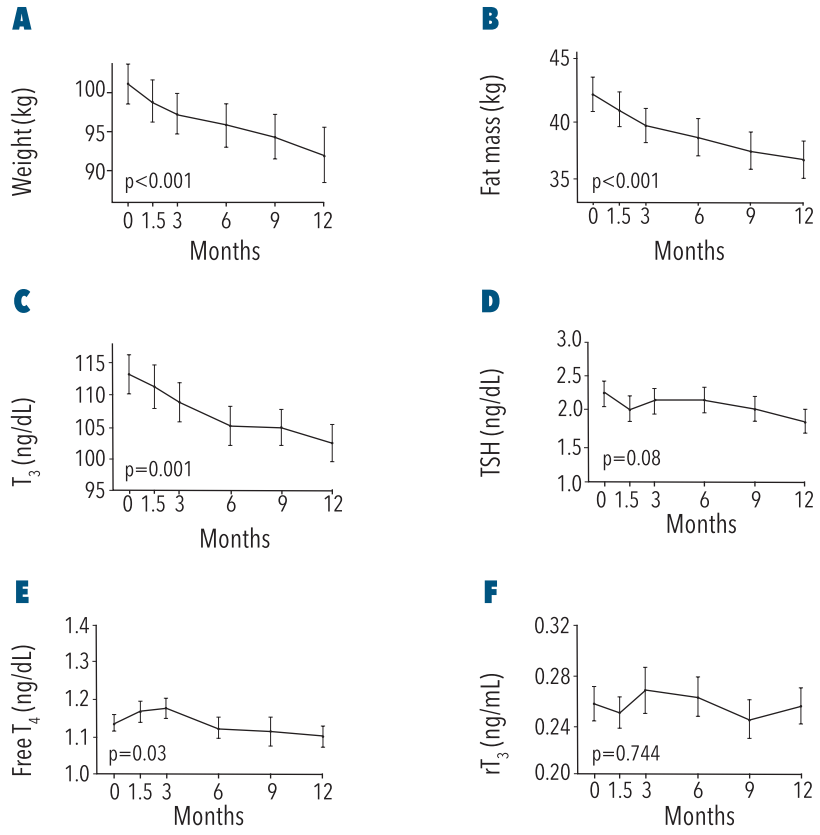

FIGURE 1: Longitudinal changes in anthropometric and thyroid hormone homeostasis parameters during the 12-month weight loss intervention. During the weight loss intervention (Panels A and B) a significant decrease in serum T_3 was observed (Panel C). A trend toward a reduction in TSH and fT_4 was also observed (Panels D and E). No significant difference was observed in the rT_3 serum levels throughout the study. Repeated measure ANOVA, data are reported as mean±SEM.

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Retinal Ganglion Cell Layer Thickness in Children with Vision Loss from Optic Pathway Gliomas

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Low-grade gliomas are the most common brain tumor in children, and when they occur in the anterior visual pathway are called optic pathway gliomas (OPGs). Accurate and reliable vision testing in young children with OPGs can be limited by their cooperation. However, since not all OPGs cause vision loss, a surrogate marker of visual pathway integrity that does not require cooperation would be helpful.

Spectral-domain optical coherence tomography (SD-OCT), the optical analog of ultrasound imaging, has emerged as a relatively noninvasive and time-efficient way to image the retina. When the visual pathway is damaged distally, the thickness of the unmyelinated retina will decreased due to axonal degeneration. SD-OCT has proven to allow for safe, quantitative measuring of important retinal layers such as the ganglion cell layer-inner plexiform layer (GCL-IPL). We explored whether structural measures of the macular GCL-IPL using SD-OCT were related to visual acuity (VA) and visual field (VF) in children with OPG.

Children with OPGs (sporadic or secondary to Neurofibromatosis type 1, NF1) enrolled in a prospective study of SD-OCT were analyzed. Enrolled subjects were included only if macular SD-OCT images were acquired and they were cooperative for VA and VF testing. Manual segmentation of the macular GCL-IPL was performed across an Early Treatment Diabetic Retinopathy (ETDRS) grid at 1.5, 3.0 and 4.5mm diameter. GCL-IPL thickness measures (microns) were compared to VA and VF outcomes.

Forty-seven study eyes from 26 children with OPGs (18 NF1-related, 8 sporadic) were included, with a median subject-age of 5.3 years (range, 2.5 – 12.8). The GCL-IPL thickness (3.0mm diameter) was decreased in the abnormal VA (61 ± 2 microns), abnormal VF (73 ± 11 microns) and abnormal VA/VF (53 ± 5 microns) groups when compared to the normal VA/VF group (92 ± 9 microns; $F = 44.9$, $p < 0.001$). GCL-IPL thickness in the abnormal VA group was not different from the abnormal VF (Post-hoc Scheffe's test, $p = .28$) and abnormal VA/VF groups ($p = 0.67$), however the abnormal VA/VF group had a lower GCL-IPL than the abnormal VF group ($p < 0.01$).

Children with vision loss (VA, VF, or both) from their OPG have decreased ganglion cell later-inner plexiform layer (GCL-IPL) thickness compared to those children with normal vision. GCL-IPL thickness could be used as a surrogate marker of vision in children with OPGs.

Safety and Efficacy in Nonendoscopic Transaxillary Breast Augmentation:

A Safe and Cost-Effective Procedure that Maximizes Satisfaction and Minimizes Complications

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Bitar Cosmetic Surgery Institute

The submuscular transaxillary breast augmentation (TBA) is an established and preferred procedure for breast augmentation due to the limited visibility of scar tissue, efficient sculpting of the implant pocket, and low rate of complication[1]. The objective of this study is to compare the complication rates of a nonendoscopic TBA approach to an endoscopic approach and to assess patient satisfaction with nonendoscopic TBA. A series of 353 TBAs were performed with saline implants and followed up by the senior author over a course of eight years, each at the same Level 1 trauma hospital with the same group of anesthesiologists under either

general or laryngeal mask anesthesia (LMA). A retrospective chart review was conducted to ascertain complication rates and a literature review was performed to compare the rate of complication of endoscopic to nonendoscopic TBAs. Additionally, satisfaction surveys were sent to the 353 nonendoscopic TBA patients via mail, email, and phone. The total complication rate, including a range of minor complications such as superficial infection to major complications such as hematoma requiring implant removal, was 9.92% (95% CI- 7.22-13.48%). See Table 1 for a detailed breakdown and comparison between this nonendoscopic approach and literate detailing risk profiles of an endoscopic approach to TBAs. The complication rates of this non-endoscopic procedure are similar to the complication rates of a review of endoscopically guided TBA literature. Of the 353 patients, satisfaction rates were received from 186 or 52.69%. Of those who responded, the breakdown of satisfaction survey received by medium includes 32.8% by email, 19.4% by standard mail, and 47.8% by phone. Level of satisfaction was measured on a 1–5 scale, 1 being poor and 5 being excellent, patients rated their nonendoscopic breast augmentations a mean of 4.46 (st. dev. 0.85) with a mean follow up time

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TABLE 1: This study's breakdown of complication rates and side-by-side comarison with other TBA studies.

	(Bitar, et al, 2012) – This Study		(Momeni, 2006)	(Howard, 1999)	(Kolker, 2010)	(Nohira, 2004)	(Tebbetts, 2006)	(Tebbetts, 2006)	(Huang, 2012)	(Garcia, 2010)
Placement	Submuscular TBA		Sub-muscular TBA	Sub-muscular TBA	Sub-muscular TBA	Sub-muscular TBA	(64 Sub-fascial, 13 Sub-muscular, 282 Dual Plane)	(22 Sub-fascial, 309 Sub-muscular)	Sub-muscular TBA	Sub-muscular TBA
Endoscopic Assistance?	No		Yes	Yes	Yes	Yes	Yes	No	No	No
Total Number of Implants	353		47	58	197	160	359	331	1,682	344
Major Complications	Number of Complications	%of Total Patients	% of Total Implants							
Capsular Contracture (Baker III/IV)	8	2.27%	2.13%	1.72%	0%	6.88%	1.39%	4.23%	1.90%	
Ripling	2	0.57%						0.54%		
Hematoma	1	0.28%		1.72%	0%	2.50%	0.28%	0%	0.12%	
Mastitis	0	0.00%			0%			0%	0.06%	
Sponaneous Implant Rupture	4	1.13%		1.72%	2.03%		1.11%	2,72%	3,57%	
Implant Extrusion	2	0.57%								0.85%
High-Riding Implants (No Resurgery)	2	0.57%			0%					
High-Riding Implants (with Resurgery)	2	0.57%			2.54%					
Total High-Riding Implants	4	1.13%	6.38%		2.54%		0.28%	1.81%		1.70%
Breast Asymmetry	2	0.57%			1.52%		1.11%	3,32%		1,70%
Low-Riding Implants	1	0.28%			1.02%					0.58%
Total Malaligned Implants	7	1.98%	6.38%	1.72%	5.08%		1.39%	5.14%	2.97%	3.98%
Hypertrophic Scar	6	1.70%			2.03%					
Cellulitis	0	0.00%			0.00%		0%	0%		
Decreased Nipple Sensation		1	0.28%			1.02%				
Seroma	0	0.00%			0%		0%	0%	0.06%	6.17%
Other	4	1.13%	2.13% ("Ptosis")		1.02% (1 Intraop. Hemorrhage, 1 Unilateral Arm Hypo-esthesia)		0.56%	1.81%		
Total	35	9.92%	10.81%	6.90%	11.17%	9.38%	4.74%	13.90%	9.22%	11.00%

SAFETY AND EFFICACY

Continued from p. 9

of 131.43 weeks (st. dev. 75.72) with a range from 1 to 470 weeks. Due to a high patient satisfaction rate and comparable complication rates, the non-endoscopic approach to transaxillary breast augmentation is a safe, elegant, cost effective, and reputable procedure maximizing satisfaction and minimizing complications.

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The Prevalence of Myofascial Tender and Trigger Points in Patients Presenting with Cervico-Thoracic and Lumbro-Sacral Spine Related Pain

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Although musculoskeletal complaints have long been associated with spine pain, a limited number of investigations have sought to correlate tender points and trigger points with spinal pathology. A tender point, typically a hallmark of myofascial pain syndrome, is a point within a muscle that is painful upon local palpation. A trigger point, typically a hallmark of fibromyalgia, is a point within a muscle that produces radiating pain upon palpation[2]. Cyriax suggests that tender points may be referred from cervico-thoracic, lumbro-sacral, and/or neural structures[1]. The current study was designed to determine whether pain perceived at the tender points or trigger points of several specific muscles of either the upper limb or the lower limb correlates to the site of injury, lesion, or pathology in the spine. A better understanding of pain referring to tender and trigger points from spinal and/or neural structures may allow for more effective therapies directed at the source of the pain, the spinal pathology, as opposed to the tender or trigger points themselves.

Following IRB approval, we performed a prospective, observational study of 50 subjects presenting with cervico-thoracic or lumbro-sacral spine pain that may or may not radiate to the upper and lower extremities respectively. Excluded patients included those with a BMI greater than 30, a history of prior neck or back surgery, receiving or applying for disability compensation, undergoing litigation related to the injury, or the history of an epidural steroid injection within the last three months. Algometry was used to measure the minimum pressure at which the patient begins to feel discomfort, as opposed to maximal pain threshold. The algometer measures the pain pressure threshold at each muscle site in kg/cm2, with a stopping point of 4 kg/cm2 (roughly the pressure required to cause an examiner's nail to blanch while testing these points manually), as is done per the standard of care.[3] If the patient feels local pain only upon algometer application, he is said to have a tender point in that given muscle. If the patient feels radiating pain, he is said to have a trigger point. If the patient does not experience pain before the algometer reads 4 kg/cm2 of force, it is deduced that the patient has neither a tender nor a trigger point in that muscle. Algometery was used to obtain pain-pressure threshold measurements of 10 muscles of the upper extremity and neck and 6 muscles of the lower extremity.

Of patients with cervico-thoracic pain, 61% were found to have tender

points and/or trigger points in specific muscles. Patients with lesions in C3-C4 presented more commonly with both tender points and trigger points located in the deltoid, trapezius, pectoralis major and triceps brachii; C5-C6 lesions with tender points in the latissimus dorsi, pectorlais major, and triceps brachii; C5-C6 lesions with trigger points in the deltoid, biceps brachii, and pectoralis major; and C6-C7 lesions with tender points in the pectoralis major, latissimus dorsi triceps brachii, and biceps brachii. Of patients with lumbro-sacral pain, 58% were found to have tender points and/or trigger points in specific muscles. Patients with lesions in L4-L5 presented more commonly with tender points located in the vastus medialis, adductor longus, and gluteus maximus; L4-L5 lesions with trigger points in the gluteus maximus; L5-S1 lesions with tender points in the vastus medialis, tibialis anterior, and gluteus maximus; and L5-S1 lesions with trigger points in the gluteus maximus. The majority of diagnoses included spondylosis, degenerative disc disease, disc bulging, and spinal stenosis.

These preliminary results suggest that tender and trigger points of selected upper and lower extremity muscles are correlated to spinal pathology. Therefore, therapy should be targeted at the corresponding spinal lesion. We expect to enroll a minimum of 100 subjects in this trial.

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Where Should Intratesticular Resistive Index Be Measured?

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Resistive Index (RI) calculated by Spectral Doppler ultrasound of the testis is a safe, non-invasive indicator of the intratesticular microcirculation. The current body of literature has shown that RI is related to spermatogenesis, with an elevated RI indicating dyspermia. However, the literature does not specify locations in the testis where the RI is best measured. It is the goal of this study to evaluate measurement of RI from multiple areas in the testes to determine if significant differences exist. A retrospective review of all testicular ultrasounds performed at our clinic from September 2011 through August 2012 yielded 214 patients and 418 testicles (10 patients with solitary testis). Spectral Doppler interrogation of a single centripetal or recurrent rami artery from the upper, middle and lower portions of each testis was performed using a BK medical Flex focus ultrasound with an 18 mHz linear array transducer by a single sonographer.

The average RI for the right and left was 0.56. When comparing the right and left testis there was no statistical difference (p-value of 0.86). In the right testis, there was no statistical difference when comparing the upper and lower values (average RI 0.56 and 0.56, respectively) to the mid-testis (average RI 0.56) with p-value of 0.68 and 0.79, respectively. There was also no statistical difference when comparing the right upper to the right lower testis, with p-value of 0.48. In the left testis, there was no statistical difference when comparing the upper and lower values (average RI 0.56 and 0.57, respectively) to the mid-testis (average RI 0.56) with p-value of 0.95 and 0.70, respectively. There was also no statistical difference when comparing the left upper to the left lower testis with p-value of 0.73.

Spectral Doppler ultrasound is a safe, non-invasive technique that adds unique real-time information about the intratesticular microvasculature and testicular function. This study found that the RI measurements are not statistically different when measured from the upper, mid, or lower testis. Therefore, as the use of RI as an assessment of testicular function increases, this work suggests that measurement of the RI can be taken from any area in the testis with equivalent results. The process of identifying an intratesticular artery and calculating the RI in the upper, middle, and lower pole of each testis can be time consuming. The ability to use a single measurement of RI from anywhere in the testis might encourage urologists to obtain this measurement as an independent marker of testicular function.

Association Between Thromboembolic Complications and Increased Mortality After Pediatric Cardiac Surgery

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Children with congenital heart disease often require surgical procedures at a young age. Thromboembolic complications (TC) are a major source of post-operative morbidity and mortality in children undergoing cardiac surgery with cardiopulmonary bypass (CPB). Thrombosis proceeding pediatric cardiac surgery are associated with platelet dysfunction, blood hypercoagulability, inflammation, and disruption of blood flow. In addition, patients' immature coagulation system results in characteristically low capacity to inhibit clot formation and elevated resistance to anticoagulants.[1, 2, 3]

Data on thrombosis associated with pediatric cardiac surgery are limited and hence association between TCs and surgical outcomes in this population is not well understood. In a retrospective study, 1,542 pediatric cardiac surgeries performed from September 2004 to December 2007 were quantified and characterized for post-operative TCs and surgical risk factors respectively. Ten percent of the patients (152/1,542) were identified to have TCs. Of those patients, in-hospital mortality for all causes was 15% (23/152), while TCs served as a primary or a secondary cause in 12/23 (52%) of all deaths. In addition, isolated intracardiac TCs or TCs in multiple vascular systems were associated with more than double the risk for cardiac arrest (P=0.04) and mortality (p=0.009) relative to patients with isolated intra-venous or intra-arterial TCs. These findings suggest that TCs after cardiac surgery are significantly associated with poor clinical outcomes and occur at a higher rate compared to the overall cases of thrombosis in the pediatric population.

To further investigate this matter, a large-scale cross-sectional study is currently in progress. This study includes experimental laboratory investigations, diagnostic protocols, and long-term patient follow-up. This would serve to strengthen previous findings and help further enhance the current understanding of TCs with respect to quantification, characterization, and risk stratification. The goal is to permit the development of effective tools necessary for prevention and early identification of TCs instead of treatment alone. Accordingly, clinicians can identify patients that may require more aggressive thromboprophylaxis, enhance assessment post-operatively, and implement more aggressive treatment strategies.

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A Variant in *SLC30A8* Gene is Associated with Skeletal Muscle Size and Damage in Young Men

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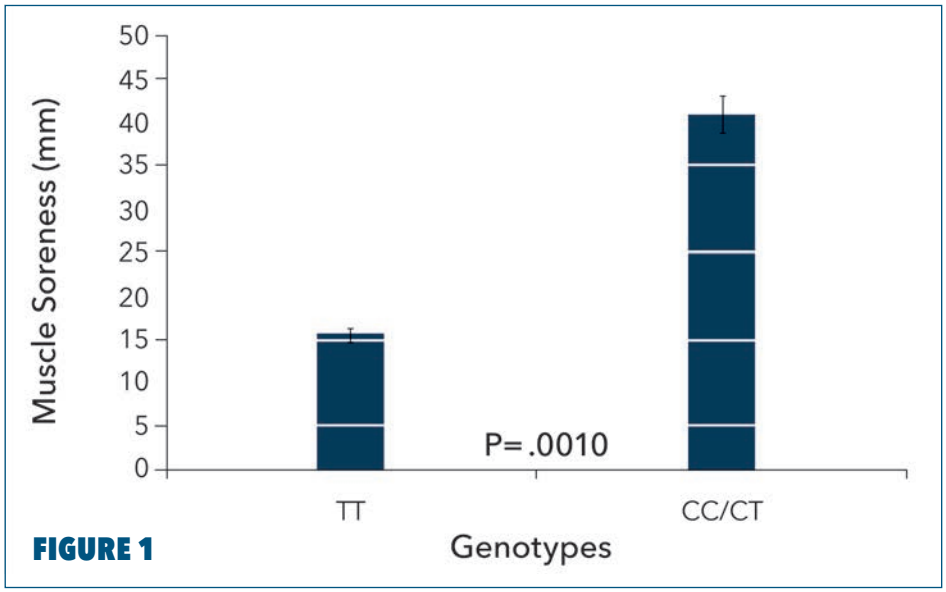

FIGURE 1

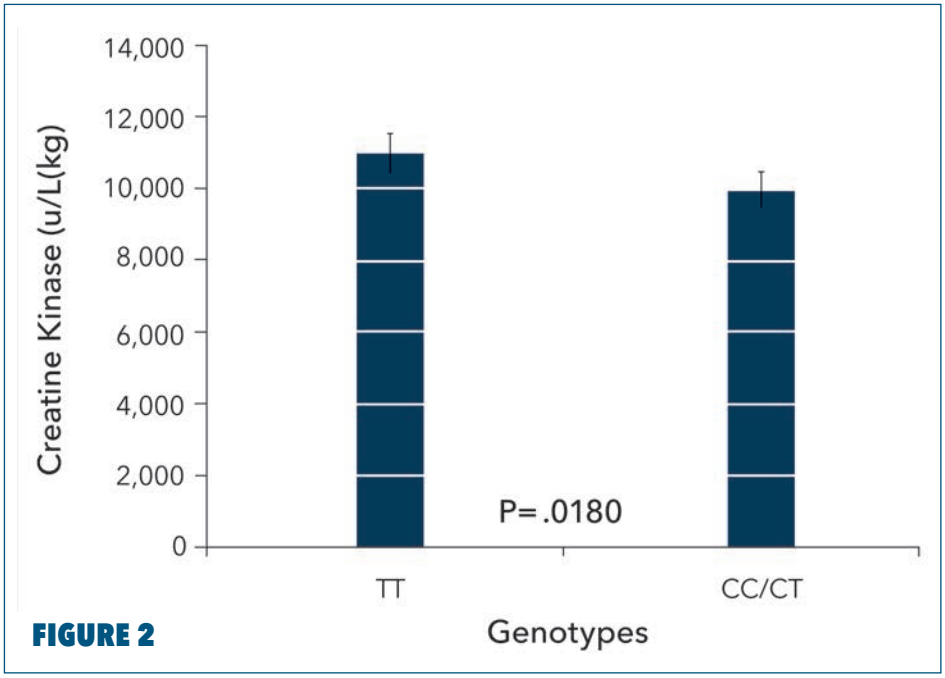

FIGURE 2

Exercise plays a major role in the prevention and management of Type 2 Diabetes (T2D) by increasing the rate at which skeletal muscle cells take up glucose. A number of clinical trials have illustrated that moderate physical activity and proper diet can decrease the progression of impaired glucose tolerance as seen in T2D[1,3]. Individuals with T2D participating in exercise interventions greater than eight weeks duration had significantly lower HbA1c levels than the individuals who did not exercise — highlighting the importance of regular exercise for T2D patients[2]. Recent genetic studies examining T2D have implicated genes involved in several potential therapeutic pathways involving those associated with β-cell dysfunction, insulin packaging and secretion. One variant, highly associated with T2D, was a non-synonymous change in the *SLC30A8* gene that encodes for the Zinc Efflux Transporter 8 protein (ZnT-8) expressed mainly in the β-cells of the pancreas — responsible for storing and releasing insulin. The variant in *SLC30A8* (rs13266634) gives rise to a Tryptophan at amino acid 325 in place of an Arginine, resulting in a defective ZnT-8 protein. In the absence of a properly functioning ZnT in vesicles, insulin cannot be synthesized and stored appropriately, disrupting glucose uptake and Adenosine triphosphate (ATP) formation downstream. The primary objective of our study was to determine whether there is a link between exercise capacity and the *SLC30A8* (rs13266634) variant gene. We hypothesized that this variant in the *SLC30A8* gene may help explain differences in muscle response to exercise, possibly due to insufficiency in glucose uptake and ATP synthesis.

Two cohorts with a total of 697 participants were subjected to one of two interventions to determine

SLC30A8 GENE *Continued on p. 14*

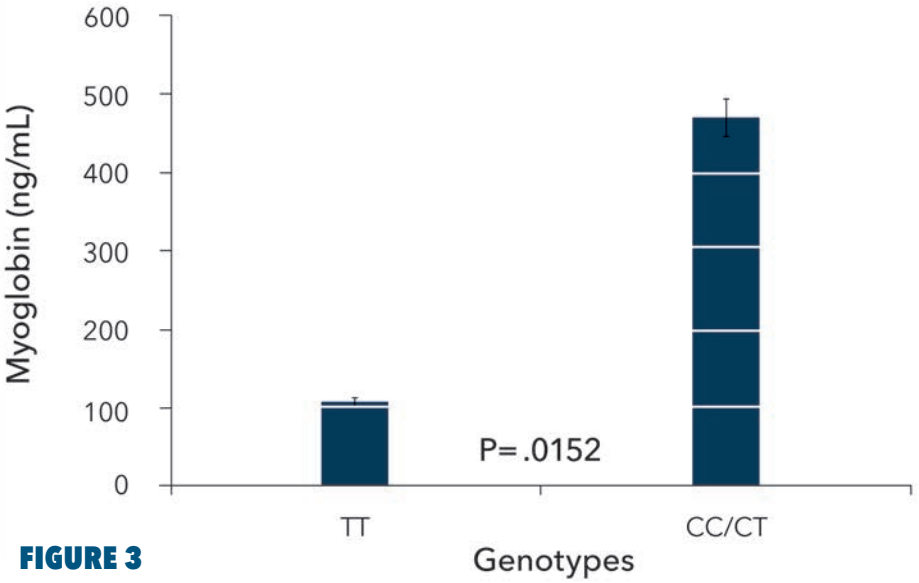

FIGURE 3

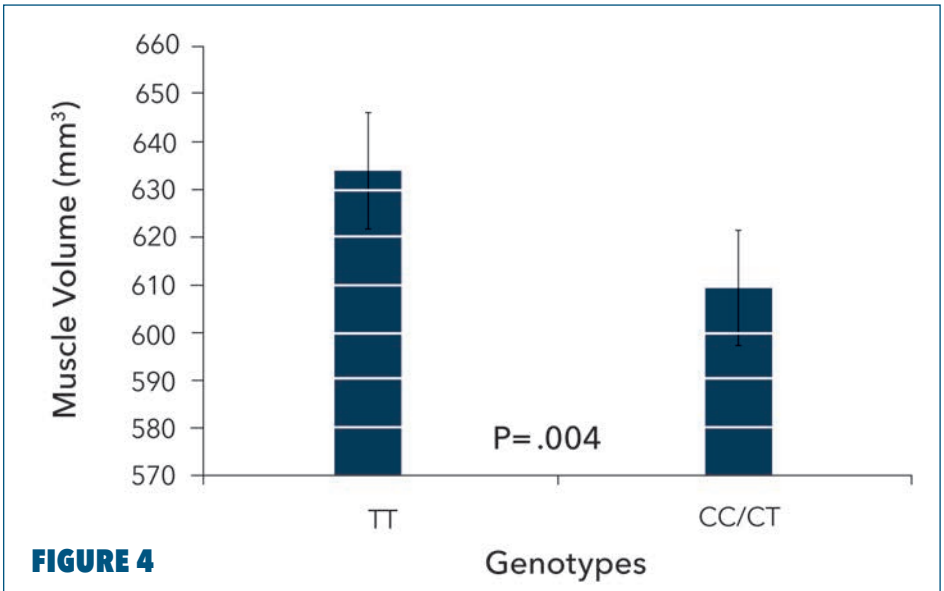

FIGURE 4

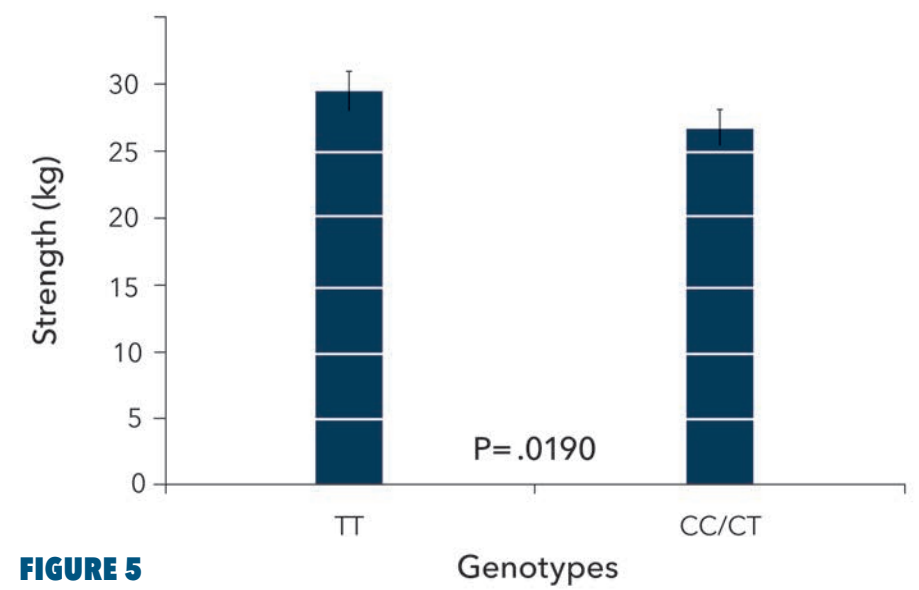

FIGURE 5

SLC30A8 GENE *Continued from p. 13*

the effects of exercise on muscle. Our results indicated that rs13266634 variant is strongly associated with several different muscle phenotypes in men but not in women. Male carriers of the common allele were more likely to demonstrate greater post-workout strength loss and greater perceived soreness (Figure 1). Increased markers of muscle damage — creatine kinase (Figure 2) and myoglobin (Figure 3) — were also strongly associated with the common allele. Furthermore, affected heterozygotes (CT) and homozygotes (CC) were more likely to have decreased baseline whole muscle volume (Figure 4) and decreased baseline 1-repetition maximum strength (Figure 5).

In this era of increasing interest in personalized medicine, there is an intense search for genetic markers that can be used in preventing and managing T2D. Clinically, the outcome of our study may help identify patients for whom resistance-training is an optimal first-line therapy in the management and treatment of T2D. We have demonstrated that the rs13266634 variant in *SLC30A8* may be used as an indicator for those individuals who may not respond to exercise as the first-line therapy for T2D, and may require an alternative method to manage their impaired glucose tolerance. Additional research is needed to determine if the presence of this single-nucleotide polymorphisms (SNP) and predisposition to post-exercise soreness leads to a decreased desire to be active, thus, promoting a more sedentary lifestyle, further amplifying their risk of developing T2D. We are intrigued by the notion that this SNP might influence several facets of T2D progression.

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Nutrition Intake in Youths with Type I Diabetes

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For youth with Type 1 Diabetes (T1D), adolescence is characterized by a period of poor adherence. One reason for poor adherence may be related to youth establishing their independence, including making their own nutritional choices[1]. Quality nutrition is strongly recommended to improve health (e.g. lower LDL plasma levels), and potentially offset risk factors for cardiovascular (CV) disease in individuals with T1D[2]. Our objective was to evaluate the rates of adherence to nutritional guidelines in youths with T1D and to examine the association of nutritional quality and Hemoglobin A1c (HbA1c).

Baseline data from a randomized controlled trial of an intervention designed to prevent deterioration of glycemic control in young adolescents with T1D were evaluated. Adolescent-parent dyads (n = 257, youth mean age = 12 years, SD = 1.2 years, 49.4% female, 64% intensive insulin regimen, mean HbA1c = 8.8, SD = 1.6) reported dietary intake via two 24-hour recall interviews as a component of their diabetes self-care. Participants were stratified by insulin regimen. Participants who reported four or more injections or use of an insulin pump were considered intensive. Conventional therapy involved a more structured insulin regimen including a set amount of carbohydrates and insulin intake per meal and fewer injections. Intensive therapy offered greater flexibility with calculating insulin needs, based on insulin to carbohydrate ratios, for each food consumed. Dietary

NUTRITION *Continued on p. 16*

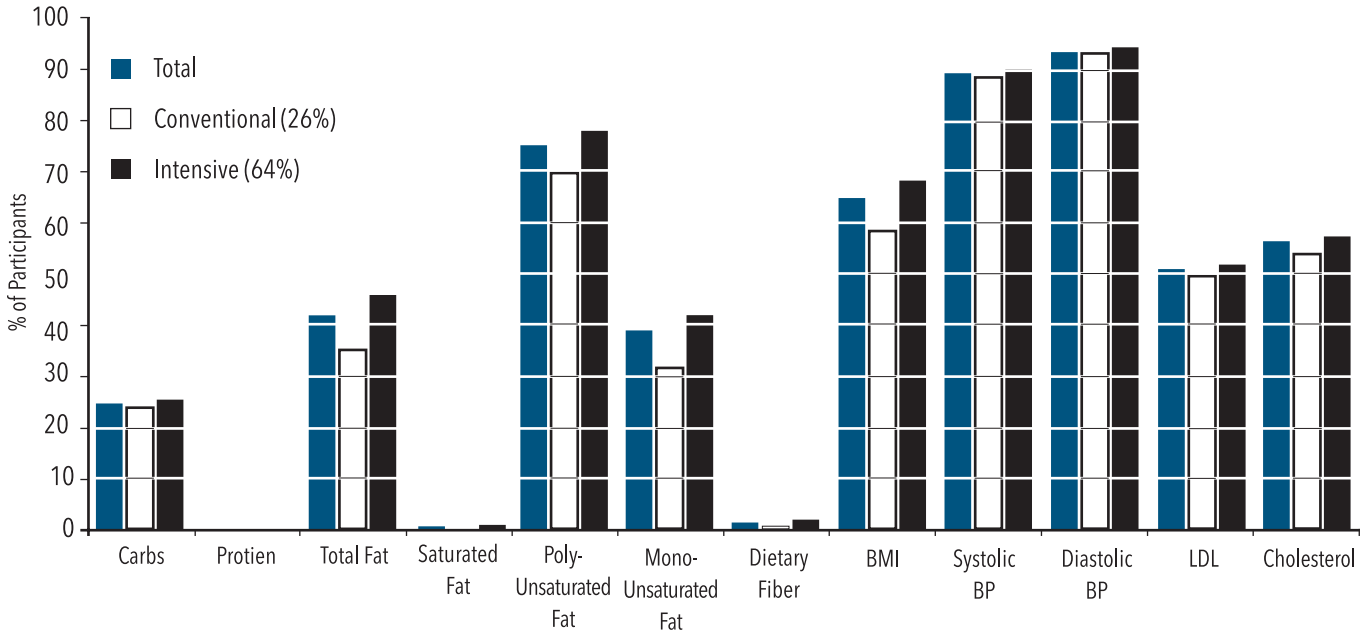

FIGURE 1: Participants Who Met Dietary Recommendations

intake was scored using The Food Processor® Nutrition Analysis Software (ESHA Research, Salem, OR, USA). Demographic variables and HbA1c data were abstracted from questionnaires and medical charts.

When compared to the American Diabetes Association (ADA) and International Society for Pediatric Diabetes (ISPAD) recommendations, many youths were not meeting nutritional guidelines. This included percent daily intake of protein, carbohydrates, fat, saturated fat, cholesterol, and dietary fiber. Furthermore, 50.2% of participants reported LDL cholesterol levels greater than recommended guidelines for primary prevention of CV disease in youths with T1D[3]. Significant positive correlations were found between HbA1c and percent of total calories from fat ($r = .24$, $p < 0.01$), polyunsaturated fat ($r = .16$, $p < 0.05$), dietary cholesterol ($r = .20$, $p < 0.01$), and LDL ($r = .24$, $p < .01$). Significant negative correlations were identified between HbA1c and percent of total calories from carbohydrates ($r = -.23$, $p < 0.01$) and dietary fiber ($r = -.13$, $p < 0.05$).

The majority of early adolescents with T1D did not meet nutrition guidelines. This may place them at increased risk for CV diabetes-related complications, which was suggested by increased LDL plasma levels reported in this adolescent study population. Further, several indices of nutrition were associated with glycemic control, suggesting that there may also be a short-term impact linked to failure to adhere to nutritional guidelines. In addition to monitoring blood glucose levels, HbA1c has utility as a risk factor for CV disease. Our study supports a link between nutritional intake, HbA1c, and risk factors for CV disease. Diabetes education efforts regarding healthy eating and dietary management may need to be enhanced to achieve recommendations and ultimately improve health outcomes for those with T1D.

TABLE 1: Recommended Guidelines for Adolescents with Type 1 Diabetes

	Recommendation	Reference
% calories from carbs	50–55%	ISPAD
% calories from protein	15–20%	ADA
% calories from fat	30–35%	ISPAD
% saturated fat	< 7% of total calories	ADA
Polyunsaturated fat	< 10%	ISPAD
Monounsaturated fat	10–20%	ISPAD
Cholesterol	< 200mg/day	ADA
Dietary Fiber	14g/1000kcal	ADA, HP2010
BMI	Overweight 85th–94th percentile (25.0–29.9 kg/m2) Obese ≥ 95th percentile (≥ 30kg/m2)	ADA
Blood Pressure	130/80 mmHg or 90th percentile for age, sex, and height	ADA
LDL cholesterol	< 100mg/dL	ADA

ISPAD = International Society for Adolescent and Pediatric Diabetes; ADA = American Diabetes Association; HP2010 = Healthy People: 2010

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Patterns of Post-Operative Venous Thromboembolism Prophylaxis in Gynecologic Oncology

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Venous thromboembolism (VTE) is a serious, potentially deadly, post-operative morbidity that occurs in up to 34.6% of gynecologic oncology patients who do not receive anticoagulant prophylaxis[1]. VTE refers to both deep vein thrombosis (DVT) and pulmonary embolism (PE). A DVT is a blood clot in a deep vein, typically originating in the leg, which runs the risk of dislodging and traveling in the bloodstream up to the lungs at which point it can become a life threatening PE. Roughly 200,000 deaths each year are caused by PEs and non-fatal instances of VTE result in prolonged hospitalization and outpatient care.

While the American College of Chest Physicians (ACCP) recommends anticoagulant prophylaxis in the general surgical oncology population, no specific recommendations are available in regards to how long to extend prophylaxis for patients within this patient population[2]. ACCP guidelines for these patients are based upon studies with small sample sizes and they tend to group all gynecologic oncology patients into one cohort.

We hypothesized that the timing of perioperative prophylaxis, patient age and BMI, tumor type and histology, and mode of surgery (laparoscopy versus laparotomy) are important risk factors in this gynecologic oncology patient population. To investigate this, we performed a retrospective cohort study of 527 gynecologic oncology patients who underwent surgery from 2008 through 2011 at a major academic institution. Prior to Jan. 1, 2010, gynecologic oncology patients were given post-operative subcutaneous heparin three times daily, total ionizing dose (TID), and they wore sequential compression stockings. Starting Jan. 1, 2010, in addition to the post-operative heparin TID and sequential compression stockings, oncology patients undergoing major gynecologic surgery were given a preoperative dose of heparin and two weeks of post-operative low molecular weight heparin after discharge.

Roughly 200,000 deaths each year are caused by PEs and non-fatal instances of VTE result in prolonged hospitalization and outpatient care.

Of our cohort of 527 patients, 28 occurrences of VTE were noted (11 DVT and 17 PE). In comparison to patients with no incidence of VTE, patients with VTE were older (mean age 64 vs. 54, $p < 0.001$) and had a higher BMI (32 vs. 29, $p=0.048$). We found that malignancy, blood transfusion, surgical tumor debulking, and wound infection were all significantly associated with VTE ($p<0.001$). Features of malignancy, in particular tumor grade and histology, were found to be statistically significant. We noted a VTE incidence of 15.1% in patients with grade three tumors in comparison to only 1.7% incidence in those with grade one or grade two tumors (RR 8.66, $p<0.001$). We hypothesized that three tumor histologies — clear cell, serous, and malignant mixed Mullerian tumor (MMMT) — put patients at a greater risk for developing a VTE. In a multivariate analysis, these three tumor histologies were 7.4 times more likely to be associated with a VTE event compared to all other histologies in our study ($p<0.001$).

As previously mentioned, the ACCP guidelines offer prophylaxis guidelines that apply to the entire gynecologic oncology patient population. We found that patient age, BMI, tumor grade and histology, as well as the nature of surgical intervention, were relevant risk factors for the occurrence of VTE. Our study suggests that further research on risk factors for VTE within the gynecologic patient population is warranted, as it may inform future clinical guidelines that would enable physicians to tailor the extension of anticoagulant prophylaxis based upon individual patient need. Current validation of a clinical prediction rule for gynecologic oncology surgery is underway.

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Emergency Department Physicians' Comfort Levels with Diagnosing and Treating Depression

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Care provided in the Emergency Department (ED) is often the first and only treatment for many people, and prior research has shown that the ED is used frequently by persons with mental health conditions[1, 2]. In 2007, 12.5% of the 95 million ED visits were attributed to mental health and/or substance abuse[3]. ED physicians increasingly come into contact with patients suffering from issues such as major depressive disorder (MDD). The American Psychiatric Association[4] defines MDD as a period, lasting at least two weeks, where the person has either depressed mood or a loss of interest in pleasure, disturbances in sleep, disturbances in appetite, low energy, lack of concentration, psychomotor retardation or agitation, guilt, and/or suicidal ideation. This study measured resident ED physician comfort levels working with this population by assessing the ED residents' attitudes toward diagnosing and treating patients who come to the ED with depression as compared to two other common disorders that the residents encounter — diabetes and hypertension.

Participants were asked how comfortable they were making a new diagnosis of hypertension, diabetes mellitus (DM), and MDD using a 5 point Likert scale in which "1" represented strongly disagree and "5" represented strongly agree. We also examined comfort levels with prescribing medications for MDD compared to hypertension and diabetes in three scenarios. The first without follow-up (no primary care provider (PCP); the second with a PCP available for follow-up but without speaking to him/her; and the third with an available PCP that is reachable by phone. We also examined perceived barriers to initiating treatment for MDD in the survey.

Residents exhibited significantly lower levels of comfort in making an initial diagnosis of major depressive disorder (MDD) when compared to either hypertension or diabetes.

Twenty residents in GW's School of Medicine and Health Sciences Department of Emergency Medicine responded to the survey. They exhibited significantly lower levels of comfort making an initial diagnosis of MDD 2.45 (95% CI 2.03, 2.87) when compared to either hypertension 3.90 (95% CI 3.28,4.52) or diabetes 4.00 (95% CI 3.52, 4.48). Residents were less comfortable prescribing medication for depression as compared to hypertension or diabetes across all scenarios. The most common barrier to treatment was lack of comfort with treating patients without follow-up.

Residents have a low level of comfort in treating MDD as compared to conditions such as hypertension and diabetes. Further research is needed to examine residents' attitudes toward diagnosing and treating depression, and its perceived barriers. Limitations of the study include the small sample size. Our study suggests that ED residents may benefit from additional training in diagnosis and treating MDD. Due to the high number of MDD patients who use ED services, resident curriculums may benefit by promoting a stronger emphasis on MDD diagnosis and treatment.

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Identifying Directional Secretomes of *In Vitro* Differentiated Normal Primary Bronchial Epithelium

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Airway epithelium is recognized as a key tissue in studying lung diseases based on its role as a polarized, differentiated barrier.[1] It simultaneously responds to airborne pathogens and environmental challenges at the apical surface while creating local and systemic changes based on these external stimuli.[2] Proteins secreted apically and basally by epithelial cells are likely to be part of a critical signaling network between airway environment and systemic milieu. Alterations in the airway epithelial barrier may lead to dysregulated signaling and subsequent clinical symptoms observed in many lung diseases such as: asthma, bronchitis, and cystic fibrosis. In asthma, previous studies have demonstrated that allergen challenge tests result in upregulation of many proteins associated with inflammation, eosinophilia, airway remodeling, tissue damage, and mucus production relative to non-asthmatics.[3] These studies on *ex vivo* airway samples suggest that through the application of proteomic techniques, such as Western Blot, ELISA, and flow cytometry to *in vitro* models, may provide a unique opportunity for global understanding of protein interactions for a given disease state and mechanisms.[4]

TABLE: Differentially Expressed Proteins in Apical vs Basolateral Compartments

Uniprot ID	Protein*	Location†	P Value‡	Fold Change§
(Apical/Basal)				
Q16787	Laminin subunit alpha-3	Secreted	0.032	-12.71
O75635	Serpin B7	Cytoplasm	0.048	-3.17
P32119	Peroxiredoxin-2	Cytoplasm	0.037	1.70
P30086	Phosphatidylethanolamine-binding protein 1	Cytoplasm	0.023	1.81
P35241	Radixin	Exosome	0.035	2.77
P60709	Actin, cytoplasmic 1	Cytoplasm	0.002	2.91
P63261	Actin, cytoplasmic 2	Cytoplasm	0.002	2.91
P68133	Actin, alpha skeletal muscle	Cytoplasm	0.042	3.08
P15311	Ezrin	Exosome	0.003	4.87
P28070	Proteasome subunit beta type-4	Cytoplasm	0.037	5.23
P27348	14-3-3 protein theta	Cytoplasm	0.019	5.99
P20618	Proteasome subunit beta type-1	Cytoplasm	0.036	6.25
Q04917	14-3-3 protein eta	Unknown	0.039	6.73
P02768	Serum albumin	Secreted	0.036	11.20

* Identified in all apical and basolateral secretions with differential expression based on Student T-test.

† Location based on Uniprot and SignalP databases; exosome distinction based on previous study(16)

‡ Based on two tailed Paired Student T-test; only proteins with $p<0.05$ are listed.

§ Based on average normalized spectral count calculated in ProteoIQ. Positive value denotes increased expression in apical secretions; negative value denotes increased expression in basolateral secretions.

Our recent data demonstrated that bronchial epithelium in treated asthmatics have only basolateral increases of specific cytokines compared to non-asthmatics, which have both apical and basolateral seceretions.[5] To our knowledge, no study has characterized the apical and basolateral secretomes of airway epithelium. Defining these secretomes in normal *in vitro* Human Bronchial Epithelial (HBE) models would lay the foundation for future comparative studies in disease. Our bioinformatic analysis of significant proteins identified in both apical and basolateral secretions detected several biological processes that appear homeostatic in nature with subtle, yet significant, differences in the distribution of these process between apical and basolateral secreted proteins (see Table). Our results revealed that certain proteins were secreted only into the apical or basolateral

DIRECTIONAL SECRETOMES

Continued on p. 20

DIRECTIONAL SECRETOMES

Continued from p. 19

compartments of the tissues and others were differentially secreted between these two compartments. All samples tested demonstrated through proteomic evaluation, that the epithelial layer directionally expresses proteins and that the purpose of this is functional in nature.

In this study we successfully characterized directional *in vitro* normal airway secretomes through comprehensive evaluation of apical and basolateral secreted proteins. Specifically, we identified the normal apical and basolateral secretomes in the gold standard model for studying mechanisms of airway diseases — *in vitro* primary differentiated bronchial epithelium. We identified intrinsic proteins uniquely expressed in both compartments and differentially expressed between compartments in cell cultures from multiple donors.

Future validation of this *in vitro* secretome model in *ex vivo* specimens will enhance our understanding of lung diseases. In addition, by establishing a model to test *ex vivo* tissue in *in vitro* technique, we have highlighted potential therapeutic markers that can be used in future airway secretome studies to allow for a more efficient and practical path towards personalization of medical care.

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An Alternative Replication Pathway Induced by Apoptosis in Cell Lines Latently Infected with Human Herpesvirus

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Human herpesviruses (HHV) are characterized by their unique ability to productively infect or remain latent in the host cell. The initiation of lytic replication can be induced by external or internal stimuli, such as cytokines or chemokines. Chemical agents such as tetradecanoylphorbol-13 –acetate (TPA), which stimulate cell signal transduction pathways, can also induce viral replication.[1] For Kaposi's Sarcoma-associated Herpesvirus (KSHV or HHV-8), the viral protein that was thought to trigger the cascade of events leading to lytic replication was the replication and transcription activator protein (RTA).[2] In an initial attempt to characterize genes expressed while RTA was inactivated, an unexpected event was observed, in which agents that induce apoptosis appeared to trigger KSHV replication suggesting that an alternative replication program induced by host cell apoptosis can initiate KSHV replication in the absence of RTA.[3]

The question is whether this alternative replication program is unique to KSHV or if it is a common feature of all herpesviruses. In particular, we focused our efforts on HHV-4 (also known as Epstein Barr Virus or EBV), HHV-6B, HHV-6A and HHV-7. If apoptosis appears to induce replication we can conclude this may be a common feature of the herpesvirus.

Here we show that 2[[3-(2,3-dichlorophenoxy)propyl]amino] ethanol (DCPE), induces apoptosis in cell lines latently infected with EBV, HHV-7, HHV-6B, and -6A by staining cells with annexin V and propidium iodide (PI) and measured using flow cytometry. Annexin V targets a protein, phosphatidylserine, expressed on the surface of cells undergoing early apoptosis. Propidum iodide binds to DNA and cannot permeate viable cell membrane so effectively detects cells in late apoptosis. Results for EBV and HHV-7 are shown in Figure 1. The known viral replication-inducing agent TPA was used as a positive induction control for normal viral replication. Cells latently infected with KSHV were also used as a positive control, since the alternative apoptosis-induced replication pathway for this virus has already been shown to exist.

We showed that apoptotic inducing agent, DCPE, induces viral replication in EBV and HHV-7 latently infected cells lines by RT-PCR assays for viral DNA.

There was a significant increase in the amount of viral DNA in EBV and HHV-7 latently infected cell lines as compared to the untreated cells when treated with either TPA or with apoptotic inducing agent, DCPE (Figure 2). We were not able to quantify viral DNA in HHV-6A and -6B latently infected cells likely due to the primers that were used. Additional experiments to quantify the viral DNAs are in progress.

Lastly, we demonstrated viral protein expression induced by apoptosis occurs for KSHV, HHV-4, HHV-6B, and HHV-7 latently infected cell lines by targeting virus-specific proteins with primary and secondary antibodies that were then visualized by confocal microscopy.

Overall, our data suggests that an alternative apoptosis-triggered replication program appears to be a general feature of the herpesvirus. The presence of an alternative replication pathway shown in EBV and HHV-7 latently infected cell lines is not surprising due to their close taxonomical relationship with KSHV, as well as the evolutionary benefit an apoptosis-induced alternative replication pathway would provide. Cytotoxic therapy is often required to treat neoplasms caused by these viruses including Kaposi's sarcoma and Burkitt's lymphoma caused by KSHV and EBV, respectively. Therefore, it may prove beneficial to treat neoplasms caused by these viruses with antiviral agents in addition to cytotoxic therapy.

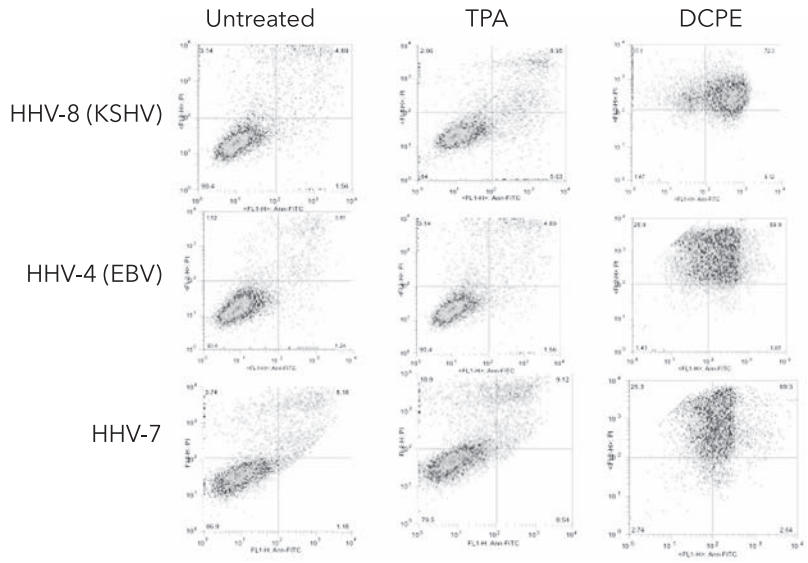

FIGURE 1: 2,3 DCPE induces apoptosis in cell lines latently infected with herpesvirus measured by flow cytometry. Latently infected cell lines were treated with TPA or 2,3 DCPE for 24hrs and then stained with annexin V and propidium iodide (PI) and measured by flow cytometry. A high percentage of cells treated with 2,3 DCPE showed annexin V and PI positivity. Note: lower left quadrant represents % live cells (annexin V - and PI -), lower right quadrant represents % cells in early apoptosis (annexin V + and PI -), upper left quadrant represents % cells in late apoptosis (annexin V - and PI +), and upper right quadrant represents % cells in early and late apoptosis (annexin V + and PI +).

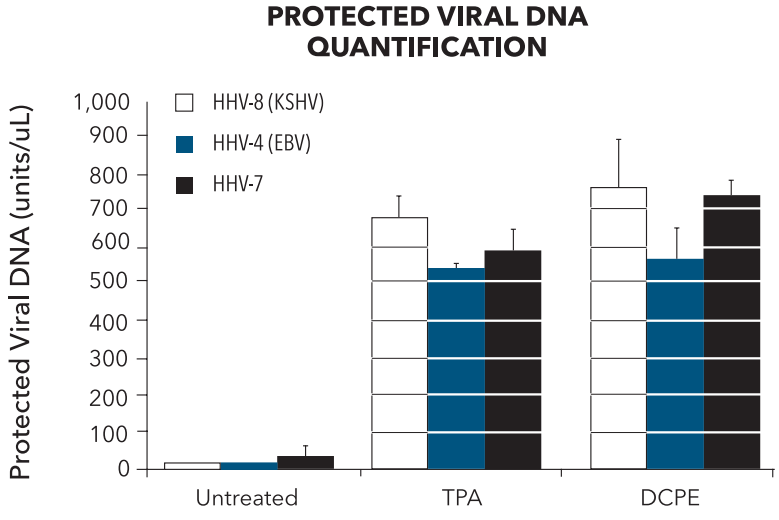

FIGURE 2: Apoptosis (2,3 DCPE) Induces High Viral DNA Replication in KSHV, EBV and HHV-7 Latently Infected Cell Lines

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The Search for Novel Atopic Dermatitis Therapies: β-Defensin-Inducing Plant Extracts

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Beta defensins are antimicrobial peptides that are part of the innate immune system and produced by the skin to combat skin infections.[1] The skin of atopic dermatitis patients is deficient in these peptides, which may increase their susceptibility to recurrent skin infections. These infections occur due to the significant barrier disruption, chronic skin inflammation, and impaired innate immune response that are characteristic of the disease.[2] Compounds that induce the production of beta defensins in the skin without concurrently inducing inflammatory cytokines have potential use in atopic dermatitis therapy and screening methods have been developed to screen plant extracts with this profile.[3]

Two such extracts, dubbed Extract A and Extract B, were identified that showed promise in this area. Each was tested on cultured keratinocytes from normal and atopic beagles to see if they induced the production of beta defensin (BD103), which is analogous to human beta defensin 3 (hBD3), without increasing inflammatory mediators. This was accomplished by allowing the keratinocytes to reach confluence and remain in that state for two days. They were then starved overnight in starving media and placed in starving media containing the concentrations of the extracts for 24 hours, along with positive (IL-1b 100 ng/ml) and negative (Dulbecco's Phosphate-Buffered Saline) controls. The production of BD103 was assessed following application of increasing concentrations of the extracts (0.2%, 0.4%, 1% for Extract A and 0.2%, 0.4%, 1%, 1.5%, 2% for Extract B) to the keratinocytes using quantitative real-time PCR, while two mediators of inflammation, IL-8 and TNF-α, were assessed using ELISA.

Analysis of the PCR and ELISA results was done through independent paired t-testing on mean values to determine statistical significance ($P < 0.05$). Extract B at 2% showed a significant increase in TNF-α in atopic keratinocytes compared to baseline (negative control) and normal keratinocytes, while also showing a significant decrease in IL-8 in normal keratinocytes compared to baseline. At 1.5%, Extract B showed a significant increase in BD103 in atopic keratinocytes compared to baseline, while also showing a significant decrease in IL-8 in atopic keratinocytes compared to baseline. Extract A at 1% showed in both atopic and normal keratinocytes a significant increase in IL-8

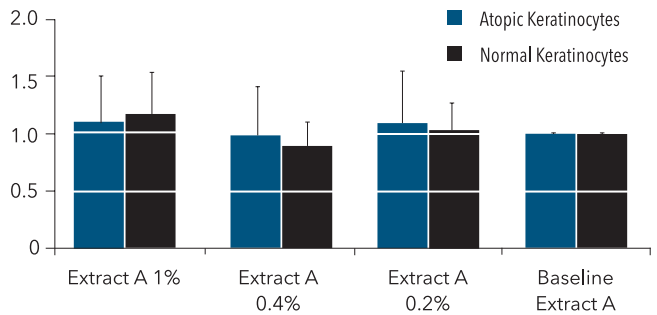

FIGURE 1: Extract A relative increase in beta-defensin 103 mRNA to baseline

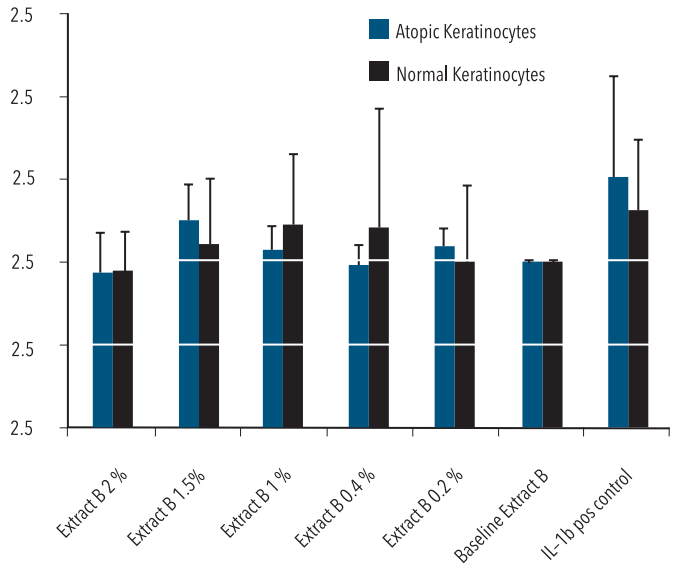

FIGURE 2: Extract B relative increase in beta-defensin 103 mRNA to baseline

compared to baseline, as well as at 0.4% in atopic keratinocytes compared to baseline. Extract A appeared to have the opposite effect to what is desired because it increased an inflammatory marker, IL-8, without increasing BD103 production.

The results from Extract B (1.5%) show that pursuing further testing on not only Extract B, but also other plant-based compounds that, through screening, show pro-beta defensin and anti-inflammatory properties, could be valid in the search for novel therapies and tools for the prevention of recurrent skin infections in atopic dermatitis patients. It is important to note that this is an ongoing study and as keratinocytes from more dogs are tested, statistical significance for different concentrations may change. As this study was in-vitro, the next step would be to test these extracts on live atopic dermatitis models in hopes of translating this potential medicine to humans as a way to protect this vulnerable population from skin infections.

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Regenerative Strategies in Bladder Outlet Obstruction

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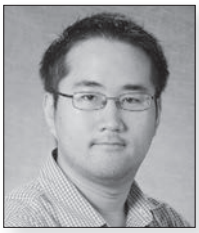

Bladder outlet obstruction (BOO) is a pathological condition characterized by increased bladder pressure and decreased urine flow that may result in the complete loss of bladder function.[1] Pathological symptoms may include abnormal thickening of the detrusor muscles and may ultimately result in the loss of bladder compliance and filling efficiency. There are many causes of BOO, ranging from spina bifida to prostate overgrowth, making BOO a difficult condition to treat.[1]

Currently, surgical correction remains the most effective treatment for BOO. However, replacement tissues used are often transplanted from the GI tract. This may result in systemic acidosis and carcinogenesis because acid secreting tissues were accidentally incorporated into the bladder.

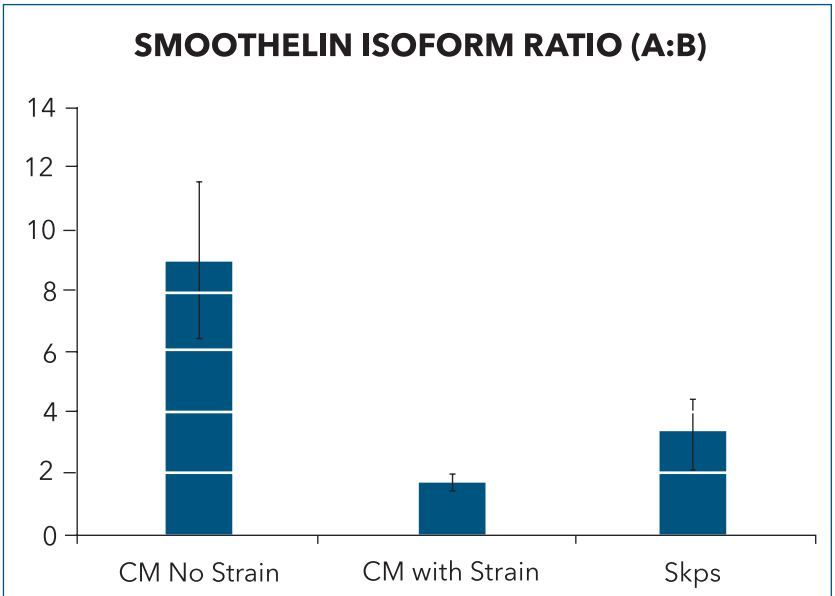

FIGURE 1: Smoothelin isoform ratio of SKPs under different conditions

A potential alternative solution for this would be to use skin-derived precursor cells (SKPs). SKPs are easily accessible, pluripotent and cost-effective. In order to determine the specificity of SKP differentiation, we performed PCR analysis, using smoothelin gene as a marker. There are two isoforms of smoothelin; A and B. Smoothelin A is expressed in bladder smooth muscle cells while smoothelin B is expressed mainly in vascular smooth muscle cells. Interestingly, when SKPS are cultured in conditioned media that is not subjected to stress, there is a high ratio of smoothelin A:B (Figure 1). This suggests that SKPs have the potential to differentiate into bladder

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smooth muscle cells in non-strained conditions, making them an ideal replacement tissue for BOO corrective surgery in the future.

Pharmacological treatment may be another option for treating BOO. Sirolimus (rapamycin), an immune suppressant that showed remarkable efficacy in treating stent stenosis and other diseases characterized by abnormal muscle proliferations.[2] Current literature also suggests that both vascular and bladder smooth muscle cell proliferation requires the mTOR pathway. Sirolimus, an mTOR inhibitor, may be an effective agent in preventing the thickening of the bladder wall and the eventual development of BOO.

In order to simulate the obstructed bladder, rat bladder smooth muscle cells were subjected to hypoxia and stretch *in vitro*. As expected, this resulted in a hypertrophic response and the cells became thicker and much more numerous (Figure 2). Smooth muscle actin expression, a protein marker for the level of differentiation in bladder smooth muscles, also became significantly down-regulated in response to both mechanical and hypoxic stress.

After sirolimus was added, the hypertrophic response elicited by hypoxia and stretch was prevented.

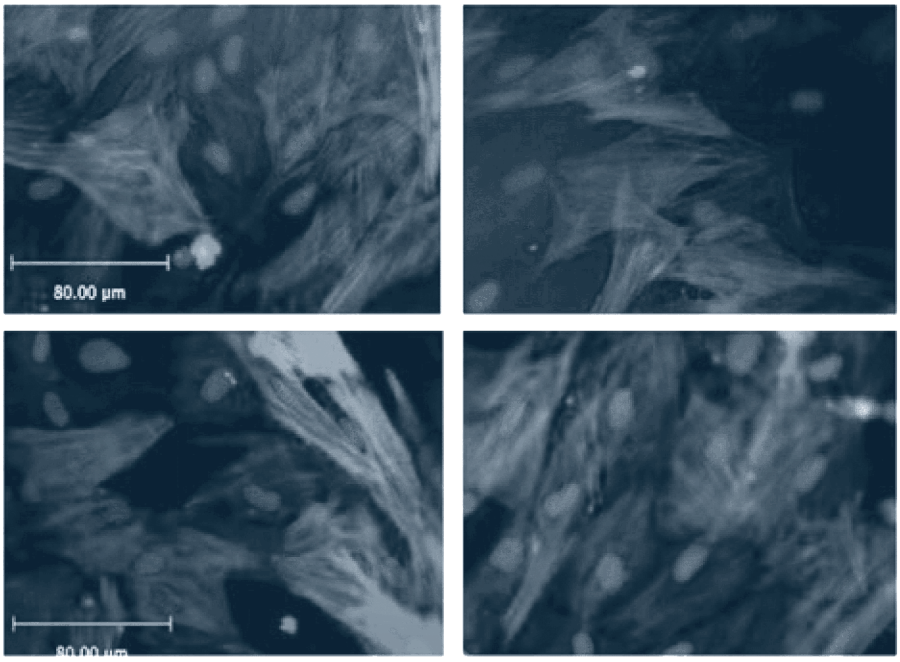

FIGURE 2: Immunostaining of bladder smooth muscle cells treated with and without rapamycin

Smooth muscle actin levels were also maintained at a high level in the sirolimus treated cells (Figure 2). This indicates that bladder smooth muscle cells maintained a differentiated and therefore functional state. This is important as much of the pathology associated with BOO is due to the improper contraction of the hypertrophic and de-differentiated bladder smooth muscle wall. Ultimately, Sirolimus administration may allow the bladder to continue to contract efficiently, even in the presence of BOO inducing stressors like injury, hypoxia and stretch. Consequently, further studies in human cells are needed for its potential to be fully used.

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Underdiagnosed Pain in HIV/AIDS Patients

Bahaa Daoud, MSIII

Human Immunodeficiency Virus (HIV) is primarily a sexually transmitted disease that depresses the body's immune system — specifically the depletion of CD4+ T-lymphocytes. Individuals with CD4+ counts of <200 cells/μL are defined as having Acquired Immune Deficiency Syndrome (AIDS). In the United States alone, there are approximately 1.1 million individuals living with HIV/AIDS with an incidence of 56,000 new infections each year.

Clinically, HIV/AIDS presents with myriad symptoms, including various cardiovascular diseases, hepatobiliary diseases, renal diseases, or, most commonly, secondary opportunistic infections. These symptoms can often be controlled with highly active anti-retroviral therapy (HAART), which effectively produces a state of chronic-treated HIV/AIDS. Chronic persistence of the virus may involve the central nervous system and lead to neurological symptoms such as cognitive impairment, gait disorders and various pain syndromes[1].

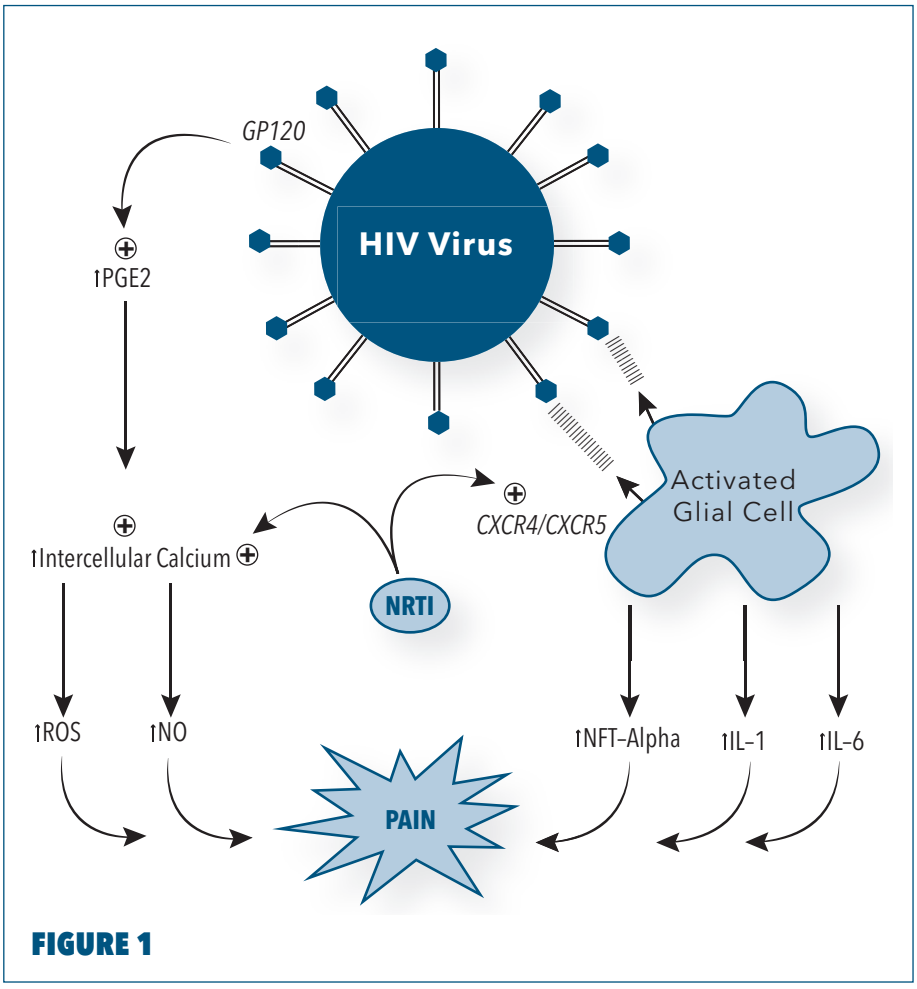

FIGURE 1

Though commonly occurring and despite the importance of pain management in chronic HIV, pain syndromes continue to be underrecognized and undertreated. Furthermore, clinicians seldom explore HIV-associated pain syndromes[2]. The most common pain syndrome occurring in HIV/AIDS patients is distal sensory polyneuropathy (DSP), which initially presents as paresthesias in the fingers and toes in a "stocking and glove distribution." Weeks later, it converts into a burning and "knife-stabbing" pain[3,4].

While the specific mechanisms of DSP are still uncertain, many studies have suggested that it is due to a combination of the virus, CNS immune response, and specific treatments. The envelope protein of the virus (gp120), spinal cord glial cells (with their respective chemokine receptors CXCR4 and CXCR5) and nucleoside reverse transcriptase inhibitors (NRTIs) may all be implicated in the formation of DSP[5]. In brief, gp120 can increase prostaglandin E2 levels and, through Kappa opioid pathways, facilitate an increase in intracellular calcium. This signals the mitochondrial to release reactive oxygen species (ROS) and nitric oxide (NO) and, ultimately, leads to pain. Another possible mechanism is through direct or indirect (viral shedding in PNS) activation of glial cells at their respective chemokine receptors. Once activated, they release pro-inflammatory cytokines (TNFa, IL-1 and IL-6) that directly promote increased neuronal sensitivity to pain. NRTIs can exacerbate these effects by increasing the number of CXCR4 receptors as well

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as directly increasing intracellular calcium, leading to an enhanced pain state (Figure 1).

HIV-related DSP appears to be resistant to most first-line neuropathic pain pharmacotherapy[5]. While many randomized controlled trials (RCTs) of pharmacological treatments for DSP have been performed, few demonstrate superiority over the placebo. The most notable of the group is the clinically available high-dose topical capsaicin [NNT 6.46, 95% CI (3.86-19.69)]. Another exception, although not recommended as routine, is smoked cannabis [NNT 3.38, 95% CI(1.38-4.10)]. Recombinant human nerve growth factor (rhNGF) has shown promise in a recent study but is not clinically available[6]. Finally opioids, especially chronic mu-receptor agonists, can be used to treat DSP but some studies have cautioned that they should only be used on a short-term basis and only when there are no alternatives due to their potential pro-nociceptive properties in HIV-DSP patients[5].

It needs to be emphasized that DSP is one of the most significantly underdiagnosed conditions in the United States[4]. Coupled with the lack of practical treatments available, providers are failing to meet the pain management needs of HIV/AIDS patients. It is imperative to find new treatment strategies for DSP in order to further improve the quality of life for HIV/AIDS patients.

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A Review of Neural Biochemical Markers for Mild Traumatic Brain Injury Characterization

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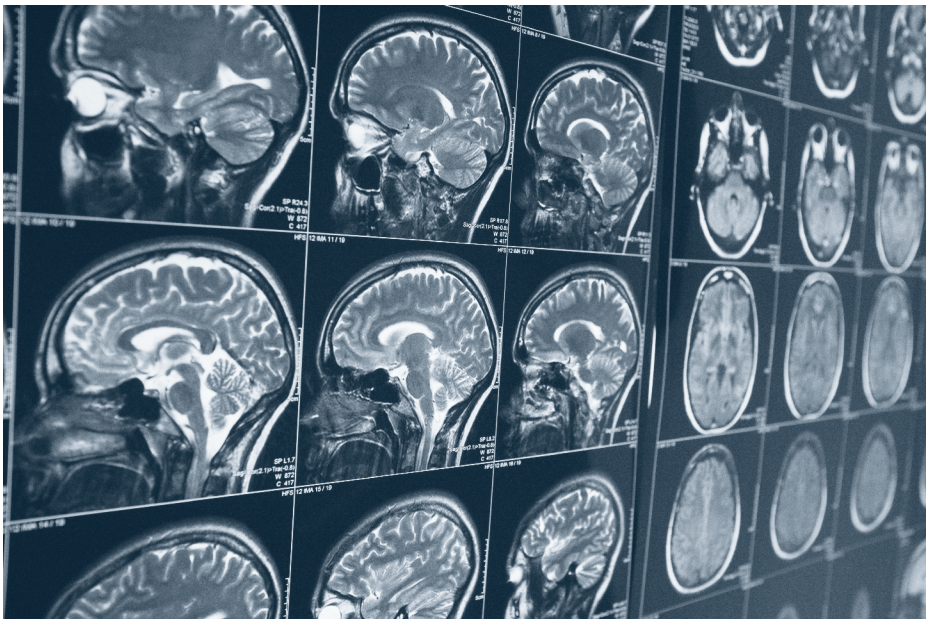
In the United States, more than 1.5 million people experience traumatic brain injury, of which approximately 75% sustain a mild traumatic brain injury (mTBI)[1]. According to the Centers for Disease Control and Prevention, mTBIs — also known as concussions — are caused by blunt force trauma to the head with one or more of the following symptoms: a period of altered mental status, impaired cognitive ability, loss of consciousness lasting less than 30 minutes, or observed signs of neurological or neuropsychological dysfunction.[1] Annual costs for injuries related to mTBI total nearly $17 billion[1]. Growing concern about injuries involving motor vehicle accidents, sports, and military combat have spurred research for mTBI[1,2,3]. However, heterogeneity of injuries and study designs have made evaluation of mTBI inconsistent2; thus, there is a need to identify effective biological markers in brain injury to allow for standardization in diagnostic criteria and qualities of prognosis[4]. This review aims to consolidate and examine existing neural biochemical markers that have been considered as possible candidates in the characterization of mTBI for both diagnostic and prognostic purposes.

A literature search was performed using PubMed and MEDLINE databases, limited to the past 10 years. Further searches used MeSH databases using keywords mTBI, serum biomarkers, and traumatic brain injury. Manual reviews of articles collected were made, examining candidate markers for mTBI with regards to their nature, effectiveness, and timing. Upon review of the literature, glial fibrillary acidic protein-breakdown products (GFAP-BDP) showed the most promising results as a biological marker for mTBI. GFAP-BDP was detected within one hour post-mTBI, and was associated with measures of



More than 1.5 million Americans experience traumatic brain injuries each year. Computed tomography (CT) scans are most commonly used soon after an injury to diagnose possible life-threatening problems. Magnetic resonance imaging (MRI) is used to identify signs of injury such as minute bleeding, small areas of bruising, or scarring that are invisible on a CT scan.

Heterogeneity of injuries and study designs have made evaluation of mTBI inconsistent; thus, there is a need to identify effective biological markers in brain injury to allow for standardization in diagnostic criteria and qualities of prognosis.

injury severity as well as focal mass lesions[4]. Ubiquitin carboxy-terminal hydrolase (UCH-L1) and alpha-II spectrin signature breakdown products (αII spectrin SBDP) require further evaluation as viable markers for mTBI, yet are more promising than older researched markers such as S100 protein beta-beta homodimer isoform (S100β), cleaved tau protein (CTP), and neuron specific enolase (NSE), which all show conflicting results and inconsistencies in published data[3,4]. The benefits remain that the availability of a biochemical marker panel for brain injury would be similar to those seen in cardiac, renal, and hepatic function panels and, as such, neural markers play a promising and necessary role in the characterization of brain injury and cost efficiency[3].

This brief review demonstrates the deficiency in research of neural biomarkers for the evaluation of mTBI[2,4]. Various research groups have begun to reevaluate the older biomarker candidates with improved guidelines, especially S100β, and research is ongoing for GFAP-BDP, UCH-L1, and αII Spectrin SBDP markers. There is a need to fully identify the pathophysiological mechanisms of traumatic brain injury in order to isolate candidate protein markers for the detection of injury severity and correlation. It is anticipated that a viable neural biochemical marker for mTBI will be attainable especially with the prospect of utilizing GFAP-BDP[4]. There is a need for longitudinal and standardized comparison testing between all promising neural markers for mTBI to increase consistency and credibility in data in contrast to previous independent studies that used varying methodologies. Once a viable neural biochemical marker has been identified, a logical subsequent step would be to consider development of a protocol for evaluating the utility of integration of neural biochemical marker assays, neuroimaging studies and neurocognitive assessments, related to early diagnostic and prognostic indications for mTBI patients.

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A Syndromic Approach to Emergency Department Surveillance for Skin and Soft Tissue Infections

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The incidence and hospitalizations due to skin and soft tissue infections (SSTIs) has steadily increased over the last decade primarily due to the emergence of community acquired methicillin resistant Staphylococcus aureus (CA-MRSA)[1,2]. The emergency department (ED) is a common site for SSTI treatment and serves populations not diagnosed by traditional surveillance, including the homeless and uninsured. However, the use of near real-time syndromic surveillance within the ED for monitoring local epidemiologic trends in SSTI presentation where laboratory data is unavailable has not been previously described. Our study sought to describe the epidemiology of ED visits for SSTIs in an urban setting with diverse neighborhood populations using Boston Public Health Commission's Syndromic Surveillance System data from 2007 to 2011. The aims of the study were: to demonstrate the use of syndromic surveillance data for tracking the patterns of SSTIs in an urban population; to estimate the burden of ED visits associated with SSTIs; and to determine potential geographic hotspots for SSTIs.

Final diagnosis International Classification of Diseases (ICD-9 CM) codes for SSTIs, as well as chief complaints with SSTI-associated words (i.e. abscess, cellulitis), were used to define SSTI-related ED visits. Identified SSTI visits were then mapped to one of 16 Boston neighborhoods, each having a unique demographic profile with differences in race, socioeconomic status, age, and population density[3]. Trends within patient demographics were examined inside potential hotspots of neighborhood clustering for SSTI visits in EDs.

We estimated unique SSTI visits to represent 3.29% (n=45,252) of all visits to Boston EDs from 2007 to 2011. During the given time frame, the overall yearly percentage of SSTI visits increased from 3.08% to 3.51%. Additionally, we observed a seasonal pattern with the peak incidence of SSTI visits occurring in the summer. The majority of SSTI visits (54%) were among patients 18–44 years old[4]. More specifically, males accounted for less than half of all ED visits for each year of the study but accounted for 52% of total SSTI visits. Although accounting for only 24% of Boston's population,4 African American patients accounted for a disproportionate 43% of total SSTI visits. Furthermore, the five-year average rate of SSTI visits for black patients (281.2 per 10,000) was 2.8 times greater [CI 2.7-3.0] than the rate for Caucasian patients (99.0 per 10,000). Overall, the five-year average percent of neighborhood-specific ED visits for SSTIs had a geographic distribution ranging from a low of 2.69% to a high of 4.11%.

Our study demonstrates the use of syndromic surveillance to track the epidemiology of community acquired SSTIs through the use of disposition data. Our results emphasize the significant burden of SSTIs in this urban population, accounting for up to 4% of all ED visits. Additionally, our syndromic surveillance methods may be useful in providing information regarding the local epidemiology of SSTIs, including the identification of neighborhood hotspots. Local syndromic surveillance systems have the potential to provide public health authorities and ED clinicians near real-time data on trends in demographic risk factors despite an unavailability of laboratory data.

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Iris Melanoma in Children: Current Approach to Management

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Iris melanoma is a rare condition, comprising 4% of uveal melanoma and having a prevalence of 5.1 cases per million population in the United States[1]. The mean age of presentation is 40–47 years, which is approximately 10-20 years younger than patients with other uveal melanomas[2]. Most patients are Caucasian (97.8%) with blue or green irides (97%), and males and females are affected equally[1,3]. Pediatric (younger than 21 years of age) iris melanoma is especially rare, representing only 8% of iris melanoma cases1. The differential diagnosis of iris melanoma includes primary iris cyst (38%), iris nevus (31%), essential iris atrophy (5.7%), iris foreign body (4.5%), peripheral anterior synechiae (2.5%), and iris metastasis (2.5%)[4]. Iris melanoma in children is characterized by smaller tumors, less seeding, and fewer cases of secondary glaucoma compared to adults1.

This report presents a case of pediatric iris melanoma to demonstrate the unavoidable possibility of recurrence and complications associated with iris melanoma in children despite standard treatment protocols and proper surgical technique. A 15-year old Caucasian male presented with one-month history of a brown nodule in the inferotemporal aspect of his left eye (Figure A). Iris nevus was diagnosed and the patient was observed. Nearly two years later the lesion had grown in basal diameter and thickness (Figure B, C, D), and the tumor was excised by partial lamellar scleral flap and sector iridectomy (Figure E). Histopathology confirmed spindle cell iris melanoma.

IRIS MELANOMA

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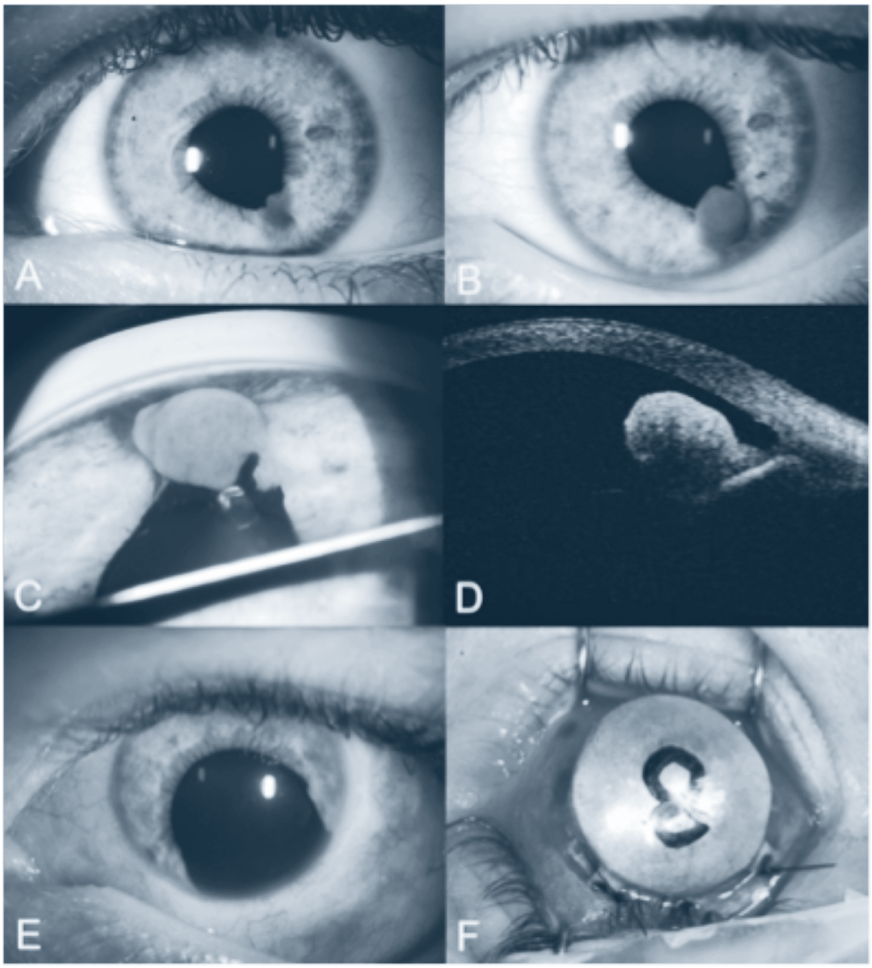

FIGURE 1: A 15-year-old Caucasian male with a pigmented iris lesion. The iris lesion was small at presentation (A) and showed growth over 2 years (B) visible on gonioscopy (C) and anterior segment optical coherence tomography (D). The lesion was excised by partial lamellar scleral flap and sector iridectomy (E). Later tumor recurrence in the anterior chamber angle with elevated intraocular pressure necessitated Iodine125 plaque radiotherapy (F).

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Two years post-operatively, tumor recurrence with anterior chamber angle involvement and secondary glaucoma developed. The presence of glaucoma in eyes with iris melanoma complicates treatment. Iris melanoma associated with glaucoma (compared to iris melanoma without glaucoma) is more likely to be thicker, involve the angle, and demonstrate iris stromal seeding.[5] The patient was then treated with custom designed Iodine[1,2,5] plaque radiotherapy (Figure F). Local tumor recurrence after resection in patients with iris melanoma ranges from 2% to 14%, depending on surgeon and surgical technique. The median time from resection to recurrence is 45 months.[3] Metastasis after local iris melanoma resection occurs in 0% to 9% of reported cases[3]. Older age, involvement of the anterior angle, elevated IOP, and extraocular extension are all risk factors for metastasis1. Resection and plaque radiotherapy for iris melanoma have remarkable local success rates but complications of therapy can lead to visual damage. Visual damage will be an unavoidable complication in this case but treatments such as plaque radiotherapy need to be implicated in cases such as this to ensure tumor eradication and preservation of life. This case report outlines current management options for pediatric iris melanoma and also demonstrates the possibility of tumor recurrence that persists despite proper initial surgical management. This report and further studies on ocular melanoma treatment and recurrence will serve as invaluable assets to improve treatment options with the goal of preventing recurrence and minimizing treatment complications.

This case report outlines current management options for pediatric iris melanoma and also demonstrates the possibility of tumor recurrence that persists despite proper initial surgical management.

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Understanding the Experience of Mature-Age Medical Students Compared to Traditional Medical Students in the Clinical Setting

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Although the average age of first-year medical students is 24, an increasing number of mature-age students, defined as those over age 30, are entering medical school. Most studies of mature-age medical students have examined academic performance using quantitative research design.[1, 2] Few studies have employed qualitative methodology to determine the experience of mature-age medical students, especially in the clinical setting.

To further study this, a recruitment email was sent to all medical students enrolled in clinical rotations. First responders were interviewed until saturation in emerging themes was achieved. Interviews were conducted and recorded in a private office setting, then transcribed. Five mature-age students and four traditional students were interviewed. Using methodology for qualitative research described by Mustakas (1994), the investigators individually coded the transcripts to identify emerging themes.[3] Coded themes underwent peer review, with triangulation of data collection, to determine the main themes. Three main themes emerged from the study. First, abundant life experience influences students' perception of their role on clinical rotations. A mature-age student explained, "Having kids, being married and divorced, helps in connecting with patients." Previous work experience shapes expectations as a physician-in-training.

While traditional students tend to be intimidated, mature-age students desire to take initiative. Age plays a role in the students' ability to relate to senior team members, as well as medical school colleagues. Traditional students note that mature-age students are "more realistic" due to their "life experience in the workplace." Mature-age students draw upon previous life experiences, which shapes role expectations, as well as medical team dynamics. These differences may have implications in training the growing number of mature-age medical students. A larger scale qualitative study including multiple medical school sites is being developed.

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