February 2013, Volume 72, No. 2, ISSN 2165-8218

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Prescription Drug Cost Reduction in Native Hawaiians After Laparoscopic Roux-en-y Gastric Bypass

Edward C.F. Lam MD; Daniel Murariu MD, MPH; Edwin Takahashi BA; Chan W. Park MD; Racquel S. Bueno MD, FACS; and Cedric S.F. Lorenzo MD

Abstract

Objective: Native Hawaiians (NH) represent a unique population where socioeconomic factors have contributed to higher incidence rates of obesity and related comorbidities than in the general population resulting in substantial prescription medication costs. Studies demonstrate that laparoscopic Roux-en-y gastric bypass (LRYGB) surgery results in significant weight loss, improvement of comorbidities, and decreased costs for prescription medications in Caucasians. This study aimed to analyze the effects of LRYGB surgery on Native Hawaiians and their prescription drug costs.

Methods: Demographics, baseline body mass index (BMI), comorbidities, preoperative, and postoperative data were analyzed for NH patients who underwent LRYGB between January 2004 and April 2009. Medication costs were determined using the online pharmacy <http://www.drugstore.com>. Generic drugs were selected when appropriate, while vitamins and nutritional supplements were not included in this study.

Results: Fifty (14 Men, 36 women) NH patients had sufficient data and follow-up for analysis. Average preoperative BMI was 49 kg/m², while at one year follow-up it decreased to 33 kg/m² (P<.001). This correlates to an average of 61% excess body weight lost (P<.001). The average number of prescription medications decreased from 3.5/patient preoperatively to 1.1/patient at one year (P<.001), equating to a monthly cost savings of US $195.8/patient (P<.001).

Conclusions: LRYGB provided substantial weight loss for morbidly obese NH patients, resulting in significantly less prescription medication use and substantial cost savings. Thus, bariatric surgery for weight management has the potential to improve the overall well-being and lower the financial burden of medical care in socioeconomically disadvantaged communities such as the NH.

Keywords
Native Hawaiians, bariatric surgery, laparoscopic roux-en-y gastric bypass, prescription costs

Introduction

Obesity is a growing epidemic across the nation. According to the Centers for Disease Control’s 2010 Behavioral Risk Factor Surveillance System Report 36.2% of adults in the United States are classified as overweight (BMI ≥25) and 27.6% as obese (BMI ≥ 30). In 2006, obese individuals spent an average of USD 1,400 more annually on medical care costs than non-obese people, while in 2008 obesity-associated medical care costs in the United States were estimated to be as high as USD 147 billion annually. This epidemic has not spared the state of Hawai‘i; furthermore, it has also been distributed unevenly in terms of ethnicity. According to the 2010 United States Census, out of 1,360,301 people in Hawai‘i, 26% of the total population identified as either partially or solely Native Hawaiian (NH). Although only 23% of Hawai‘i’s total adult population is obese, over 44% of Native Hawaiians are classified as obese. Consequently, the obesity epidemic also disproportionately impacts Native Hawaiian patients financially as the burden of their prescription drug costs are higher. Native Hawaiians increasingly have sought bariatric surgery as means of weight loss and comorbidity reduction per the Queen’s Medical Center’s unpublished data on bariatric surgery utilization in the Native Hawaiian community.

Unfortunately, like other indigenous peoples in the United States, Native Hawaiians suffer from some of the worst health. According to the US Department of Health and Human Services Office of Minority Health, Native Hawaiians have more than twice the prevalence of diabetes and are more than 5.7 times as likely as Caucasians to die from diabetes. Native Hawaiians are also 30% more likely to be diagnosed with hypertension than Caucasians. This is compounded by the fact that Native Hawaiians are socioeconomically disadvantaged compared to other ethnicities and have a more difficult time accessing adequate healthcare. According to the 2010 Census Bureau data, Native Hawaiian and Pacific Islander family median income was more than USD 9,800 lower than the median income for non-Hispanic Caucasian families; furthermore, 16% of Native Hawaiian and Pacific Islander families were living at the poverty level compared to only 10% of non-Hispanic Caucasian families.

Laparoscopic Roux-en-y gastric bypass (LRYGB) surgery has proven to result in substantial weight loss and comorbidity improvement or resolution. Studies examining the effects of bariatric surgery have demonstrated concomitant reduction in prescription medication use and cost. One such study, involving 77 morbidly obese patients, reported a decrease from 2.4 unique prescriptions treating gastroesophageal reflux disease, diabetes mellitus, hypertension, and/or hyperlipidemia to 0.2 unique prescriptions at one year postoperatively. This represented a mean monthly medication cost decrease from USD 196 preoperatively to USD 28 at one year postoperatively. Another study on 78 patients showed a reduction from 4.2 to 1.4 unique prescription medications per month per patient for obesity-associated comorbidities at one year after laparoscopic Roux-en-y gastric bypass, equating to a monthly drug cost reduction from USD 368.6 to USD 118.7 per patient, a 68% reduction.

Overall, Native Hawaiians represent a unique population within the United States which is plagued with high rates of obesity and obesity-associated comorbidities and is at increased risk for negative outcomes due to socioeconomic factors that render them least able to cope with the economic burden of prescription drug costs. No studies as of yet have determined if the effect of laparoscopic Roux-en-y gastric bypass surgery on prescription drug costs can be reproduced in a minority population. This study seeks to determine whether a population like the Native Hawaiians that suffers from higher obesity rates, obesity-associated comorbidities and detrimental socioeconomic factors compared to Caucasians can successfully benefit from...
laparoscopic Roux-en-y gastric bypass surgery as evidenced by postoperative prescription drug cost reduction.

Methods
A retrospective chart review was conducted on Native Hawaiian patients over the age of 18 years undergoing laparoscopic Roux-en-y gastric bypass surgery at a tertiary medical center with a comprehensive, multi-disciplinary surgical weight program between January 2004 and April 2009. Only patients with postoperative follow-up for at least one year were included. Medical records were reviewed for demographic data, height, weight, preoperative comorbidities, medication prescriptions, BMI, and excess body weight (EBW). Native Hawaiian ethnicity was determined by a self-reported questionnaire. Medication prescribed to patients before and after bariatric surgery was documented by nursing staff at the medical center. This study included patients who identified themselves as either part or full Native Hawaiian. Outcome measures included amount of weight lost, changes in the number of prescription medications, and prescription drug cost changes postoperatively. Weight loss was reported as the percentage of excess body weight loss (EWL), which is standard in the bariatric surgery nomenclature. Percent EWL was calculated in the following manner:

\[
\text{\% EWL} = \frac{\text{preoperative weight} - \text{postoperative weight}}{\text{preoperative weight} - \text{ideal weight}} \times 100
\]

Successful weight loss after laparoscopic Roux-en-y gastric bypass was defined as a patient achieving greater than 50% of excess body weight lost (>50% EBW) at one year postoperatively.

Medication costs were determined using the online pharmacy (http://www.drugstore.com) and costs were determined for a 30-day supply of all medications each patient was prescribed. Generic versions of medications were substituted for their name-brand counterparts whenever generics were available in both preoperative and postoperative medication cost calculations in order to ensure the estimated cost savings were truly attributable to the experimental factors of laparoscopic Roux-en-y gastric bypass surgery. Vitamins and nutritional supplements were not included in this study. Statistical analysis was performed using IBM SPSS 16.0 (Somers, NY). Chi-squared test analysis was used for independent variables and Student’s T-test analysis was performed for continuous variables, with criteria for statistical significance set as \(P<.05\). This study protocol had been reviewed and approved by the Queen’s Medical Center’s institutional review board.

Results
Out of 105 Native Hawaiian patients receiving weight loss surgery during the study period, 50 (14 men, 36 women) had sufficient one-year follow up data for analysis. The average preoperative BMI was 49 kg/m\(^2\) (±7.3), while average BMI at one-year follow-up was 32.6 kg/m\(^2\) (±5.6; \(P<.001\)), (Figure 1). The average percentage of preoperative EWL was 61.5% (\(P<.001\)). Most of the prescription medications were for, but not limited to, obesity-associated comorbidities such as hypertension, diabetes mellitus, gastroesophageal reflux disease, and polyarthralgia and numbered 3.5 (±2.5) unique prescriptions per patient. At one-year postoperatively, the average number of all prescription medications decreased to 1.1 (±1.1) per patient.
representing a 67% reduction ($P<.001$; Figure 2). The average preoperative monthly prescription drug cost was USD 263.1 per patient, while the average cost one year after surgery decreased to USD 67.3 per patient, representing a 74% reduction in prescription drug costs ($P<.001$) and a calculated annualized cost-savings of USD 2,349.6 per patient (Figure 3). No statistically significant differences between male and female patients were found in terms of their preoperative BMI, postoperative weight loss, or reduction in prescription medication costs.

**Discussion**

Native Hawaiians are burdened by the highest rates of obesity and obesity-associated comorbidities in Hawai‘i, compounded by poor socioeconomic factors. Complications of obesity-associated comorbidities in Native Hawaiians are also significantly higher when compared to the Caucasian population, resulting in disproportionately higher morbidity and mortality. This health burden is superimposed on a population that is less able to compensate for this significant disease burden. Native Hawaiians have less access to higher education and are more likely to suffer from poverty when compared to the general population. The Native Hawaiian population as a whole has less income than the general population, and are thus less able to afford health care or address the fiscal consequences of obesity-associated comorbidities. The high prevalence of morbid obesity coupled with high rates of impoverishment generates high morbidity and mortality that not only diminishes the quality of life for a disproportionately higher number of Native Hawaiians but also underscores the importance of any health cost savings the medical community can provide.

Definitive treatment, rather than long-term management, is a better way to reduce the negative impact of the factors listed above on a population’s health while simultaneously lessening their financial burden. Reviews and meta-analyses on bariatric surgery have found Roux-en-y gastric bypass surgery to be very effective in inducing weight loss in obese patients, with the mean percentage of excess weight loss for patients to be at approximately 61.6% at one year. Concurrently, a substantial majority of patients with diabetes, hyperlipidemia, hypertension, and obstructive sleep apnea experience either significant improvement or complete resolution of the listed comorbidities following surgery. Similar studies have shown that this reduction in weight results in substantial prescription drug cost reductions as these comorbidities resolve. Prescription drug cost-savings of 57% to 85% have been demonstrated at one-year follow-up after laparoscopic Roux-en-y gastric bypass surgery.

These studies, however, were conducted on an undifferentiated obese population with no consideration for the degree of socioeconomic impoverishment and ethnicity. This is a significant shortcoming as socioeconomically disadvantaged populations would most stand to benefit from any measure that reduces the health and financial burden of obesity. Thus, our study provides a unique opportunity to observe how laparoscopic Roux-en-y gastric bypass surgery can positively impact the health and economic well-being of a socioeconomically disadvantaged group like the Native Hawaiian population.

With an average excess weight loss percentage of 61% and a 74% reduction in prescription drug costs, our study reveals that Native Hawaiians stand to substantially benefit from laparoscopic Roux-en-y gastric bypass surgery in a manner equal to that of Caucasians (Table 1). This finding suggests that while disadvantaged ethnic populations may be disproportionately at risk for obesity and its comorbidities, they may stand to benefit more from laparoscopic Roux-en-y gastric bypass surgery as the savings represent a larger portion of their income.

A few limitations must be noted. We did not compare the drug cost reduction in Native Hawaiians to patients of other ethnicities who underwent bariatric surgery. This drawback extends beyond the scope of this current study which focuses solely on the expenditure for prescription medications by Native Hawaiians. Secondly, we did not compare the cost/savings ratio for the price of bariatric surgery to the financial benefit from the reduction in medication. However, the price for surgery varies widely from patient to patient, as well as by location and physician experience. Therefore, this latter issue would be poorly generalizable to a larger population, even within the same institution. Third, the analysis conducted in this study was limited to patients who had sufficient one-year follow up data. A lack of follow up may be related to suboptimal compliance with recommendations, thereby correlating with poorer outcomes.

**Conclusion**

Our study demonstrates that laparoscopic Roux-en-y gastric bypass surgery is a very effective way to treat obesity in Native Hawaiians while simultaneously relieving them of the financial burden of prescription drug costs. Prescription drug cost savings achieved by Native Hawaiians were comparable

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**Table 1. Review of prescription drug cost reduction studies in patients undergoing laparoscopic Roux-en-y gastric bypass surgery (with at least 1 year of follow-up).**

<table>
<thead>
<tr>
<th>Study</th>
<th># of Patients</th>
<th>Mean Preoperative BMI</th>
<th>% EWL*</th>
<th>AMDC** Preoperatively (USD)</th>
<th>AMDC** Postoperatively (USD)</th>
<th>Prescription Drug Cost % Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lam, 2012</td>
<td>50</td>
<td>49</td>
<td>61.5</td>
<td>263.1</td>
<td>67.3</td>
<td>74</td>
</tr>
<tr>
<td>Nguyen, 2006</td>
<td>77</td>
<td>47</td>
<td>67</td>
<td>196</td>
<td>28</td>
<td>85</td>
</tr>
<tr>
<td>Snow, 2004</td>
<td>78</td>
<td>48</td>
<td>N/A</td>
<td>368.7</td>
<td>118.7</td>
<td>68</td>
</tr>
<tr>
<td>Monk, 2004</td>
<td>64</td>
<td>57</td>
<td>N/A</td>
<td>317</td>
<td>135</td>
<td>57</td>
</tr>
</tbody>
</table>

to those achieved by Caucasian counterparts in other studies. Furthermore, if current trends in obesity for the general population continue unabated, the increased disease burden of obesity will no longer be limited to minorities but will represent the general condition of the population as a whole. It is likely that the disease and socioeconomic burden that Native Hawaiians face today will be the exact same burdens that the general population will have to face in the future. Our disadvantaged communities may act as a leading indicator of the health and socioeconomic concerns of the nation as a whole, especially in a challenging economic climate where an increasingly larger percentage of the general population is becoming unable to manage the high costs of healthcare in America. As such, the more we understand and learn from the Native Hawaiian population, the better prepared we will be to deal with and intervene to reduce obesity and obesity-associated comorbidities. Our study demonstrates that although underserved populations may be at greater risk of obesity and its associated comorbidities, they in fact stand to benefit equally from laparoscopic Roux-en-y gastric bypass surgery.

Conflict of Interest
The authors do not have any conflicts of interest to report.

Authors' Affiliation:
- ARTEMIS (Association of Research, Training and Education in Minimally Invasive Surgery) Research Group, Department of Surgery, University of Hawai‘i John A. Burns School of Medicine, Honolulu, HI

Correspondence to:
Cedric S.F. Lorenzo MD; Department of Surgery, John A. Burns School of Medicine, University of Hawai‘i; 1356 Lusitana Street, 6th Floor, Honolulu, HI 96813; Ph: (808) 586-2920; Email: clorenzo@hawaii.edu

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Angioleiomyoma in a Rare Location: A Case Report

Ashley D. Willoughby DO; Andrew T. Schlussel DO; Judy H. Freeman MD; and Kevin Lin-Hurtubise MD

Abstract
A case report of a 38-year-old man with a 10-year history of left buttock mass associated with pain and numbness. A computed tomography scan showed a subcutaneous enhancing 1cm lesion that was not communicating with surrounding structures to include neurovascular structures. The mass was removed without complication and sent to pathology for extensive review. This case report signifies the importance of maintaining a broad differential with a subcutaneous mass presentation and includes thorough histology and pathology for angioleiomyoma.

Introduction
Soft tissue tumors are defined as mesenchymal proliferations that occur in the extraskeletal, nonepithelial tissues of the body, including the viscera, dura, and lymphoreticular system. They have many different origins including muscle, fat, fibrous tissue, vessels, and nerves. A leiomyoma is a benign smooth muscle cell tumor. Therefore, an angioleiomyoma is a benign tumor of the vascular wall; the muscularis media. Three subtypes of angioleiomyoma include solid type, cavernous, and venous, with solid type being most common.

The frequency of soft tissue tumors is difficult to estimate because most benign lesions are not excised for pathologic examination. As many as half of all angioleiomyomas diagnosed will be asymptomatic; therefore many patients may choose not to have them excised until they become painful or for cosmetic reasons.

Although one study from 1983 reported a series of over 500 angioleiomyomas, these soft tissue tumors have not been as frequently reported in the recent literature. In a study of 562 cases, 2.5% of cases were located on the trunk with 79% of those occurring in females and 85% consistent with the solid type. We present a case of a male patient with an angioleiomyoma of the buttock, a location that has not been described in previous publications.

Case Report
The patient is a 38-year-old healthy man who reported to the general surgery clinic with a ten-year history of a left buttock mass. The mass was previously asymptomatic until a few months ago when it began to manifest symptoms of pain and numbness around the region, however it had not changed significantly in size. There was no skin discoloration or retraction, and the patient had no gross neurologic deficits of the lower extremity. The patient’s exam was remarkable for a one-centimeter by one-centimeter circumscribed mobile soft subcutaneous nodular mass located centrally on the left buttock without skin dimpling or fixation to the underlying muscle. There was a minimal amount of overlying skin hyperpigmentation. A computed tomography (CT) scan showed a subcutaneous enhancing one centimeter lesion not connected to underlying muscle and not related to adjacent neurovascular structures, Figure 1. The patient underwent an excisional biopsy with surgically negative margins.

The mass was removed just superficial to the fascia of the gluteus maximus muscle, Figure 2. Histological analysis revealed a sharply circumscribed subdermal nodule composed of bland spindle cells encircling vascular lumina, Figure 3. Large sinusoidal vessels were observed with small slit-like channels, Figure 4. The stroma contained varying amounts of fibrous tissue and myxoid change. Mitotic activity was absent and there was no evidence of necrosis or hemorrhage. Histologically all surgical margins were negative. Some of the vessels had a smooth muscle layer of moderate thickness, Figure 3. The morphologically bland appearing spindle cells separating the sinusoidal vessels generally had a poorly defined membrane, with pink cytoplasm, and elongated nuclei with rounded cigar-shaped ends. In several areas, these cells merged with the smooth muscle cells. Immunohistochemical evaluation demonstrated that both the spindle cells and the smooth muscle cells surrounding the vessels were strongly immunoreactive for vimentin, smooth-muscle actin, and desmin, Figure 5. There was absence of immunoreactivity for S100 protein excluding a tumor of melanocytic or nerve sheath origin. CD34 highlighted the endothelial cells within the rounded and branching vascular structures. These histologic features support a diagnosis of angioleiomyoma.

Discussion
A superficial soft tissue tumor is a common consult seen by a general surgeon. Despite the benign nature of angioleiomyoma, it is important for this diagnosis to be a part of the differential. The patient described above received the appropriate treatment due to his presentation of pain and abnormal enhancement on CT scan. The histologic findings and presentation are consistent with an angioleiomyoma.

Sixty-seven percent of patients with this tumor will present in their fourth, fifth, or sixth decade. Angioleiomyomas of the solid type have a strong female predominance, whereas the venous and cavernous types are slightly more common in males. Approximately 89% occur in the extremities with 67% occurring in lower extremity and they are typically <2 cm in size. The most common complaint is pain that is often paroxysmal and initiated by the slightest touch or exposure of the tumor to environmental stimuli. The development of multiple lesions is thought to be hereditary and transmitted as an autosomal dominant trait.

The most definitive diagnostic method to make a diagnosis is from histologic analysis of an excisional biopsy, along with confirmatory immunohistochemical evaluation. Characteristics of an angioleiomyoma on CT scan have not been well described;
Figure 1. CT scan demonstrating enhancement of the left buttock angioleiomyoma.

Figure 2. Gross specimen of left buttock angioleiomyoma demarcated by solid arrow.
Figure 3. Immunoreactivity for desmin highlights the prominent smooth muscle component of this tumor.

Figure 4. Circumscribed nodule composed of intersecting fascicles of smooth muscle cells encircling numerous vascular channels lined by bland endothelial cells.
however, MRI has been frequently used as it is more sensitive for discerning between the soft tissue layers and can demonstrate a non-specific, well defined, round or oval mass in the subcutaneous or dermal tissue. These lesions are usually either isointense or hyperintense to skeletal muscle on T1W1 (low signal magnetic resonance image) images and heterogeneous on T2W1 (high signal on magnetic resonance imaging). Often a hypointense fibrous capsule can be identified forming the peripheral rim.

Angioleiomyomas consist of a proliferation of spindle cells that tend to intersect with each other at right angles. Immunohistochemical characteristics for angioleiomyoma include vimentin, muscle specific actin (MSA), type IV-collagen, and smooth muscle actin. These lesions are benign and rarely demonstrate invasion into surrounding structures. They can occur in any tissue containing smooth muscle including arrector pili, smooth muscle walls of arteries, and genital tissues (vulva, nipple, and scrotum). They can also arise anywhere in the gastrointestinal tract and may present with obstruction, intussusception, or volvulus. Cardiac tissue, being comprised of both skeletal and smooth muscle, is also a potential location for angioleiomyoma.

An important distinction to make is between angioleiomyoma, angiomyolipomas, and leiomyosarcomas. Angiomyolipomas are most well known as a renal tumor with an association to tuberous sclerosis. However, angiomyolipomas can also occur as a soft tissue tumor. Beer and colleagues make the distinction that renal angiomyolipomas are HMB45 positive and cutaneous lesions are HMB45 negative. The cutaneous angiomyolipoma is distinguished from angioleiomyoma by the presence of mature adipose tissue within the tumor. Adipose tissue is present in only 2.5% to 3% of angioleiomyomas, whereas it can occupy approximately 20% to 30% of angiomyolipomas.

Leiomyosarcomas account for 10% to 20% of all soft tissue sarcomas and generally present as a painless firm mass. There is a female predominance and leiomyosarcomas usually involve the skin, deep soft tissue of the extremities, or retroperitoneum. Histologically the tumor nuclei will typically be cigar-shaped and arranged in interweaving fascicles. Lesions located in skin or deep soft tissue of extremities are typically <2cm in size. Tumors located in the retroperitoneum can be very large and remain undiagnosed until found incidentally or compressive symptoms develop.

Treatment options for angioleiomyoma include observation with close interval follow up, biopsy, or surgical excision. There is a recurrence rate of 0.4% when excised. Ultrasound guided biopsy of the lesion may be indicated if rapid growth of the mass is observed. If malignancy is suspected or found upon fine needle aspiration, then excisional biopsy would be recommended.

Leiomyosarcoma treatment depends on the size, location, and grade of the tumor. Superficial or cutaneous leiomyosarcomas are usually small and have a good prognosis, whereas those of the retroperitoneum are large, often cannot be entirely excised, and cause death by both local extension and metastatic spread. Since the 1983 review of solitary cutaneous and subcutaneous leiomyomas, several case reports have been published and demonstrate the most common presentation is the solid type of the lower extremity with a female predominance and mean age of being 47 years. This case report defies this commonality, emphasizing the importance of maintaining a broad differential for cases that have a common presentation.

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Conflict of Interest
The authors report no conflicts of interest.

Authors’ Affiliation:
- Department of General Surgery, Tripler Army Medical Center, Honolulu, HI (A.D.W., A.T.S., K.L-H)
- Department of Pathology, Tripler Army Medical Center, Honolulu, HI (J.H.F.)

Correspondence to:
Ashley D. Willoughby DO; Department of Surgery/General Surgery, Tripler Army Medical Center; 1 Jarrett White Road, Tripler AMC, HI 96859; Ph: (808) 433-3479; Email: ashley.willoughby@amedd.army.mil

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Birth Size and Later Central Obesity Among Adolescent Girls of Asian, White, and Mixed Ethnicities

Rachel Novotny PhD, RD; Vinutha Vijayadeva PhD; John Grove PhD; Unhee Lim PhD; and Loic Le Marchand MD, PhD

Abstract
Birth size has important implications for health and disease in adulthood. This study examined the association of birth size with central body fat distribution in late adolescence. Data were from a cross-sectional survey of adolescent girls (N = 143, 13-18y) of Asian, White and Mixed Asian-white ethnicity collected in 2005-2007 in Hawai‘i, USA. Central body fat distribution was assessed with dual-energy x-ray absorptiometry and birth size from birth certificates and parent recall. Food diaries (3-day) were used to determine energy intake and metabolic equivalents of energy expenditure. The proportion of Asian ancestry was determined by questions and anthropometry was performed. T-tests compared groups, and multiple regression examined predictors of central body fat distribution, adjusting for potential confounders. Asian girls had a lower mean weight and gestational age at birth than White girls, and a lower mean dietary fat intake in adolescence. Girls of Asian and Mixed Asian-white ancestry had a more body fat distribution than White girls. Lower birth weight was associated with greater central body fat distribution (0.1 or 10% higher central body fat distribution for every 10 grams lower birth weight), after adjusting for age, ancestry, physical activity, energy intake, and bi-iliac breadth, and gestational age. Further adjusting for birth length attenuated the birth weight effect, and shorter birth length was the significant predictor of central body fat distribution. (0.1 or 10% higher central body fat distribution for every 0.01mm shorter length). If confirmed, these findings would suggest that linear growth may be more relevant to metabolic programming than growth in mass.

Keywords
birth size, ethnicity, body fat, adolescence, body composition

Introduction
Health consequences of obesity range from increased risk of premature death due to serious chronic conditions such as Type 2 diabetes, coronary heart disease (CHD), hypertension, stroke, and certain cancers. Birth size has been found to have important implications for health and disease in adulthood. According to the Barker’s “thrifty phenotype” hypothesis, chronic disorders, such as hypertension, insulin resistance and obesity in adult life originate from inadequate intrauterine growth, followed by excessive energy intake after birth.1,2 Fetal development affects biological programming whereby disease risk results from a mismatch between the exposure of the fetus and the environment after birth.

For example, if a fetus is exposed to malnourishment “in utero,” it may be programmed in expectation of a postnatal environment higher metabolic efficiency and lipid storage. When exposed to nutritional abundance in postnatal life, this greater metabolic efficiency leads to obesity and related diseases. Birth size is an indicator of fetal response to the in utero nutritional environment.3 Indeed, birth weight has been inversely associated with increased risk for Type 2 Diabetes in adulthood.4 Obesity and central body fat distribution is associated with metabolic risk factors, especially among Asians. In fact, new guidelines for “obesity disease” in Japan defined obesity as a BMI ≥25; and the greatest worldwide increase in adult diabetes is projected to occur in Asian populations.5 Asian-Americans relative to Whites are predisposed to central body fat or trunkal body fat distribution (upper body fat or “Apple” shape). However, the causes of obesity have been less studied in Asians than in Whites, especially during adolescence. The third US National Health and Nutrition Examination Survey (NHANES III) examined adiposity distribution in relation to birth weight among White (n = 759), Black (n = 916) and Hispanic (n = 813) children, aged 5-11.6 Birth weight was negatively associated with subscapular skinfold thickness and central adiposity (trunkal fat mass as measured by dual-energy x-ray absorptiometry [DXA]). Birth weight was also inversely associated with iliocostal thickness in Blacks and Hispanics (P < .01), and with sum of four skinfolds (Blacks P < .05). Data were not provided for birth length for Asians in Hawai‘i, or in NHANES III (or previous NHANES surveys). Birth weight adjusted for gestational age was found to be inversely associated with DXA trunk fat mass/total body fat mass in a study of 107 adolescents of African-American, Hispanic, Asian/Other and White ethnicities in New York.7 Data are limited on birth length. One study found both low and high birth length to be associated with obesity assessed by BMI.8 No studies were identified that examined the influence of birth length on central body fat distribution, in adolescence or adulthood, or in Asian populations. In this study we examine the relationship of birth length and Mixed Asian/White ethnic ancestry with central body fat distribution in 13-18 year old adolescent girls.

Methods
Population, Design and Recruitment
This study presents data collected in 2005-2007 on Asian, White and Mixed Asian/White girls from the Female Adolescent Maturation (FAM) Study 3 (N = 143, aged 13-18). Subjects were recruited from the Kaiser Permanente Health Maintenance Organization membership living on the island of Oahu. The target population was healthy girls of Asian and White ancestry. The overall goal of the FAM Studies was to determine past and current lifestyle patterns for optimal bone growth and for reduced cancer risk factors, such as early puberty and higher central adiposity. The study was approved by the University of Hawai‘i Committee on Human Studies, Hawai‘i Pacific Health Review Board, and the Kaiser Permanente Institutional Review Board.

Measurements
Ethnic Ancestry
We used the BLEND methodology, developed for the FAM studies, to characterize admixed ancestries.9 We asked parents/
Food Intake Assessment
A 3-day food record was collected at each study visit and included two weekdays (Thursday and Friday) and one weekend day (Saturday). A measuring cup, spoon, and ruled paper were provided to help subjects estimate quantities of food items eaten, as well as dietary supplements. A food record collection form was sent to eligible participants for completion prior to their scheduled study visit. At the visit, the food record was probed for clarity and completion using food models. The food record data were processed and individual intake of nutrients was estimated by the Nutrient Support Shared Resource Core at the University of Hawai‘i Cancer Center using its comprehensive food composition database which contains national, local and ethnic foods.

Physical Activity Assessment
Participants completed a physical activity questionnaire, developed for adolescents, at each study visit. For each activity they took part in more than ten times in the past year, participants were asked how many months/year, how many days/week and how many minutes/day they spent doing that particular activity, which was then converted to average number of hours/week. The metabolic equivalent (MET) values for all activities were calculated for the specified duration (MET of each activity x duration of each activity). The sum of all MET values per week was used as a proxy measure of activity energy expenditure in the past year.

Dual Energy X-Ray Absorptiometry (DXA) Assessment of Body Fat
We used DXA (GE Lunar Prodigy) to measure total body fat mass (grams) and percent body fat. We calculated a measure of central body fat distribution, trunk-to-periphery fat ratio (TPFR) as fat mass in the trunk over the sum of the fat mass in the arms and legs. A certified radiographic technician trained by the GE Lunar Corporation operated the DXA using standard protocols. Manufacturer quality control procedures were performed on a routine basis, and a manufacturer phantom was measured for calibration. Participants with a positive pregnancy test (n = 1) did not undergo the DXA exam.

Anthropometric Assessment
Anthropometric measures were taken during the visit to the University of Hawai‘i Clinical Research Center. Anthropometric measurements included weight, height, skinfold thicknesses, and body breadths. Weight was measured with a digital scale (Seca, Hanover MD) in pounds, and converted to kg for analyses. Height was measured in cm using a digital stadiometer (Measurement Concepts, North Bend WA). Skinfold measurements were taken at the subscapular and triceps sites using a Lange Skinfold Caliper from Beta Technology Incorporated (Cambridge, Maryland).

Circumferences (arm, abdomen, buttocks) and ulna length were measured with an inextensible measuring tape (Rollfix, Hoechst, Mass, Germany). Bi-iliac and biauricular breadth were measured with a Lafayette Caliper. Each measurement was taken at least twice; a third measurement was taken if the two measures differed by two-tenths of a unit or more, with the average of the two closest values used in the analysis.

Tanner Pubertal Stage of Maturation
Tanner breast and pubertal stages were assessed in a clinical examination by trained and standardized medical personnel.

Birth Characteristics
Birth weight and gestational age were obtained preferentially from birth certificates and when the birth certificate information was missing, recalled values were used. As a result, birth weight and gestational age were obtained from the girl’s birth certificate for 76% of FAM participants or by parent’s recall for the remaining 24% of the participants. Birth length was obtained only by parent’s recall. The Spearman correlation coefficient for birth data from recall and birth certificates was 0.95 for birth weight and 0.7 for gestational age. A paired t-test of difference in means of birth weights from birth certificates and self-report showed a non-significant 10g (174.9 SD) difference (t = 0.55, P = .58, n = 102). One implausible birth length value (of 88.9 cm) was dropped from analyses.

Data Entry, Cleaning, and Statistical Analysis
All data were double entered using a Fox Pro database. Two entries were compared and any data that did not match were corrected using the original hard copy of the data. The first level of data cleaning was done to check for duplicates. The second level of cleaning was done to check for missing entries. A third level of cleaning was done to check for outliers, by calculating the mean, maximum and minimum values of every continuous variable and frequency tables for categorical data.

SAS version 9.1.3 was used for all analyses. A General Linear Model (GLM) for univariate analysis of variance (ANOVA) was used to test the differences between the means for White, Asian, and Mixed Asian/White participants. The P-values were adjusted for Tukey’s Honest Significant Difference method, which allows for all possible pair wise tests. Residual analyses were done to check the adequacy of a fitted multiple linear regression model; the residuals had a distribution with moments similar to a normal distribution, with only moderate skewness (0.34), virtually no kurtosis (coefficient of kurtosis -3 = -0.01), and no obvious outliers. Multiple linear regression based on ordinary least squares estimation was used where
TPFR was regressed on birth weight (reflecting fetal growth in mass) and the same covariates considered in our previous analyses, including age, ancestry, physical activity, energy intake, and bi-iliac breadth (indicator of pubertal maturation in pelvic size). In the current analysis, the girls are older and have completed most of their growth. Models were run with and without further adjustments for gestational age and birth length (to account for early fetal linear growth). Interaction of birth weight and ethnicity was tested and was not significant.

**Results**

**Ethnic Differences**

There were 41 (100%) Asians, 31 (100%) Whites and 72 Mixed Asian/White girls. The 72 Asian/White Mixed girls had a mean proportion of Asian of 0.51 ± 0.16 (range of 0.25 ± 0.24) and a mean proportion White of 0.49 ± 0.16 (range of 0.06 ± 0.75). The girls were tested for ethnic differences in anthropometry, DXA, diet, physical activity, and birth measures for differences between the ethnic groups (Table 1). Girls were approximately 15.5 years old; age did not vary by ethnic group. Asian girls were smaller than either White of Mixed Asian/White girls in various anthropometric dimensions (weight, height, waist circumference, hip circumference, biacromial breadth, biiliac breadth, biceps skinfold thickness, calf skinfold thickness, total fat mass, peripheral fat mass), but similar in several anthropometric measure of body fat: subscapular skinfold thickness, triceps skinfold thickness, biiliac skinfold thickness, and trunk to periphery fat mass ratio compared to the other two groups. Birth weight was significantly greater among Whites, compared to Mixed Asian/White girls (by about 4g/day). There were no ethnic differences in energy intake or physical activity level.

**Birth Size and Central Body Fat Distribution**

A model was built to incorporate known influences on central body fat distribution (TPFR), in addition to the ethnic and birth size variables of interest. Birth weight was introduced to models first, followed by birth length, and then both variables were examined in the same model. The association between Asian ancestry and TPFR (measured by DXA) was not significant ($P=0.08$), adjusting for physical activity, energy intake, biiliac breadth, and birth weight. Birth weight was significantly inversely associated with TPFR (-0.096 ± 0.032, $P=0.0027$, adjusting for age, Asian ethnicity and bi-iliac breadth). Adjusting for Tanner pubic hair stage instead of biiliac breadth, as an indicator of maturity, birth weight was also inversely and significantly associated with TPFR (result not shown). Birth weight remained inversely associated with TPFR after adjusting for gestational age and other previously mentioned covariates in the model (birth weight: regression coefficient = -0.099, $P=0.005$; gestational age: regression coefficient = 0.007, $P=0.40$). In the final, full model (with birth length added), birth weight was no longer significantly associated with TPFR, after adjusting for birth length (birth weight: regression coefficient = -0.0339, $P=0.36$, Table 2). Birth length, was significantly associated with TPFR (regression coefficient = -0.012, $P=0.04$) Bi-iliac breadth was a highly significant positive predictor of TPFR, controlling for age, ethnicity, physical activity, energy intake, birth weight, and birth length.

**Discussion**

In this study of an Asian/White ethnic population, smaller birth size models (weight or length) were both associated with greater central adiposity, and ethnicity was not significant. In the full regression model that included both birth weight and length simultaneously, only birth length remained significant. Bi-iliac breadth was another strong indicator of central adiposity. Thus, factors limiting linear skeletal growth may be especially indicative of risk for future central body fat distribution.

This study contributes novel data on the relationship of birth length with later obesity (in adolescence), which is extremely limited in the literature. Low birth weight has been found important to predict later catch up growth and to be inversely associated with central vs peripheral adiposity (as measured by skinfold thicknesses) in Black and Hispanic US children (aged 5 to 11), to a greater degree than in White children. 6 Childhood and adolescent overweight and obesity have been found in a recent systematic review to significantly increase risk of premature mortality and cardiometabolic morbidity (diabetes, hypertension, ischaemic heart disease, and stroke; hazard ratios ranging from 1.1–5.1) and later disability pension, asthma, and polycystic ovary syndrome symptoms. 15 Both low and high birth weights have been associated with higher DXA fat mass in a cross-sectional study of body composition among 9-18 year olds of African-American, Hispanic, Asian/Other, and White children who were participants in the Pediatric Rosetta Study in New York (1995–2000). 7 Controlling for current weight and Tanner stage, the New York study found that higher birth weight was associated with higher fat mass and percent body fat, while a low birth weight was associated with higher central body fat distribution measured by trunk fat mass adjusted for total fat mass. In our study, the relationship between birth weight and central body fat distribution was inverse and linear. Additionally, our analysis controlled for more potentially confounding covariates (age, bi-iliac breadth, energy intake, and physical activity level) than most previous studies. Our results suggest that the relationship of smaller birth size with more central body fat distribution reflects fetal influences on body composition and metabolism on adolescent body fat distribution.

In previous cross-sectional examination of 107 Asian and white adolescent girls aged 11-16 in this population, we showed that DXA trunk-to-periphery fat ratio (TPFR), taken as a measure of central adiposity, was associated with Asian ancestry, lower
Table 1. Mean ± SE Anthropometric Variables, Physical Activity and Dietary Intake for FAM3 Study Participants, (age 13-18) by Race/Ethnic Group, 2005-2007.

<table>
<thead>
<tr>
<th></th>
<th>100% Asian (n=41) Mean ± SE</th>
<th>Mixed* (n=72) Mean ± SE</th>
<th>100% White (n=31) Mean ± SE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anthropometry</strong></td>
<td></td>
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</tr>
<tr>
<td>Age (y)</td>
<td>15.6 ± 0.3</td>
<td>15.8 ± 0.2</td>
<td>16.7 ± 0.3</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>50.4 ± 1.9×</td>
<td>57.6 ± 1.4c</td>
<td>59.6 ± 2.2</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>158.0± 0.9×</td>
<td>160.9 ± 0.7c</td>
<td>163.8 ± 1.1</td>
</tr>
<tr>
<td>Bi-acromial breadth (cm)</td>
<td>35.4 ± 0.3</td>
<td>36.3 ± 0.2c</td>
<td>36.1 ± 0.3</td>
</tr>
<tr>
<td>Bi-iliac breadth (cm)</td>
<td>26.9 ± 0.4</td>
<td>28.2 ± 0.3c</td>
<td>28.0 ± 0.4</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>64.6 ± 1.3×</td>
<td>69.5 ± 1.0c</td>
<td>69.7 ± 1.5</td>
</tr>
<tr>
<td>Hip circumference (cm)</td>
<td>90.2± 1.4×</td>
<td>95.5 ± 1.1c</td>
<td>96.7 ± 1.6</td>
</tr>
<tr>
<td>Subscapular skinfold (mm)</td>
<td>14.0 ± 1.1</td>
<td>16.5 ± 0.8</td>
<td>16.0± 1.2</td>
</tr>
<tr>
<td>Triceps skinfold (mm)</td>
<td>17.6 ± 1.0</td>
<td>19.3 ± 0.8</td>
<td>20.8 ± 1.1</td>
</tr>
<tr>
<td>Biceps skinfold (mm)</td>
<td>9.7 ± 0.8×</td>
<td>12.3 ± 0.6c</td>
<td>13.3 ± 0.9</td>
</tr>
<tr>
<td>Iliac skinfold (mm)</td>
<td>19.4 ± 1.6</td>
<td>22.9 ± 1.2</td>
<td>22.6 ± 1.8</td>
</tr>
<tr>
<td>Calf skinfold (mm)</td>
<td>16.9 ± 1.1</td>
<td>20.2 ± 0.8c</td>
<td>22.0 ± 1.2</td>
</tr>
<tr>
<td>Pubic Tanner Stages (I-V)</td>
<td>3.8 ± 0.1×</td>
<td>4.1 ± 0.1c</td>
<td>4.4 ± 0.1 (n=23)</td>
</tr>
<tr>
<td><strong>DXA measures</strong></td>
<td></td>
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<tr>
<td>DXA total fat mass (kg)</td>
<td>13.9 ± 1.3c</td>
<td>18.3 ± 1.0c</td>
<td>19.0 ± 1.5</td>
</tr>
<tr>
<td>DXA trunk fat mass (kg)</td>
<td>6.7 ± 0.7</td>
<td>9.0± 0.6c</td>
<td>9.1 ± 0.8</td>
</tr>
<tr>
<td>DXA peripheral fat mass (kg)</td>
<td>6.6 ± 0.6c</td>
<td>8.6 ± 0.5c</td>
<td>9.3 ± 0.7</td>
</tr>
<tr>
<td>DXA trunk-periphery fat ratio (TPFR)</td>
<td>1.0 ± 0.0</td>
<td>1.0 ± 0.0</td>
<td>1.0 ± 0.0</td>
</tr>
<tr>
<td><strong>Physical activity' and Dietary intake' (3-day food record)</strong></td>
<td></td>
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<tr>
<td>Physical activity (MET hr/wk)</td>
<td>95.2 ± 9.2</td>
<td>88.7 ± 6.6</td>
<td>115.2± 10.3</td>
</tr>
<tr>
<td>Energy intake (kj/d)</td>
<td>7247 ± 320</td>
<td>7861 ± 238</td>
<td>6629 ± 372</td>
</tr>
<tr>
<td>Protein (g/d)</td>
<td>64.6 ± 3.3</td>
<td>69.8 ± 2.5</td>
<td>60.3 ± 3.8</td>
</tr>
<tr>
<td>Fat (g/d)</td>
<td>62.1 ± 3.8b</td>
<td>73.4 ± 2.8</td>
<td>64.8 ± 4.4</td>
</tr>
<tr>
<td>Carbohydrate (g/d)</td>
<td>232.0 ± 11.0</td>
<td>238.5 ± 8.2</td>
<td>206.5 ± 12.7</td>
</tr>
<tr>
<td>Saturated fat (g/d)</td>
<td>20.1 ± 1.4</td>
<td>24.7 ± 1.1c</td>
<td>23.0± 1.6</td>
</tr>
<tr>
<td><strong>Birth measures</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gestational age (wks)</td>
<td>39.4 ± 0.3b(n=40)</td>
<td>39.6 ± 0.2c (n=71)</td>
<td>40.7± 0.3</td>
</tr>
<tr>
<td>Birth weight (kg)</td>
<td>3.1 ± 0.1b (n=41)</td>
<td>3.2 ± 0.1b (n=71)</td>
<td>3.5 ± 0.1 (n=31)</td>
</tr>
<tr>
<td>Birth length (cm)</td>
<td>49.6 ± 0.6b(n=29)</td>
<td>50.8 ± 0.4 (n=62)</td>
<td>51.6 ± 0.6 (n=25)</td>
</tr>
<tr>
<td>Ponderal Index (kg/m³)</td>
<td>2.5 ± 0.1 (n=29)</td>
<td>2.5 ± 0.1 (n=62)</td>
<td>2.6 ± 0.1 (n=25)</td>
</tr>
</tbody>
</table>

*Mean proportion Asian 0.51 + 0.16 (range of 0.25 + 0.24); mean proportion White 0.49 + 0.16 (range of 0.06 + 0.75)

†Significantly different from White, P <.01 values are adjusted for multiple comparisons using Tukeys’ method (26)

‡Significantly different from Asian, P <.01 values are adjusted for multiple comparisons using Tukeys’ method

* n = 141, missing information on two girls for DXA scan: Mixed Asian/White, n = 69

†Physical activity: Asian, n = 36; Mixed Asian/White, n = 71; White, n = 29

‡Dietary Intake: Asian, n = 39; Mixed Asian/White, n = 70; White, n = 29

Birth weight, and greater bi-iliac breadth. Asian ethnicity was not as strong a predictor of central body fat distribution in this study of girls aged 13-18 (P = .08), as it was in the younger age group (9-16) (P = .001). This may be due to the differential timing of maturation between the ethnic groups, as Asians were less mature than Whites or Asian/White Mixed girls at the time of measurement in late adolescence. Bi-iliac breadth, an indicator of pelvic size, which typically matures late in adolescence, remained a highly significant predictor of central body fat distribution, as it was in our previous study with the younger age group (9-16) of girls. Factors influencing shape and size of the skeleton (ie, bi-iliac breadth) are worthy of further study as potential moderators of central body fat distribution.
was more strongly associated with overweight (including higher waist-to-height ratio, analogous to the TPFR), and with earlier menarche, in White girls.17 Girls with a lower pubic hair stage (more of the Asian girls), may be experiencing a thelarcheal pathway of maturation, and a greater tendency to central body fat distribution. For example,17 a one unit of increase in BMI Z score has been found associated with earlier breast bud appearance (earlier occurrence of Tanner breast stage 2), by a median of 5.6 months. Thus, as the study girls mature further, an Asian tendency toward central body fat distribution may become more pronounced.

Our results are consistent with a number of epidemiologic studies that have shown an association between perinatal characteristics and adult chronic diseases, including an inverse association between birth weight and subsequent risk of Type 2 diabetes.18–21 Our findings also support the hypothesis proposed by Barker and others1 22,23 that metabolic programming occurs during fetal and early postnatal periods, persists throughout growth, and ultimately affects the risk of overt metabolic disorders in adulthood. The finding that birth length may be more important than birth weight would suggest that early gestational linear growth would be even more relevant to metabolic programming than later gestational growth in mass (when most of the weight is accrued). Our study further suggests that these health consequences in adulthood may be mediated through the development of central body fat distribution in adolescence, an established risk factor of various chronic diseases in adults.1

Our study is limited by a lack of longitudinal measures, other than maternally recalled birth data. Also, we did not have birth certificate birth length data to validate reported birth length measures. However, other research has shown excellent maternal recall of birth length data, with no significant difference from medical records.24 The Asian ethnic group is a highly diverse group composed of Oriental East Asians, Filipinos, Southeast Asians, and South Asians. These groups have different genetic ancestries and have population variability in disease rates. Within the Asian ethnic group South Asians have higher body fat mass and Chinese have lower body fat mass.25 Nonetheless, the ethnic group shows a number of differences from White populations that warrant further examination. Further, we demonstrate novel differences between Mixed Asian/White populations and the Asian and White populations. While values tend to fall between the two groups, as expected, Mixed Asian/White body size more closely resembles the larger White values. Further, the dietary data suggest higher intake among Mixed Asian/Whites than either single ethnic group. We hypothesize that the Mixed Asian/White group consumes foods for both cultural backgrounds, especially celebratory foods that are of higher fat and calorie value, resulting in overall higher dietary fat intake.

In conclusion, our data show that smaller birth size, especially smaller birth length, adjusted for gestational age and adolescent growth parameters, predicts central body fat distribution of girls in late adolescence. The study suggests that low birth length, in addition to low birth weight, should be further examined for use as a risk indicator for subsequent abdominal obesity and associated health risks.

Table 2. Final Models of Predictors of DXA Trunk-to-Periphery Fat Ratio (TPFR) Among Asian, White, and Mixed Asian/White Participants in the FAM3 Study (Multiple Linear Regression), 2005-2007.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Model 1 (n=133)</th>
<th>Model 2 (n=110)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Regression Coef</td>
<td>SE</td>
</tr>
<tr>
<td>Intercept</td>
<td>0.506</td>
<td>0.232</td>
</tr>
<tr>
<td>Age (y)</td>
<td>0.001</td>
<td>0.009</td>
</tr>
<tr>
<td>Asian ancestry (%)</td>
<td>0.071</td>
<td>0.041</td>
</tr>
<tr>
<td>Physical activity (METs, hrs/wk x 10000)</td>
<td>-0.136</td>
<td>0.262</td>
</tr>
<tr>
<td>Energy intake (kcal x 1000)</td>
<td>0.001</td>
<td>0.007</td>
</tr>
<tr>
<td>Bi-iliac breadth (cm)</td>
<td>0.026</td>
<td>0.006</td>
</tr>
<tr>
<td>Birth weight (kg)</td>
<td>-0.085</td>
<td>0.031</td>
</tr>
<tr>
<td>Birth length (cm)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Missing data: age, Asian ancestry, bi-iliac breadth and birth weight missing for 2 girls; physical activity missing for 9; energy intake missing for 7 and birth length missing for 29.

Sources of Funding
This work was supported by the Breast Cancer Research Fund of the US Department of Defense [BC032028] and the University of Hawai'i Cancer Center Developmental Funds and the Research Centers of Minority Institutions at the National Center for Research Resources of the National Institutes of Health [P20 RR119091] and the National Research Initiative of the US Department of Agriculture [99-00700].

Conflict of Interest
The authors report no conflict of interest.

Authors' Affiliation:
- Department of Human Nutrition, Food and Animal Sciences, University of Hawai'i at Manoa, Honolulu, HI

Correspondence to:
Rachel Novotny PhD, RD; Department of Human Nutrition, Food and Animal Sciences, University of Hawai'i at Manoa, 1555 East West Road, Honolulu, HI 96822; Ph: (808) 956-3848; Email: novotnry@hawaii.edu
References

Case Report and Literature Review on Good’s Syndrome, a Form of Acquired Immunodeficiency Associated with Thymomas

Mark Henry Joven MD; Melvin P. Palalay MD; and Charlie Y. Sonido MD

Abstract

Thymoma is an uncommon and slow-growing neoplasm that usually presents with mass-associated respiratory symptoms, superior vena cava syndrome or parathyroid syndromes. We present a patient with thymoma and hypogammaglobulinemia who had recurrent sinopulmonary infections and diarrhea, diagnosed as Good’s syndrome. A 75-year old male with thymoma was admitted in our institution due to severe dehydration secondary to a 2-week history of non-bloody watery diarrhea refractory to anti-motility medications. His condition started 3 years ago when he had repeated outpatient visits and hospital admissions either from diarrhea or respiratory tract infections. Work-ups included colonoscopy showing benign tubular adenoma, multiple stool tests, and cultures, all of which were negative. He also had numerous sputum cultures, including a bronchoalveolar lavaged fluid, all unrevealing. He did not have fevers or chills, abdominal pains or any other gastrointestinal symptoms during this admission. Review of systems showed weight loss of 30 pounds over 3 years and chronic non-productive cough.

Two years earlier, a chest computed tomography (CT) revealed a 4.9 cm anterior mediastinal mass (Figure 1) and multiple pulmonary nodules with the largest measuring 2.2 cm on the left upper lobe. Positron emission tomography scan showed hypermetabolic nodules in both lungs and anterior mediastinum without evidence of extrathoracic metastasis. The anterior mediastinal mass was biopsied and found to be spindle cell thymoma, World Health Organization (WHO) histologic Type A15 (Figure 2). Biopsy of the left upper lobe lung mass showed necrotizing granulomatous inflammation presumed to be from pulmonary tuberculosis despite negative acid-fast bacilli (AFB) and fungal stains and cultures. The patient was empirically treated with a 6-month course of anti-tuberculosis medications. Abdominal CT showed bilateral adrenal masses presumed to be thymoma metastases. Serum and urine metanephrines and cortisol were normal. CT of the abdomen done a year later showed new liver masses, which were biopsied and found to be composed of spindle shaped cells (Figure 3) consistent with metastatic thymoma. He refused any form of medical, radiotherapy, or surgical intervention. Six months prior to this admission, he developed easy fatigability and was noted to have a hemoglobin of 4 g/dl, requiring numerous blood transfusions. There was no evidence of gastrointestinal bleeding. Bone marrow biopsy showed pure red cell aplasia (Figure 4) with 18% plasma cells. He has been transfusion dependent ever since.

The patient’s past medical history was significant for treated Hansen’s disease 12 years earlier. Nine years prior, he had progressive distal muscle extremity weakness thought to be from central canal stenosis with associated cervical and lumbar cord impingement. Electromyographic and nerve conduction studies revealed severe axonal polyneuropathy. Additional workups included heavy metal levels, rheumatoid factor, antinuclear antibody, vitamin B 12, folate and erythrocyte sedimentation rate which were all negative. He was found to have serum IgA lambda and faint IgA kappa monoclonal proteins and was diagnosed with monoclonal gammopathy of undetermined significance (MGUS) with 10% plasma cells on bone marrow biopsy. He did not have anemia, hypercalcemia, lytic bone lesions, or renal failure during that time. He chronically had elevated transaminases, aspartate transaminase (AST) ranging from 54 to 68 IU/L (normal value [NV] of 0-37 IU/L), alanine transaminase (ALT) ranging from 66 to 82 IU/L (NV...
Figure 1. CT chest demonstrating the anterior mediastinal mass (arrow)

Figure 2. CT-guided biopsy of anterior mediastinal mass. Low power objective view. (Arrow) Tumor cells show bland spindle morphology, consistent with spindle cell thymoma (WHO Type A).
Figure 3. CT Guided right lobe liver lesion biopsy. This biopsy showed tumor composed of spindle shaped cells with hyperchromatic nuclei and fibrillary cytoplasm. Tumor shares histologic features with the patient’s thymoma.

Figure 4. Bone marrow biopsy. Smear shows scant cellular particles, with increased megakaryocytes. Maturing granulocyte precursors are present; erythroid precursors are markedly decreased to absent. Findings consistent with pure red cell aplasia.
of 0-40 IU/L), alkaline phosphatase ranging from 93 to 141 IU/L (NV of 33-130 IU/L) with normal bilirubin and gamma-glutamyltransferase. Hepatitis panel were negative. CT abdomen showed intrahepatic and extrahepatic biliary duct dilatation with no ampullary or head of the pancreas mass lesion and no distal common bile duct calculus. This was periodically monitored. The patient’s overall condition had progressively worsened over a period of 5 years with significant limitations in activities of daily living, being wheelchair bound for the past 6 months prior to this hospitalization.

Physical examination on admission revealed a patient who was severely cachectic, not in respiratory distress. His saturation measured 99% on ambient air. Vital signs were normal. He had sunken eyeballs and dry mucous membranes. Lung and cardiac examinations were normal. Abdominal skin turgor was decreased. He had a soft, scaphoid, non-tender abdomen with normoactive bowel sounds. There was no hepatosplenomegaly. Stool Guaiac was negative. Examination of his limbs showed generally atrophy without any visible fasciculations. Neurologic examination was normal except for motor strength graded 3 to 4/5 on all limbs and hypoactive deep tendon reflexes. Extremity muscles were generallyatrophyed without any visible fasciculations.

The patient was vigorously hydrated with intravenous fluids. Laboratory data showed white cell count of 6,200 cells/μL with 76% neutrophils, 8% bands, and 15% lymphocytes. Hemoglobin level was 11.3 g/dL and platelet count was 281,000 cells/μL. He was found to have combined anion gap and non-anion gap metabolic acidosis (sodium 127 mEq/L, chloride 94 mEq/L and a bicarbonate level of 7 mEq/L with a mixed venous pH of 7.17) and was started on bicarbonate drip. Creatinine was 4.4 mg/dL and BUN was 60 mg/dL. ALT was elevated (78 IU/L) as well as alkaline phosphatase (187 IU/L). AST, bilirubin and calcium were normal. There was no proteinuria. Extensive stool evaluation including numerous cultures, stool H. pylori, stool cytomegalovirus (CMV), Yersinia, E. coli O157, cryptosporidium, Clostridium difficile toxin and stool leukocytes were done, all of which came back negative. There was no increase in qualitative fecal fat. TSH and serum lipase were normal. Human immunodeficiency virus (HIV) testing was negative. Other laboratory examinations including RPR, striatiunal muscle antibodies, anti-MuSK antibodies, acetylcholine receptor antibody, acetylcholine receptor blocking and binding antibodies were negative.

The patient’s hospitalization was complicated by hypotensive episodes from hypovolemia. He was started on hydrocortisone for possible adrenal insufficiency and aggressive intravenous fluids. Broad spectrum antibiotics were started because of presumed healthcare associated pneumonia and pulmonary infiltrates were noted on subsequent chest radiographs. Adrenocorticotropic hormone stimulation test subsequently done was normal. Mantoux test, AFB sputum smears, and cultures were negative. Blood cultures were also negative. Further investigation as to the cause of the patient’s recurrent diarrhea and respiratory infections were made. Serum protein electrophoresis showed hypogammaglobulinemia. His serum levels of IgM and IgG were both also low. IgA was found to be 3.8 times elevated from the upper limit of normal. Total lymphocytes, and helper CD4 T cell counts were found to be low. He had an elevated suppressor CD8 T cell percentage; this resulted in a marginally low helper-suppressor ratio of 0.41. (Table 1) A diagnosis of Good’s Syndrome (GS) was made. The patient clinically improved during this hospital admission. His renal function and metabolic acidosis resolved. Diarrhea improved with cholestyramine and octreotide. He was subsequently discharged and sent home on oral antibiotics. Because of his recent acute kidney injury and resolving infection, immunoglobulin therapy was not given during this hospitalization.

The patient came back two weeks later for pneumonia. At

<table>
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<th>Table 1. Patient’s immunologic work-up during hospitalization.</th>
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<td><strong>Patient’s value</strong></td>
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<td>Total protein</td>
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<tr>
<td>Helper-inducer CD4 T cell % / absolute count</td>
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<td>Suppressor-cytotoxic CD8 T cell % / absolute count</td>
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<td>Helper/Suppressor Ratio</td>
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<td>Total T CD3 % / Total T CD3 absolute count</td>
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that time, immunoglobulin therapy was considered but because of his severe debilitation and progressive decline in function, the patient and his family elected for hospice care. He expired two months later.

**Discussion**

This patient with metastatic thymoma presented with repeated sinopulmonary bacterial infections, chronic diarrhea, lymphosyndrome, hypogammaglobulinemia (noted on flow cytometry with immunofixation), and low CD4 T cell counts consistent with the diagnosis of GS. His recurrent history of diarrhea and sinopulmonary infections (either viral or bacterial) was a result of his immunodeficiency in the absence of acquired immunodeficiency syndrome (AIDS). He also had PRCA, a known parathyroid dysfunction. Work-up for MG was negative. The weakness and neuropathy he experienced could possibly be a result of his prior Hansen’s disease or central canal stenosis. He has concomitant plasma cell dyscrasia with 18% plasma cells on his recent bone marrow biopsy which is likely a progression of his MGUS. There was no evidence of end organ damage related to his plasma cell dyscrasia. His renal insufficiency and anemia were related to prerenal disease and PRCA respectively. There was no hypercalcemia or evidence of lytic bone lesions. This is consistent with the diagnosis of smoldering myeloma. Although plasma cell dyscrasias including myeloma and MGUS can be associated with hypogammaglobulinemia; these conditions are not associated with thymomas.16-17

First described in 1954 by Robert Good, this rare syndrome has no recognized diagnostic criteria yet.2-6-8 Patients with GS usually have low to absent B cells in the peripheral blood, hypogammaglobulinemia, and cell-mediated immunity defects in the presence of thymoma.2-4,6-9,13,18 The immunodeficiency appears to affect both humoral and cellular components, predisposing them to sinopulmonary infections, similar to that of X-linked agammaglobulinemia (XLA) and common variable immune deficiency (CVID) as well as opportunistic infections seen in AIDS.3,67 In contrast to XLA and CVID, which occur usually in the pediatric population, GS has a poorer prognosis with a high mortality of about 44.5% to 57%, mainly because of infectious diseases.2,4,9-11-12

Patients with GS commonly present between the ages of 40 and 70 years with a mean age of initial presentation of 56 – 59 years, and a mean age of recognition of both thymoma and hypogammaglobulinemia of 62 years.2,6-9,11-12 Both sexes are equally affected.2,4,6 Hypogammaglobulinemia is seen in 6% to 11% of patients with thymoma.26-18-20 Approximately 10% of patients with adult onset hypogammaglobulinemia have coexisting thymoma.2,6-7,20 Within the first 6 years of presentation, patients with GS developed either thymoma or infectious complications of their immunodeficiency.6

In a systematic review of 132 patients with GS by Kelesidis and Yang, the diagnosis of thymoma preceded the diagnosis of hypogammaglobulinemia, infection or diarrhea in 42% of patients with an interval of 3 months to 18 years.6 Thymoma was diagnosed after documentation of hypogammaglobulinemia or infection in 19.7% with an interval of 3 months to 15 years.6 About 37.9% of patients were simultaneously diagnosed within 2 months of each other and the rest were diagnosed only on autopsy.6 The most common histological form of thymoma is the spindle cell form, accounting for 52% of cases as in this case report; this is followed by lymphoepithelial tumors (19%), and epithelial thymoma (11%).26 Malignant thymoma accounted for 10% of the cases.2,6

The initial clinical presentation is varied, ranging from symptoms related to the thymoma itself like cough, chest pains, dysphagia, dyspnea, hoarseness, superior vena cava syndrome, Horner’s syndrome, or masses on the neck to infections resulting from immunodeficiency associated with the thymoma.2

Diarrhea which commonly presents in 50% of patients with GS, is either from infections or malabsorptions.2,6,7,18 The mechanism by which hypogammaglobulinemia and thymoma causes diarrhea is unclear; it has been postulated that it may be related to mucosal lesions resembling villous atrophy, which might resolve with reinstatement of immunologic status.6-7-21 Patients are susceptible to gastrointestinal pathogens, particularly viruses.21 Most of the cases reported failed to identify definite pathogens.2,6-7 Among those where infection was identified as an etiology, Salmonella spp was the most common pathogen.2,6 Other causes were CMV, Campylobacter spp and Giardia lambia.2,6 Primary sclerosing cholangitis (PSC) and ulcerative colitis have also been reported with this syndrome and could potentially explain a number of the diarrhea symptoms.2,23-22 Our patient was noted to have intraperitoneal and extrahepatic biliary ductal dilatation without an obvious pancreatic mass on history. Although this might be suggestive of PSC, no further diagnostic work-up was done to arrive at the diagnosis.

Infections are commonly described in patients with GS and could present even after resection of the thymoma.11 Recurrent sinopulmonary infections are the most commonly reported form, often resulting in bronchiectasis.26-18 Others like enteric, urinary tract, bone, joint, skin infections, CNS, and bacteremia have also been reported.2-3,6 Infections, which are thought to be due to defects in humoral immunity, are similar to that of XLA and CVID.25 Except for Pseudomonas spp. (22.6%), encapsulated bacterial pathogens like Hemophilus influenzae (24% to 24.5%), Klebsiella spp (13.2%), and Streptococcus pneumoniae (8% to 13.2%) were most commonly isolated in sinopulmonary infections.2,6-9 More than half of the cases with GS reported showed no isolates.2,6-9 Approximately 40% of patients with GS had viral infections; the most common pathogen was CMV (24%).3 Only 2 cases of mycobacterial tuberculosis have been reported.2,6-9 Defects in cell-mediated immunity in GS predispose to opportunistic infections (fungal and viral) seen in AIDS. These include severe CMV infections, mucocutaneous Candida infections, Aspergillus infections, Pneumocystis jirovecii pneumonia, Herpes zoster, Herpes simplex virus infections, and Kaposi sarcoma.2,6-9,11 To date, there have been no reports of GS having a history of Hansen’s disease other than this case report.

GS is often associated with numerous hematologic manifesta-
tions as well. Anemia is present in 50% to 86% of patients. PRCA, aplastic, hemolytic, and pernicious anemia, myelodysplastic syndromes are known associations. Leukopenia was seen in 46.5% to 55% of patients. Lymphocytopenia was seen in 35.1% of patients, 87% had low or absent peripheral B cells, and 15% had low T cell counts. Low CD4 count was seen in 73.2% of GS cases; whereas 55% of GS patients had a high CD8 count. This usually resulted in a low CD4/CD8 ratio seen in 76.1% of patients. Monoclonal gammopathy, which was noted in this case, was seen in 3.4% of cases reported.

Numerous clinical entities have been described in association with GS, most commonly MG and PRCA. (Table 2) Kitamura and colleagues mention that similar to MG and PRCA wherein autoimmunity to the post-synaptic acetylcholine receptors and erythrocytes respectively exists; autoimmunity to the B cell lineage causes paucity in B cells and hypogammaglobulinemia, resulting in acquired immunodeficiencies in GS. Hypogammaglobulinemia was present in all 152 patients in a systematic review by Kelesidis and Yang. In a review of literature by Taniguchi, and colleagues in 2009, they mentioned that the association of two or more paralytic syndromes was rare with only 12 case reports presenting with thymoma, hypogammaglobulinemia and PRCA as in this patient.

The etiologic relationship between thymoma and hypogammaglobulinemia in GS remains unclear, although some evidence point to a basic defect in the bone marrow. Pre-B cell arrest, impaired maturation of erythroid and myeloid precursors, disturbance in B cell lineage differentiation due to assumed bone marrow-derived humoral factors and T cell dysfunction causing disturbed B cell lineage differentiation have all been proposed mechanisms. All these mechanisms are thought to predispose patients with GS to recurrent infections. Only IgG, IgA, and IgM play a role in anti-infectious immunity. Panhypogammaglobulinemia was seen in 74.5%. Isolated low immunoglobulins, IgG and IgA, was seen in 9.1% and 1.8% respectively. A decreased IgA and IgG was seen in 4.5% of patients; whereas a decreased IgG and IgM, as seen in our patient, was seen in 2.7% of patients with GS. Hypogammaglobulinemia can also be from other primary immunodeficiencies such as XLA and CVID. GS is also similar to CVID but occurs in an older age group and is associated with thymoma. It is also important to note that secondary hypogammaglobulinemia can also be seen in conditions like chronic lymphocytic leukemia, AIDS (HIV infection is generally associated with hypergammaglobulinemia), lymphoma, and multiple myeloma. Medications such as antiepileptics, disease modifying treatments for chronic inflammatory rheumatism, targeted biotherapies, corticosteroids, and immunosuppressors are known causes of hypogammaglobulinemia and has to be excluded in GS.

Immunologic investigations including T cell subsets, B cells, and quantitative immunoglobulins should be considered a part of diagnostic search in patients with thymoma who present with recurrent infections or diarrhea. Even if initially negative, tests should be periodically done if GS is suspected because of the interval diagnosis of immunodeficiency and/or thymoma and infection.

To date, no definitive treatment protocol has been set for GS. Thymectomy generally prevents invasiveness of the thymomas and the most important indicator of long term prognosis is the completeness of resection. It has favorable effects on other paralytic syndromes like MG and PRCA. This however, is usually ineffective in improving immunologic deficiencies in patients with GS. Use of immunoglobulin replacements has been reported in numerous case reports to improve outcomes by decreasing infections in patients with GS. Around 37.5% had decreased infections after treatment. Diarrhea in some patients may respond to cholestyramine therapy, immunoglobulin injections as well. Anemia, is present in 50% to 86% of patients. PRCA, aplastic, hemolytic, and pernicious anemia, myelodysplastic syndromes are known associations. Leukopenia was seen in 46.5% to 55% of patients. Lymphocytopenia was seen in 35.1% of patients, 87% had low or absent peripheral B cells, and 15% had low T cell counts. Low CD4 count was seen in 73.2% of GS cases; whereas 55% of GS patients had a high CD8 count. This usually resulted in a low CD4/CD8 ratio seen in 76.1% of patients. Monoclonal gammopathy, which was noted in this case, was seen in 3.4% of cases reported.

Conclusion

Good’s Syndrome should be ruled out in patients with thymoma who develop severe, recurrent opportunistic infections. No definite treatment therapy protocol has been established.

Table 2.

| Autoimmune manifestations described in 89 patients with Good’s Syndrome. |
|-----------------------------|-----------------------------|
| Pure red cell aplasia (34.8%) |
| Myasthenia gravis (15.7%)    |
| Oral lichen planus (12.4%)   |
| Aplastic anemia (7.9%)       |
| Macrocytic anemia (5.6%)     |
| Autoimmune hemolytic anemia (3.4%) |
| Monoclonal gammopathy (3.4%) |
| Paroxysmal nocturnal hemoglobinuria (1.1%) |
| Agranulocytosis (1.1%)       |
| Thrombocytopenia (1.1%)      |
| Idiopathic myelofibrosis (1.1%) |
| Dermatomyositis (1.1%)       |
| Primary sclerosing cholangitis (1.1%) |
| Sweet’s syndrome (1.1%)      |
| Ulcerative colitis (1.1%)    |
| Vulpovaginal gingival lichen planus (1.1%) |
| Myelodysplastic syndrome (2.2%) |
| Diabetes mellitus (2.2%)     |
| Polyarthropathy (2.2%)       |

Although rare, this relentless syndrome needs to be identified so that treatment is instituted. Prognosis in patients with GS is thought to be worse than other immunodeficiencies. Clinical outcomes are dependent on the severity of infections, and associated hematologic and autoimmune diseases rather than the thymoma itself. Hence, early recognition to avoid complications is imperative.  

The diagnosis of GS can be difficult. Various presentations associated with this syndrome can occur during different periods, sometimes with intervals of several years. The signs and symptoms a patient present with may not initially be interrelated. GS can be easily missed especially because of its protean manifestations of autoimmune and parathymic syndromes. It is crucial that once a diagnosis of thymoma is made, a thorough history and evaluation with longitudinal follow-up and surveillance be done to rule out various syndromes associated with this condition.

Disclosure Statement/Conflict of Interest

The authors have no financial disclosures. No financial support of any kind was received.

Authors’ Affiliation:
- University of Hawai‘i, John A. Burns School of Medicine, Honolulu, HI

Correspondence to:
Mark Henry Joven MD;1356 Lusitana Street, 7th Floor, Honolulu, HI 96813;
Ph: Email: h_joven@yahoo.com

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In recent years, the term “patient-centered” has become very popular. “Patient-centered medical home,” “patient-centered medical care,” “patient-centered medical interviewing,” and “patient-centered communication” are several examples of concepts that explicitly recognize patients as the primary focus and/or customer in the provision of healthcare.

There will be increasing emphasis on “patient-centeredness” in the practice and training of healthcare professionals, as national healthcare programs such as the Patient Protection and Affordable Care Act move forward. Similarly, with increasing emphasis on interprofessional education, “patient-centeredness” will likely prove to be a unifying educational requirement that is shared across multiple healthcare professions, leading to more interdisciplinary training activities.

At the level of national medical school accreditation, the Liaison Committee on Medical Education (LCME) is also encouraging medical student curricula to include patient-centered care. As an example, accreditation standard ED-19 states, “the curriculum of a medical education program must include specific instruction in communication skills as they relate to physician responsibilities, including communication with patients and their families, colleagues, and other health professionals.” Also accreditation standards ED-20-22 include specific references to related patient-centered concepts such as, “the medical consequences of common societal problems,” “an understanding of the manner in which people of diverse cultures and belief systems perceive health and illness,” and “address(ing) gender and cultural biases.”

**Patient-Centeredness at the John A. Burns School of Medicine**

For years, the medical student curriculum at the University of Hawai‘i John A. Burns School of Medicine (JABSOM) highlighted and promoted patients as the centerpiece of the educational process. The JABSOM Objectives for Graduation, which serve as the foundation for all medical student educational experiences at JABSOM, include requirements such as, “approaching each patient with an awareness and sensitivity to the impact their age, gender, culture, spiritual beliefs, socioeconomic background, family support, sexuality, and healthcare beliefs may have on the development, diagnosis, and treatment of their illness,” “incorporating patient-centered and shared decision-making principles into their practice,” and “stating the important non-biological determinants of poor health and the economic, psychological, social, and cultural factors that contribute to the development and/or continuation of illness.” These examples of JABSOM’s Objectives for Graduation reflect the value placed on patient-centeredness throughout the curriculum. The JABSOM medical student curriculum further highlights patient-centered medical education through the following educational experiences:

**Problem-Based Learning**

Problem-based learning (PBL) is a form of case-based teaching first developed by Dr. Howard Barrows that incorporates the following six characteristics:

1. Use of problems as the starting point for learning.
2. Small-group collaboration.
3. Flexible guidance of a tutor.
4. Limited number of lectures.
5. Student-initiated learning.

While the majority of medical schools today utilize some form of case-based teaching, JABSOM remains relatively unique in the use of classic PBL methodologies, and the degree of emphasis placed on small-group, faculty-facilitated, student-directed learning focused around the study of PBL cases about patients, their families, and their communities. Rather than reading like traditional medical case reports, JABSOM PBL cases are about people who live in Hawai‘i and are patients in the health care system. To provide a rich opportunity for patient-centered learning, the biological, clinical, populational, and behavioral issues that impact their health are woven into the case to create an engaging narrative and characters that students care about. Dialogue in the cases model the principles of patient-centeredness. Student learning about relevant biological sciences, clinical sciences, patient communication, and professionalism are contextualized by, and applied to, the patients in their PBL cases.
Patient-Centered Panels and Presentations
With greater emphasis on small-group PBL, there is less lecture time available in the JABSOM curriculum than most medical schools in the United States. Still, some of this lecture time is used to reinforce the concepts of patient-centeredness. Panel presentations that include both physicians and patients are among the most highly-rated learning sessions, and patient-centered communication skills and professional behavior are also stressed prominently throughout the curriculum.

Early Clinical Experiences
Clinical learning experiences begin early in the JABSOM curriculum. Exposure to patients helps students see the connections between their responsibilities as physicians and the material they are learning in the classroom. Students are exposed to both hospitalized and ambulatory patients near the start of their first year of medical school. Patient-centered medical interviewing, communication skills, patient safety, and team-based care models are prominent components of the curriculum.

Standardized Patients
At JABSOM a large number of patient simulation learning experiences are provided. Standardized patients are used for face-to-face, personal interactions and each student’s ability to respect the culture and beliefs of their patients is assessed.

Manikin-Based Simulations
Manikin-based simulations begin within the first two months of medical school, and occur in virtually every required course and clerkship at JABSOM. The manikins are able to respond to questions by medical students in real-time and can simulate a variety of physical findings that allow students to apply what they have learned to specific patient scenarios. Both standardized patients and manikin simulations are integrated with the PBL curriculum so that characters from the cases are “brought to life.”

Community Health Experiences
Another unique component of the JABSOM curriculum is a Community Health requirement that spans the first-year of the MD curriculum. Within this weekly course, students work with community organizations and learn the importance of patient advocacy and service.

Diverse Learning Environments
While learning in tertiary care centers within urban settings is strongly valued in the curriculum, JABSOM believes that students should have opportunities to learn within and across a wide range of communities and practice settings. JABSOM provides opportunities for preclerkship students to complete portions of their first year of medical school on Hawai‘i Island. In this option, students live in Hilo for three months and complete their coursework, including clinical skills training, within this community. Similarly, in their third-year of training, students can opt to complete a six-month longitudinal clerkship option in rural areas within the state including clinical sites on the islands of Hawai‘i, Kaua‘i and Maui. Currently JABSOM is exploring expanding its education into North Hawai‘i. By living in the same community as their patients, students have a unique opportunity to learn about the different cultures within their state and better appreciate their patient’s perspective on health care.

Patient-Based Evaluations
Exam questions generated by JABSOM faculty in the preclerkship curriculum include patient names and a clinical scenario that requires students to apply the health sciences to the patient described in the question. This practice reinforces that important physician decisions, even those rooted within the traditional basic sciences, are still made with the best interest of the patient in mind. In addition, Objective Structured Clinical Examinations (OSCE) and manikin simulations are also used for formative and summative student assessments.

In total, JABSOM’s medical student curriculum and educational environment demonstrate a strong commitment to patient-centeredness in terms of content, philosophical approaches, methodologies, and evaluation system.

Patient-Centered Medical Education: A New Term Defining an Old Educational Paradigm
Current national movements have used the term “patient-centered” to describe new models, paradigms, or ideals. Similarly, at the John A. Burns School of Medicine, we propose that over the past decade our educational program has purposefully evolved to what is best described as “Patient-Centered Medical Education.” The following definition for this educational approach is offered by JABSOM:

Patient-Centered Medical Education is an approach to medical education that places the patient at the center of the learning experience, and requires students to consider the patient in all aspects of learning. Curricular goals and objectives should explicitly reflect these values and expectations. Content included in the curriculum should reflect knowledge, skills and attitudes of greatest need by patients, including areas such as physician-patient communication; ethics and professional behavior; and patient safety. Methods that encourage Patient-Centered Medical Education include problem-based learning or other case-based learning strategies that explicitly include personal and/or social issues relevant to their care; clinical experiences – whether they be with actual patients or simulations – that require students to learn or apply knowledge or skills in the context of specific patient circumstances; or other educational experiences that meld the biomedical, clinical, populational and/or behavioral aspects of the patient experience. Finally, both learner evaluation and curriculum evaluation should regularly review outcomes related to patient-centered learning objectives across the curriculum.

JABSOM believes that for a medical school to define their own curriculum as “patient-centered,” they would need to meet the criteria outlined above related to goals, objectives, content, methods, and evaluation. This approach would not be suitable for all medical schools, but may be an organizing structure that would appeal to some.
The Future of Patient-Centered Medical Education at JABSOM

As the potential of a newly-named paradigm for medical student education is realized, there are a number of exciting opportunities ahead of us. Curricular areas that may have previously sat on the outskirts of a more biomedical model for medical education are now more clearly front-and-center in a patient-centered medical education model. These include topics like patient safety, quality improvement, cultural competency, and appreciation of diversity, communication, counseling skills, and professional behavior.

Further exploration of these content areas will also necessitate revisiting JABSOM’s curricular goals, objectives, methods, and evaluation processes, which in turn will lead to additional opportunities for educational scholarship and research.

The ultimate goal of realizing the potential of Patient-Centered Medical Education will be to graduate outstanding physicians who truly appreciate the importance of the patient in medical practice, they will become leaders and champions of patient-centeredness in the larger healthcare system.

Authors’ Affiliation:
- Richard T. Kasuya MD, MSEd; Associate Dean for Medical Education; John A. Burns School of Medicine, University of Hawai‘i, Honolulu, HI
- Damon H. Sakai MD; Director, Office of Medical Education; John A. Burns School of Medicine, University of Hawai‘i, Honolulu, HI

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Developing the Ho‘ouna Pono Substance Use Prevention Curriculum: Collaborating with Hawaiian Youth and Communities

Susana Helm PhD and Scott K. Okamoto PhD

ABSTRACT
This article briefly outlines a collaboration among communities on Hawai‘i Island and a university-based research team to develop, implement, and evaluate a school-based substance use prevention curriculum called Ho‘ouna Pono. In addition to providing a rationale for the project, the goal of this paper is fourfold. First, an overview of the Ho‘ouna Pono research results to date (2007-2013) is provided. Second, within this overview, the ways in which selected results informed program development are highlighted. Third, the curriculum is briefly described, and finally, the role of the students and community in the video production is described.

BACKGROUND
Of grave concern across communities in Hawai‘i and the Pacific region is the lack of evidence-based practice in substance use prevention targeting Hawaiian youth. Substance use and abuse contribute to significant and persistent health disparities among Native Hawaiians. Hawaiian youth initiate drug use earlier than their non-Hawaiian peers,9,10 and report higher use rates.11 Although there are national registries recommended to communities for identifying rigorously developed and tested drug prevention practices,12-13 a paucity of options exist for indigenous Hawaiian communities.5,8 Specifically, nationally recognized evidence-based practices have not been culturally grounded in Hawaiian epistemology.5,6,8 Despite the fact that substance use and abuse has been a serious health concern among Native Hawaiians for decades.10,14-18

PROJECT RATIONALE
Empirical evidence indicates that Hawaiian cultural interventions are preferred among Hawaiian adults and youth,19-20 and an indigenous approach is effective for substance use and related problems among Hawaiian youth.5,6,8-20-21 Therefore, Native Hawaiian communities may need to develop their own contextually-relevant evidence-based practices.1-3 This article briefly outlines such a collaboration among communities on Hawai‘i Island and a research team affiliated with Hawai‘i Pacific University and the University of Hawai‘i who are developing a middle school curriculum (6th, 7th, 8th grades) to prevent substance use. The individual studies in this program of research each have been reviewed and approved by the Department of Education, Systems Accountability Office; University of Hawai‘i Human Studies Program; and Hawai‘i Pacific University IRB Committee. These studies have been published elsewhere, and the reader is referred to those articles for additional methodological details, and greater depth and breadth of results and their implications.

Ho‘ouna Pono Research
Program development has focused on rural middle school-aged adolescents by using an eco-developmental22-24 approach to defining etiology and risk and protective factors. The intervention development phase, which started in 2006, concluded recently in 2012. The current implementation phase is underway with a pilot study to determine feasibility and effect size of the proposed intervention (2012-2014). A summary of the initiatives and their most salient results are provided here. Demographic characteristics for each study are provided in Table 1. All participating schools are public schools located in rural areas, and include youth in middle school (grades 6-8), except for K01 (K01 refers to the National Institute on Drug Abuse grant number: K01 DA019884) study 4; the sampling frame for school-communities has remained the same from 2007 to present. For K01 Study 4, adults and older youth participated. In addition, we included high school aged youth in R34 (R34 refers to the National Institute on Drug Abuse grant number: R34 DA031306) Study 1.

- K01 Study 1 – 2007. Focus group interviews with girls and boys indicated a variety of situations in which drugs – defined as alcohol, tobacco, marijuana, and other drugs – had been offered.5-22-25 Study 1 results were used to develop the Hawai‘i Youth Drug Offer Survey (HYDOS).24 Drugs most commonly offered in these scenarios were beer, hard liquor, marijuana, or cigarettes, which reflects the extant literature for this age group. The bulk of participants’ narratives indicated a distinction between direct-relational and indirect-contextual drug offers. Direct-relational offers occurred in nearly half of all drug offer scenarios, in which a specific individual explicitly offered drugs to the participant. However, in indirect-contextual offer scenarios, no explicit drug offer occurred. Rather, narratives suggested that middle school youth often find themselves (wittingly or unwittingly) in situations
in which alcohol, marijuana, or cigarettes are being used. The drug offer is made implicitly by the drug-using context itself, not by a particular person. This has implications for drug prevention, because the prevailing paradigm emphasizes direct offers.

- **K01 Study 2 – 2008.** HYDOS was administered to Hawaiian and non-Hawaiian youth to determine frequency of exposure to drug offers, and difficulty in refusing drugs in these situations. Native Hawaiian youth indicated a higher frequency of exposure to drug offers, but rated the difficulty to refuse to be lower than their non-Hawaiian peers. Among the Hawaiian youth, girls indicated more frequent exposure to drug offers and more difficulty in refusing compared to boys. Also among Hawaiian youth, three factors accounted for 63% of the variance: peer pressure (23%), family offers and context (21%), and unanticipated drug offers (19%).

The family factor has implications for prevention, in that most prevention programs focus on peer-to-peer offers. For Hawaiian youth, prevention must also highlight the need for refusal skills with family members. This finding is corroborated by Studies 1 and 3.

- **K01 Study 3 – 2009.** Focus groups were held in which youth brainstormed possible socio-culturally competent drug refusal strategies to the 15 most frequent and difficult drug offers as defined from Study 2, and then youth described the pros and cons as well as rationales for the variety of refusals. These responses and associated drug offers were collated as primary or secondary responses, and incorporated into a web-based survey for Study 4. Primary drug resistance strategies are a single response, or first part of a two part response; while secondary drug resistance strategies were those that were used in tandem with the primary drug resistance strategies. A response type may be used as a primary response, or a secondary response. Over half of the responses reflecting primary drug resistance strategies fell into three different categories (“refuse”, “explain”, or “angry refusal”), while over half of the responses reflecting secondary drug resistance strategies represented one category (“explain”). Implications for prevention focus on the finding that variations in the frequency of using different strategies were based on the type of drug offerer (family versus friends/peers). The family factor has implications for prevention, in that most prevention programs focus on peer-to-peer offers. For Hawaiian youth, prevention must also highlight the need for refusal skills with family members. This finding is corroborated by Studies 1 and 3.

- **R34 Study 1 – 2011-2012.** The prevention intervention has been designed as a school-based curriculum, enhanced with videos depicting drug offers and drug refusal options. As part of curriculum development, youth participated in focus group discussions for the purpose of adapting and validating video scripts to make them more realistic. Youth affirmed the situations described in the scripts, and suggested changes to make the scripts more culturally specific. In the scripts where drug offerers were a parent or peer/friend, the participants appeared to favor non-confrontational drug resistance strategies. Such strategies may be a method by which rural Hawaiian youth preserve their social relationships with peers and friends in the school setting and relational harmony within the family system.

- **R34 Study 2 & 3 – 2012-2014.** Participating schools have been randomly assigned to either the intervention or comparison group. Pre- and post-intervention surveys have been or will be administered during the second semester of the 2012-2013 academic year in both intervention and comparison schools. Surveys ask about ethnicity & culture; risk & protective factors, academic year in both intervention and comparison schools. Surveys will be collected at 6 months and 12 months at both intervention and comparison schools.

### The Curriculum

Intervention schools participate in the video-enhanced curriculum, which includes a teacher’s manual that aligns with Hawai‘i Content and Performance Standards in Health Education. (These standards can be accessed online: http://165.248.30.40/hcpsv3/search_results.jsp?contentarea=Health&gradecourse=6-8&rand=&showbenchmark=benchmark&showspa=spa&showrubric=rubric&Go%21=Submit), as well as national education standards for middle school grades. Comparison schools participate in the standard health education curriculum. For the pilot test, seven lessons are delivered once weekly for seven weeks. Lessons are based on the drug offers identified in Study 1 and Study 2, and the drug refusal options identified in Study 3 and Study 4. Each lesson follows a similar pattern. To begin,
a video is shown depicting a drug offer, and three possible drug refusal options, often incorporating refusing, explaining, and other nuances that emerged from Study 3. Next, critical thinking skills have been designed to emphasize key terms and concepts in drug prevention and Hawaiian culture, and these are depicted in the video. Finally, applied practice activities have been designed to enhance skill acquisition with respect to the drug refusal options seen in the video, as well as those the youth generate on their own. Practice activities include role playing for example, and other small group co-learning. Table 2 outlines several examples of the drug offer situations depicted in the videos, along with still shots from the videos. While these examples only show alcohol offers, the other situations not shown involve marijuana offers.

<table>
<thead>
<tr>
<th>Video Title</th>
<th>Drug Offer Situation</th>
<th>Still Photography from Video production</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paina</td>
<td>You are at a family party where the adults have coolers full of beer. They are getting drunk, so you and your cousins can take a beer without the adults noticing. One of your cousins says to you, “Let’s grab one.”</td>
<td>![Still from Paina video]</td>
</tr>
<tr>
<td>Pulehu</td>
<td>Your dad, uncles, papa, and dad’s friends are making pulehu in the yard, and you are with them. Your mom is inside the house. They are drinking a lot of beer, probably already drunk. Your dad offers you a beer.</td>
<td>![Still from Pulehu video]</td>
</tr>
<tr>
<td>Vodka Recess</td>
<td>Your friends bring vodka to school and mix it with juice. They are drinking it on campus during recess. They offer you some.</td>
<td>![Still from Vodka Recess video]</td>
</tr>
</tbody>
</table>

**Community Contributions**

Of note is the tremendous generosity of the many Hawai‘i Island community members who volunteered their time and talents during the video production phase. Youth and adults were cast in each video, and for the most part they were amateur and first-time actors/actresses. With exception to the professional producer - Matt Yamashita of Quazifilms Media, and the professional freelance cameraman – Randy Mills, the production crew consisted of student volunteers from nearby schools with video production curricula. An opening night celebration was held in their honor at UH-Hilo so that the talent, crew, and their families would have an opportunity to view their videos post-production, after which the audience was invited to name the curriculum. “Ho‘oula Pono” was selected among a number
of excellent options, and signifies sending forth or enveloping oneself in doing/making the right choice. The name was rec-
commended along with a "hoomu" icon, because the turtle’s shell suggests a protective envelope around one’s being.

Next Steps
The next steps in program development will focus on two primary aspects. First, we will use results from this pilot phase to improve the existing curriculum. These results will be shared with our community partners later this year, as well as in several scholarly venues (eg, national academic meet-
ings, peer-reviewed publications). We also are in the process of formalizing the community advisory board so that we can learn more about the schools and communities where the ma-
ajority of Native Hawaiian middle school youth reside, which will improve the research design and curricular content and implementation. Second, we plan to scale up the intervention to include more sessions (pilot phase includes 7 sessions), as well as to use a larger sampling frame.

Acknowledgements
We would like to mahalo our student assistants who were integral to the video production, from Hawai'i Pacific University – Suzanne Pel and Janai Hayashida, and from Punahou School – Mia Masuda. We also greatly appreciate the hard work of Keoni Chin in logistics and coordination during production, as well as Natek Penn for her film and video production support. Also, our national expert in school-based drug prevention curriculum development has been a joy to work with, Dr. Pat Dustman. The research featured in this article was funded by the National Institutes of Health/National Institute on Drug Abuse (K01 DA019884 and R34 DA031306) and the Trustees’ Scholarly Endeavors Program, Hawai'i Pacific University. Resources used for preparation of this article were funded by the National Institutes of Health/National Institute on Drug Abuse (R34 DA031306).

Authors’ Affiliations:
- Susana Helm PhD; Associate Professor, Department of Psychiatry, John A. Burns School of Medicine, University of Hawai'i at Manoa
- Scott K. Okamoto PhD; Associate Professor, School of Social Work, Hawai'i Pacific University, Honolulu, HI

Correspondence to:
Susana Helm PhD; 1441 Kapiolani Blvd, Suite 1803, Honolulu, HI 96814; Ph: (808) 945-1462; Email: HelmS@dop.hawaii.edu

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FIDO, DON’T SNIFF THAT LADY IN HEAT, WE NEED YOUR NOSE HERE.

At first glance it sounds like voodoo, but Labrador retrievers can be trained to detect aberrations in blood sugar levels for type one diabetics. The dog’s accuracy and speed can beat medical devices, such as glucometers and continuous sugar monitors. According to doctors, owners, and trainers, the dogs are able to react to a scent that researchers have not been able to identify. They are especially helpful in detecting dangerous blood sugar levels in children. Type-one diabetes is an autoimmune disease characterized by the absence of insulin production. The number of people affected in the United States is between 1.3 and 2.6 million. Prolonged high blood sugar levels can lead to heart disease, kidney failure and neuropathy. Low blood sugar can be lethal with unconsciousness. These wonder dogs can be trained to react with various signals when the blood sugar is too low or when too high. One problem is price; a fully trained dog goes for $20,000. Still, trainers cannot keep up with demand.

HERE’S THE RECEIPT BILL. THIS ONE IS UNDER 50 MILLION.

The Bill and Melinda Gates Foundation is spending heavily to fund research for a malaria vaccine. This largely tropical disease killed 655,000 people in 2010, most of them children in Africa. A vaccine “RTS,S” developed by GlaxoSmithKline was administered together with childhood vaccines, and reduced the risk of developing malaria by 31% in 6,500 infants between six and 12 weeks of age. The results, published in the New England Journal of Medicine, revealed that researchers have a long way to go before they find a vaccine that is highly effective against malaria. Since there are at least four species of Plasmodium, the parasite that causes malaria, finding a vaccine to cover all is a huge challenge. Moreover, this parasite is so clever in hiding when it is not active.

SHE WENT PALE? NO PULSE? BUT SHE JUST DELIVERED TEN MINUTES AGO!

More than four million births occur annually in the United States with about 52,000 women affected by severe complications. In the decade ending in 2009, Centers for Disease Control and Prevention (CDC), recorded a 75% increase in emergencies during delivery. Cardiac arrest, respiratory distress, and kidney failure increased and severe complications following delivery more than doubled in the same time frame. A big reason for the increase is more women are older, obese, or have chronic conditions such as diabetes and kidney disease. Post partum hemorrhage is the most common cause of death after delivery. A nearly 60% increase in the rate of Caesarean section delivery since 1996 is no doubt a factor. “There is a clarion call now to address the problem of maternal complications,” said William Callaghan, CDC chief for maternal and child health. “When things go wrong they can go south very fast, and you need a well-oiled team trained to respond in times of crisis.”

PANDORA? SHE HAD THAT IN THERE TOO?

Voters in the state of Washington elected to legalize marijuana without a doctor’s prescription. Gathering in public places like the Space Needle, pot-heads counted down to midnight, then began to fire up joints, bongs and pipes. People 21 and older can legally carry up to an ounce of marijuana. The state Liquor Control Board has one year to define standards for growing plants, and police must decide how to enforce the existing laws. Will law enforcement people be able to measure one ounce? Colorado voters approved a similar marijuana law last month. Meanwhile possession remains a federal offense and so far the U.S. Justice Department has not clarified a position. With two states ready to accept modest use of marijuana will other states fall like dominos?

GOT NO MATCHES? FORGET IT MAN. AND HAVE ONE OF MY HOMEMADE COOKIES.

And for those who are eagerly preparing to light up, it is well to recognize studies coming from New Zealand. Their study of 1037 individuals published in the Proceedings of the National Academy of Sciences, found that heavy use of marijuana has been linked to neuro-psychological impairment, particularly when use begins early in life. An Australian study published in the Archives of General Psychiatry cited data from 20,000 people. Their findings were among people diagnosed with mental illness. Those who had smoked marijuana when they were younger developed symptoms of mental illness nearly three years earlier than those who had not used marijuana at all.

HERE’S MY REPORT. JOE BIDEN HELPED ME WRITE IT.

Retractions of scientific papers are an uncommon occurrence, but are increasing. While one might believe that honest errors are the primary cause, in fact only 21.3 percent of biomedically related life sciences studies were withdrawn for legitimate errors. Arturo Casadevall, a microbiologist at Einstein College of Medicine in New York City and his research team, studied 2,047 retracted journal articles. Retraction notices often do not explain why a study is being withdrawn, or the real reason may be covered up. Scientific misconduct accounted for 67.4 percent according to the study. Plagiarism accounted for 9.8 percent and duplicate publication for 14.2 percent of retractions. Publishers now use software that may explain why retractions are up. The culture of science may be to blame for a recent increase in fraud. Journal publications are widely used to gauge a scientist’s potential and success. Hard-to-get grant money breeds a climate ripe for wrongdoing. As all academicians know it is “publish or perish” in the cut-throat competition for foundation and philanthropic dollars.

AT AGE NINETY WHO GIVES A DAMN.

A 31-year-old armed man broke into a home in Greenbrae, California, and tied up the 90-year-old occupant. The elderly man broke free, grabbed a gun and pointed it at the intruder. The burglar fired first striking the old man in the face, but he promptly returned fire pumping several bullets into the burglar. Both men survived. The burglar was convicted of all charges and sentenced to life in prison. Now he has brought a law suit against the old man alleging that he “negligently shot” him, calling him a vigilante and asking for a six figure settlement for damages. A trial attorney actually took this case?!

IT IS NOT EXACTLY A LION’S ROAR, BUT IT IS A VOICE.

In January Congress convenes for the 113th time. Medicine will be represented by three physicians in the Senate and 15 physician members in the House of Representatives. They are a long way from the overwhelming number of attorneys, realtors and educators, but they will have a voice.

ADDENDA

- The first reported American auto theft took place in St. Louis, Missouri, in 1905.
- More soda is consumed in the United States than any other country at a rate of 50 gallons per person annually. Ireland is second at 33 gallons. Burp.
- Joseph Coors, founder of Coors brewery died at age 88. His body was cremated and the urn smashed against a frat guy’s forehead.
- Target stores have a big bullsye painted on the roof. Flying over it looks sooo tempting.
- The reason there are two senators for each state is so that one can be the designated driver.
- The French know how to kiss. If it weren’t for them you would wonder, “What the heck am I supposed to do with my tongue?”

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